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ENDO 2013
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CASE MANAGEMENT

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ENDO 2013
FORWORD

The opportunity to discuss the management of clinical cases with an expert in the field is one of the most highly valued aspects of The Endocrine Society's annual meetings. The popular "Meet-the-Professor" and "Case Management Forum" sessions are case-based sessions where audience members have an opportunity to discuss perplexing endocrine questions with some of the world's most renowned experts in the field. There are almost 70 "Meet-the-Professor" and "Case Management Forum" sessions in the ENDO 2013 program, and these sessions cover a broad range of common endocrine disorders. The experts have been chosen for their deep understanding of the session topic, their clinical experience, and their pedagogic skills.

The "Meet-the-Professor" and "Case Management Forum" sessions are lively and interactive. For clinicians, these sessions always represent some of the highlights of the Annual Meeting. Since it is never possible to attend all of these sessions at a single meeting, this book is intended to provide readers with some of the intellectual excitement and clinical knowledge that are found in these sessions. Although it is no substitute for attending in person, this book captures much of the intellectual content of the live sessions.

Physicians learn best by active participation in case-based clinical discussions. When physicians are actively engaged in the didactic process, learning is most enjoyable and enduring. We have designed the format of this book to create interactive learning modeled after the live sessions. We asked speakers at the live sessions to provide learning objectives, a concise up-to-date review of their topic, a summary of the cases discussed during the live sessions followed by a brief discussion of the cases. This format allows the reader to learn actively by "testing themselves" on common questions of clinical endocrinology.

I am deeply grateful to the many experts who contributed to these sessions and made this book such a useful didactic tool for endocrinologists and primary care providers. I am also very grateful to the Endocrine Society staff whose efforts help to ensure the high quality of the "Meet-the-Professor" and "Case Management Forum" sessions and the successful publication of this book.

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ADRENAL

Adrenal Insufficiency: Diagnosis, Management, and Hormone Replacement Therapy

M59
Tuesday, June 18
12:15–1:00 PM

Eystein Husebye, MD, PhD
Haukeland University Hospital
Bergen, Norway
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SIGNIFICANCE OF THE CLINICAL PROBLEM

Up till the 1940s Addison's disease was a deadly disease, but the synthesis of corticosteroids in the late thirties and forties revolutionized treatment, transforming Addison's disease into a chronic, treatable disease. Unfortunately, untimely but preventable fatalities from adrenal crises still occur (1).

Despite state-of-the-art treatment with corticosteroids, patients are at risk of osteoporosis and fractures (2), and there are concerns about long-term cardiovascular complications related to treatment. Quality of life and working ability are reduced in many patients, and there are concerns about fertility and sexual function. Since Addison's disease has a prevalence of 10-15 per 100 000 inhabitants (3), which defines it as a rare disease, most physicians and even specialists in endocrinology rarely manage more than a few patients. Thus it is reasonable to believe that procedures for diagnosis, treatment and follow-up vary greatly.

BARRIERS TO OPTIMAL PRACTICE

- International guidelines are missing
- Physiological replacement therapy is not available
- Modalities for early intervention in autoimmune Addison's disease are missing

LEARNING OBJECTIVES

- To diagnose adrenal insufficiency and its causes
- Optimising replacement therapy
- Strategies for follow-up of patients

SUCCINCT REVIEW- STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Diagnosis

Diagnosis of adrenal insufficiency

Primary adrenal insufficiency can be diagnosed in several ways. In most cases the combination of high levels of adrenocorticotrophic hormone (ACTH) and low levels of cortisol is sufficient to secure the diagnosis. In unequivocal cases a tetracosactide (synacthen) stimulation test can be performed. Other common laboratory findings are elevated plasma renin activity/renin concentration, low aldosterone and dehydroepiandrosterone sulphate (DHEAS), hypercalcaemia, normochromic anaemia, sometimes eosinophilia, and elevated liver transaminases. TSH levels can be slightly increased due to lack of cortisol-mediated inhibition of pituitary TSH production.

Etiological diagnosis

The most common cause of Addison's disease in industrialized countries is autoimmunity, typically affecting females between 20 and 50 years of age. Other organ-specific autoimmune diseases are very common, such as autoimmune thyroid disease, type 1 diabetes, autoimmune gastritis, celiac disease, vitiligo, alopecia and ovarian insufficiency (4). The combination of Addison's disease and/or autoimmune thyroid disease and type 1 diabetes is denoted autoimmune polyendocrine syndrome type 2 (APS-2). The diagnostic marker used is 21-hydroxylase autoantibodies (21OH-Ab) (5). A commercial assay is preferable,

although many in-house radiobinding assays show the same performance. An alternative is the immunofluorescence using adrenal tissue slides; however this technique has lower sensitivity and is more difficult to standardize than the 21OH-Ab assays. If 21OH-Ab is positive, one should consider the rare autoimmune polyendocrine syndrome type 1 (APS-1) defined by the presence of two of the three main components, Addison's disease, chronic mucocutaneous candidiasis, and hypoparathyroidism (6). This disease commonly starts in childhood, but late debut and milder phenotypes are sometimes seen. 21OH-Ab has also been reported in Kearne-Sayre syndrome, a mitochondrial disease.

Although autoimmune adrenalitis cannot be completely excluded by a negative 21OH-Ab assay, a more thorough investigation is warranted guided by medical history, symptoms and signs (*Figure 1*). The antibody-negative group will have another age composition with higher representation of children, adolescents and elderly. A computer tomography of the adrenals should be done. It can reveal atrophy, tumours, calcifications as a sign of tuberculous adrenalitis (thought to be common in developing countries), or signs of bleeding. Assay for very-long chain fatty acids should be performed in males to identify those with the X-linked adrenoleukodystrophy.

Therapy

Adrenal crisis

Acute adrenal crisis is a life-threatening emergency that requires immediate diagnosis and treatment. It is not rare; 6-8 episodes per 100 patients each year has been reported (7). Vomiting and/or diarrhea is commonly implicated as a precipitating cause. The symptoms are malaise, nausea, fatigue, vomiting, severe abdominal pain, muscle pain or cramps. Dehydration and hypotension with progression to circulatory shock is not uncommon. Hyperkalaemia can be life-threatening.

It cannot be stressed to often that treatment must not be delayed by diagnostic procedures. A blood sample for serum cortisol, ACTH (if the diagnosis is not known), sodium,

FIGURE 1

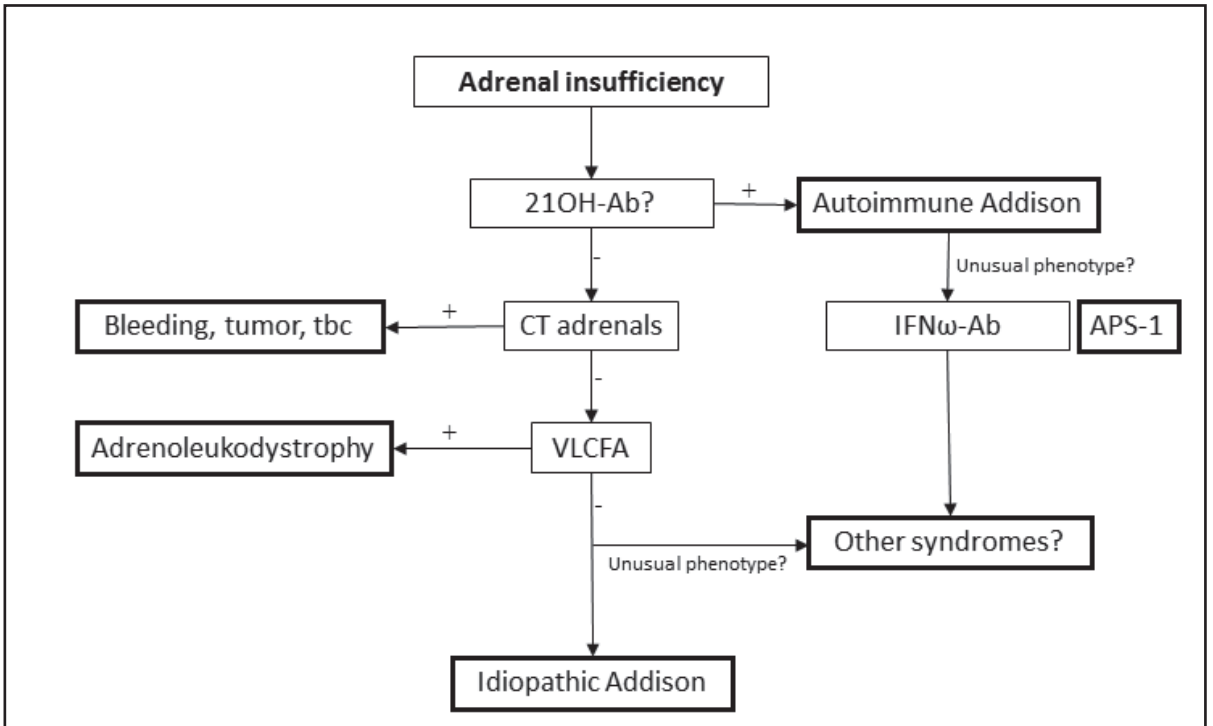

Figure. Algorithm for diagnostic workup of Addison's disease

potassium, creatinine, urea, glucose and other tests for precipitating causes (bacterial or viral infections) should be drawn and therapy initiated immediately by giving an intravenous bolus of 100 mg hydrocortisone (HC) and saline infusion. If a treatable precipitating condition is identified, it should be handled. Parenteral glucocorticoids should be continued and 3-400 mg per 24 hours and tapered over 1-3 days if the underlying condition permits. The patient should be equipped with a steroid card and injectable glucocorticoids and educated on the use of stress doses of glucocorticoids.

Chronic replacement therapy

Patients with primary Addison's disease require lifelong glucocorticoid and mineralocorticoid treatment; salt intake should not be restricted. Glucocorticoids are secreted in a diurnal rhythm with peak on awakening and nadir at bedtime. Secretion comes in pulses creating a superimposed ultradian rhythm. Normal cortisol production rates are between 5-10mg/m^2 body surface equivalent to an oral replacement dose of 15-25mg per day of HC and 20-30 mg cortisone acetate (CA). CA has a slightly delayed peak, but a longer half-life compared to HC. CA is converted to HC by 11β-hydroxysteroid dehydrogenase type 1. Both HC and CA are taken in 2 or 3 divided doses, with the first dose upon waking (even before awaking may work better) and the last dose approximately 4-6 hours before bedtime. Type 1 diabetes patients may need an evening dose to prevent nocturnal hypoglycaemia. Prednisolone can be used in selected cases with severe compliance problems, but dexamethasone has no place in replacement therapy for Addison's disease.

CYP3A4 is the key drug metabolising enzyme affecting HC clearance and concomitant administration of several drugs can affect HC levels. Liquorice and grapefruit juice potentiate the mineralocorticoid effect of HC and should be avoided in Addison's patients. Monitoring of glucocorticoid therapy relies on clinical assessment with a keen eye to symptoms and signs of over replacement (weight gain, insomnia, recurrent infection, peripheral oedema) and under-replacement (lethargy, nausea, poor appetite, weight loss, hyperpigmentation, joint pain). Detailed questioning about the patient's daily pattern can help fine-tune doses and times of intake. Some patients respond better to 4 or 5 small doses of 5 mg HC or CA, rather than the regular twice or trice daily regimen. Serum or salivary cortisol day curves can be useful to monitor treatment and sometimes as a pedagogic tool to convince the patient that a morning dose of 25 mg CA is too much.

Mineralocorticoid replacement

Mineralocorticoids are vital for maintaining water and electrolyte homeostasis. The synthetic mineralocorticoid, 9α fludrocortisone is used for replacement. Patients should be advised to eat sodium salt and salty foods *ad libitum*. A once daily dose of 50-200 μg is usually sufficient for most patients dependent on individual fluid and electrolyte intake and losses. The currently available fludrocortisone preparations include 0.1 and 0.05 mg tablets.

Mineralocorticoid replacement is evaluated clinically by asking about patient salt cravings and orthostatism. Measuring blood pressure in the supine and standing positions can help unmask under replacement if the blood pressure drops. Serum sodium, potassium, and plasma renin activity gives additional information. Sufficient fludrocortisone replacement is important to avoid adrenal crises.

Essential hypertension in Addison's disease should be treated by anti-hypertensives, not by stopping mineralocorticoid. Angiotensin converting enzyme inhibitors or calcium blockers can be used.

Adrenal androgen replacement using DHEA

Female Addison patients are androgen deficient, but androgens can easily be replaced by oral dehydroepiandrosterone (DHEA). Daily doses from 10 to 37.5 mg are sufficient to bring testosterone and androstenedione back into the normal range for women. There is only limited objective evidence of clinical benefits, mostly from small and short-time studies (8); long-term studies are lacking. Pragmatically, female patients with lack of libido and/or low energy

levels despite optimized glucocorticoid and mineralocorticoid replacement can be offered DHEA replacement to test its effects on these symptoms.

Treatment in special situation

Free cortisol levels rise during the third trimester, resulting in an increased requirement for HC (by 2.5 or 10 mg daily). Serum progesterone has anti-mineralocorticoid effects and hence the fludrocortisone dose may sometimes need to be increased during late pregnancy. During delivery, a bolus dose of 100 mg parenteral HC should be given, and repeated if necessary. The oral dose should be doubled for 24-48 hours *post partum*. Patients with Addison's disease also need to increase their steroid doses during surgery and medical procedures according to the degree of stress induced. Under regular, accustomed and time-limited physical activity do not generally need to make dose adjustments. However, if exercise is intense or prolonged an increase in HC and salt intake may be necessary based on what patients report.

Newer treatment modalities

Two slow-release preparations of hydrocortisone have been tested in the last few years, Chronocort and Duocort. Chronocort is still under development. It is taken at bedtime and has a "time-lock" device that delays release of HC. In this way Chronocort taken once or twice daily can roughly mimic the diurnal variation. Duocort, which is now marketed in Europe under the name Plenadren™, is a dual release table with a rapidly releasable coating and an extended release core that can be taken once daily in the morning at awakening (9). Studies comparing these new formulations to standard treatment are in want. Finally, early intervention with rituximab has been tried in a small pilot study (10) which hopefully will be followed by similar studies.

Management

The annual follow-up should focus on complaints possibly related to Addison's disease. Questions about episodes of adrenal crisis, medication, particular extra doses, compliance and timing are important. Questions with the aim of optimizing replacement therapy considering as positive responses good appetite, stable weight, full professional activity, and normal sexual activities.

Physical examination should include weight, blood pressure, and degree of pigmentation keeping in mind the possibilities of autoimmune co-morbidities such as autoimmune thyroid disease (most often with hypothyroidism), autoimmune gastritis with vitamin B12 and iron deficiency, celiac disease, and ovarian insufficiency.

Recommended routine laboratory analyses include serum sodium and potassium, especially if under-replacement is suspected. Plasma renin activity can be useful to evaluate fludrocortisone replacement. Surveillance for other autoimmune disorders is necessary but the ideal intervals are not known. A regular monitoring of thyroid function every 12 months is reasonable (TSH, FT4, and thyroperoxidase antibodies (TPO-Ab). Autoimmune thyroid disease is seen in about half of autoimmune Addison's patients and subclinical thyroid disease may contribute to fatigue, which is a common complaint in Addison patients. Moreover plasma glucose levels, HbA1c and haemogram to search for diabetes mellitus and anaemia, respectively should be taken. In patients with gastrointestinal complaints screening for celiac disease should be considered. Women of fertile age should be informed about the possibility of the development of ovarian insufficiency; antibodies against side-chain cleavage enzyme are an immunological marker for this complication.

MAIN CONCLUSIONS

- Diagnosis of adrenal insufficiency is relatively easy; the challenge is to consider it as a differential diagnosis as symptoms often are unspecific. Specific clinical hints are hyperpigmentation, orthostatism, and salt craving.
- Most cases in Europe and North America are caused by autoimmunity, often as part of an autoimmune polyendocrine syndrome. Other causes such as genetic

(adrenoleukodystrophy, DAX1-mutations), tumour infiltration, infections and thrombosis/haemorrhage is more frequent in the young and old.
- Replacement therapy includes HC or CA in 2 or 3 divided doses, and fludrocortisone; no restriction in salt intake. The role of DHEA-replacement is still under debate. A new slow-release formulation is marketed in Europe.
- Patients should be followed up at least annually with focus on steroid replacement and autoimmune co-morbidities
- Patient education to avoid adrenal crisis is crucial. The patient should be equipped with a steroid card and injectable hydrocortisone. Care should be organized so that patients have easy access to emergency care.

CASES WITH QUESTIONS

Case 1

A 27 year old woman presented with fatigue, dizziness, weight loss and a peculiar color of the skin. She sought help from 6 different physicians without getting an explanation for her complaints. In desperation, her friend brought her to her own general practitioner who happened to be the son of an endocrinologist.

Questions:

1. What was the diagnosis or diagnoses?

2. How would you treat and follow the patient?

Case 2

A 24 year old nurse had felt dizzy and lacked appetite. During the summer she acquired a deep brown tan that didn't fade as winter approached. During a virus infection she collapsed and was admitted to the hospital. Addison's disease was diagnosed. After starting replacement therapy she developed problems with recurred candida vaginitis. Her brother had type 1 diabetes and vitiligo. Otherwise her history was unremarkable.

Questions:

3. What was the cause of adrenal insufficiency?

4. She asked about the risk of familial Addison's disease, what would you tell her?

Case 3

A 39-year old plumber was diagnosed with Addison's disease at another hospital. He was started on CA and fludrocortisone. However, he had extreme fatigue and bradycardia. He required 75 mg CA per day, but despite this high dose showed no signs of Cushingoid side effects. The 2OH-Ab assay was negative.

Questions:

5. What was the cause of cause of adrenal insufficiency in this patient?

6. How could his replacement therapy be improved?

DISCUSSION OF CASES AND ANSWERS

Case 1

The 27 year old woman was immediately admitted to hospital. She had hypotension, hyponatraemia and normokalaemia. She was given i.v. saline and tests for cortisol, ACTH, TSH and total T4 were taken. When a low cortisol of 98 nmol/L was found, cortisone and fludrocortisone therapy was given. TSH was 82 mU/L and total T4 41 nmol/L. Was the TSH elevation due to lack of cortisol or an autoimmune thyroiditis? Since thyroid microsomal antibodies were strongly positive, L-thyroxine replacement was started. She rapidly improved, but required high doses of CA (50-75 mg per day). She was followed annually with emphasis on replacement therapy and signs and symptoms of over and under replacement, as well as screening for autoimmune co-morbidities. Twenty-four years later she presented with parietal cell and intrinsic factor antibodies. Gastroscopy revealed gastritis in the fundus region. Methylmalonic acid was elevated at 0.62 μmol/L with homocysteine 12.8 μmol/L and cobalamine 294 pmol/L. Vitamin B12 injections were started. One year later she called and complained about blurry vision and polyuria. Glucose was 21.6 mmol/L and HbA1c 8.5%. Autoantibodies were initially negative, but later she became IA2-Ab positive. She is now in insulin pump treatment, but has had problems with nocturnal hypoglycaemia and hypoglycaemia unawareness.

Answers:

1. Diagnosis: Autoimmune polyendocrine syndrome type 2
2. Regular replacement therapy with corticosteroids; consider late evening CA or even prednisolone to avoid nocturnal hypoglycaemia; annual screening for autoimmune co-morbidities?

Case 2

The 21-hydroxylase antibodies were checked and found positive, the diagnosis of autoimmune Addison's disease was made. Ten years later her diabetic brother developed leg cramps and paresthesias in fingers and toes at age 42. Low calcium, elevated phosphate, and low PTH was found with normal renal function consistent with a mild to moderate hypoparathyroidism. Family history prompted analyses of APS-1-specific autoantibodies. Both sister and brother had interferon omega antibodies and were NALP5-Ab positives. Disease causing mutations in the *autoimmune regulator* (*AIRE*) were found. The case makes the point that APS-1 patients can have a relatively mild phenotype with late debut. Interferon omega antibodies are positive in almost all patients with APS-1.

Answers:

3. Diagnosis: Autoimmune polyendocrine syndrome type 1
4. In APS-1 there is a 25% risk for siblings to develop the disease. About 10% of patients with Addison's disease (APS-1 excluded) have a family history of Addison's disease.

Case 3

He was initially thought to have idiopathic Addison's disease; maybe 21OH-Ab had been positive initially, but then become negative? However, the patient's fatigue was very pronounced. Cramps in his hands led to a MRI of cerebrum showing distinct pathologies in white substance. Adrenoleukodystrophy was considered, but very-long chain fatty acids in serum were normal. The combination of Addison's disease, extreme tiredness, bradycardia and early cataract led to suspicion of dystrophia myotonica; a gene test confirmed the diagnosis of dystrophia myotonica type 1, an autosomal dominant disease. One of his 4 children has inherited the disease. In order to improve symptoms he was treated with subcutaneous cortisol infusions. On this treatment his condition improved somewhat and he was able to start work part-time. Subcutaneous infusion of HC may prove valuable in patients with low quality of life and working inability.

Answers:

5. Diagnosis: Dystrophia myotonica type 1
6. In this case, subcutaneous cortisol infusion improved his general well-being and increased his working capacity.

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ACTH Independent Macronodular Adrenal Hyperplasia: Diagnosis and Management

M27
Sunday, June 16
1:00–1:45 PM & 3:00–3:45 PM

Andre Lacroix, MD
CHUM Université de Montréal
Montreal, Canada
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SIGNIFICANCE OF THE CLINICAL PROBLEM

ACTH-Independent Macronodular Adrenal Hyperplasia (AIMAH) represents less than 1% of endogenous overt Cushing's syndrome (CS). Considering the increase of incidentally found adrenal lesions (2-4% of population), of which ~ 10% are bilateral, AIMAH with sub-clinical cortisol secretion is increasingly recognized (1); its prevalence has not been estimated however in population studies.

BARRIERS TO OPTIMAL PRACTICE

- AIMAH needs to be distinguished from other causes of bilateral adrenal lesions such as metastatic disease, congenital adrenal hyperplasia, cortical adenomas, lymphoma, infection (e.g., tuberculosis, fungal), haemorrhage, ACTH-dependent Cushing's, pheochromocytomas, amyloidosis and other infiltrative diseases of the adrenal glands.
- Careful revision of adrenal imaging with a radiologist experienced in adrenal pathologies is essential to characterize the nature of the bilateral adrenal lesions.

LEARNING OBJECTIVES

- AIMAH needs to be distinguished from other causes of bilateral adrenal lesions such as metastatic disease, congenital adrenal hyperplasia, cortical adenomas, lymphoma, infection (e.g., tuberculosis, fungal), haemorrhage, ACTH-dependent Cushing's, pheochromocytomas, amyloidosis and other infiltrative diseases of the adrenal glands.
- Careful revision of adrenal imaging with a radiologist experienced in adrenal pathologies is essential to characterize the nature of the bilateral adrenal lesions.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Clinical and Laboratory Features of AIMAH

Most AIMAH patients with CS present in the fifth and sixth decades of life, a later age of onset compared to unilateral adenomas or PPNAD (1). AIMAH was found to be equally distributed between genders initially, but more recent series report a female preponderance similarly to adrenal tumors (1, 2).

AIMAH frequently presents with sub-clinical and less often with overt cortisol excess. In some patients there is co-secretion of aldosterone and cortisol, cortisol and estrogens, or androgens only (1-4). In patients with sub-clinical CS, there is an absence of classical clinical signs of CS associated with subnormal suppression of fasting plasma cortisol following the 1-mg overnight dexamethasone suppression test (>50 nmol/L or 1.8μg/dL), a partially suppressed ACTH and/or elevated midnight plasma cortisol, and normal 24-hr urinary free cortisol production (3,5). Depending on the extent of cortisol hypersecretion, plasma ACTH and its stimulation by CRH will become progressively suppressed in AIMAH (1-3,5). In patients with ectopic GIP receptors expression in AIMAH, cortisol secretion occurs after meals and plasma cortisol may be low fasting in the morning when ACTH and GIP levels are both low (6). Transient CS can occur during pregnancies and became sustained only after menopause in patients with AIMAH expressing aberrant adrenal receptors for LH/

hCG (7).The natural history of AIMAH causing sub-clinical CS is largely unknown; some reports indicate progression from sub-clinical CS to overt CS, but its prevalence is unknown (1).

The ACTH receptor (*MC2R*) remains expressed in AIMAH though at lower levels than normal adrenals; the majority of patients respond to exogenous ACTH 1-24 administration with relatively large increase of cortisol (1,2). This response can help to distinguish AIMAH from other causes of bilaterally enlarged adrenals such as metastatic or infiltrative diseases. The hormone secretion in AIMAH results from an increase in the number of adrenocortical cells rather than an augmented synthesis per cell; as there is a relatively inefficient hormonal synthesis in AIMAH with decreased expression of several steroidogenic enzymes compared to normal adrenal (1). As a result, steroid precursors such as plasma 17-OH-progesterone or urinary 17-OH-corticosteroids (U17OHCS) can be increased or proportionally more than urinary free cortisol (2,8). This inefficient steroidogenesis may explain the frequent sub-clinical cortisol secretion despite massive adrenal enlargement.

Imaging in AIMAH

The adrenal glands are enlarged bilaterally with presence of numerous nodules up to 5cm in diameter; however, diffuse adrenal enlargement without nodules has also been described (1). On CT, the nodules present hypodensity and can have marked contrast enhancement. On MRI, T1-weighted images are hypointense relative to the liver and isointense relative to muscle. T2-weighted images tend to be hyperintense relative to the liver (9). This helps to differentiate the nodules of patients with chronic ACTH stimulation that appear isointense relative to the liver on T2-weighted MR images. The glands can demonstrate a signal dropout at chemical shift imaging, suggesting the presence of intracellular lipid. Occasionally there is an asymmetric development of nodules in AIMAH, leading to the erroneous diagnosis of unilateral pathology, as the development of macroscopic contralateral disease can occur several years later (6). Iodine 131-6-β-iodomethyl-19-norcholesterol (NP-59) scintigraphy usually shows bilateral uptake (1). A recent report indicated possible increased FDG-PET signal in AIMAH despite absence of malignancy; the frequency of such increased FDG-signal uptake needs to be verified in larger studies (10).

Pathology

The mean combined weight of both adrenal glands in one series was 132 grams and could reach 200 grams per gland (1). On cut sections, the nodules are yellow due to their high lipid content. The nodules are composed of two cell types either with clear cytoplasm (lipid-rich) that form cordon nest-like structures, or with compact cytoplasm (lipid-poor) that form nest or island-like structures. In contrast with McCune Albright in which inter-nodular atrophy is present, in AIMAH a diffuse inter-nodular hyperplasia is found. AIMAH is a benign neoplasia that has not yet been shown to acquire a malignant potential in long term follow–up of patients.

Aberrant Hormone Adrenal Receptors in AIMAH

The regulation of cortisol hypersecretion in AIMAH while ACTH of pituitary origin becomes suppressed has been clarified in the last decades. Steroidogenesis in most patients with AIMAH with sub-clinical or clinical CS is regulated by various hormones via the aberrant adrenal expression of G-protein coupled hormone receptors (11,12). The aberrant stimulation of steroidogenesis can be driven by two kinds of receptors: ectopic receptors which are not expressed in zona fasciculata cells, such as the glucose-dependent insulinotropic peptide or gastric inhibitory polypeptide (GIPR), β-adrenergic receptors, vasopressin (V_2-V_3-vasopressin receptor), serotonin (5-HT_7 receptor) and probably angiotensin II receptor (AT1R), alpha1 adrenergic receptor and glucagon receptor. Other normally expressed eutopic receptors can present increased expression or altered activity with increased coupling to steroidogenesis such as: vasopressin (V_1-vasopressin receptor), luteinizing hormone/

human chorionic gonadotropin (LH/hCGR), serotonin (5-HT_4 receptor) and leptin receptor. The activity of one or several aberrant receptors in the same AIMAH tissues has been described (11,12). The molecular mechanism responsible for the aberrant adrenocortical specific expression of these receptors is not yet known, but genetic studies are currently underway. Their expression in bilateral hyperplasias suggests the occurrence of a germinal mutation in the familial cases while an initial event occurring during embryogenesis could be responsible for the sporadic cases. Somatic mutations would result in the unilateral adenomas expressing aberrant receptors (11).

Investigative protocols have been developed to study systematically patients with adrenal CS or sub-clinical CS to identify the regulation of steroid production by one or several aberrant receptor (1,2,11). The strategy consists of modulating the plasma levels of diverse hormones (endogenous or exogenous ligands) for the potential aberrant receptors, while monitoring plasma levels of cortisol, other steroid hormones and ACTH. All tests are performed following an overnight fast and in a supine position for at least 1h. For patients with sub-clinical CS, the studies are conducted under suppression with 1 mg dexamethasone every 6 hours, beginning 48-hours before the tests in order to avoid any effect of ACTH on steroidogenesis. The initial screening is performed in 3 days and involves during the first day a posture test to screen for receptors to angiotensin II, vasopressin, or catecholamines; a standard mixed meal to assess the presence of GIP or other gastrointestinal hormone receptors; and cosyntropin test (ACTH 1-24 250 µg IV). During the second day, the administration of GnRH 100 µg i.v. evaluates responses to LHRH, LH and FSH; TRH 200 µg i.v. screens for modulation by THR, TSH or prolactin. On the last day, the protocol is completed with the sequential administration of glucagon 1mg i.m.; vasopressin 10UI i.m. and 10 mg metoclopramide orally as a serotonin 5-HT_4 agonist. Serial measurements of ACTH, cortisol and other steroid hormones are performed at 30 to 60 min intervals during 2-3h following the intervention. The increment of 25-49% from the baseline of the steroid levels in the absence of an increase in ACTH level is defined as a partial response and an increase more than 50% is considered a positive response; the test should be repeated to confirm the response to the specific ligand and its reproducibility. Fluctuations of the putative ligand hormones of interest are also measured to better characterize the modulator of the response. When a positive response following this initial screening is confirmed, further stimulatory tests should be undertaken to precisely define the hormone and the specific receptor type implicated.

Other Pathogenesis

A constitutive ACTH receptor (MC2R) mutation is not a common cause of adrenal hyperplasia or tumor formation (1,11). In the McCune-Albright syndrome (MAS), activating mutations of the Gsα subunit occur in a mosaic pattern in early post-zygotic embryogenesis resulting in constitutive activation of the cAMP pathway, nodular hyperplasia and CS (11). Rarely in CS due to AIMAH without classical MAS, two different *gsp* mutations at codon Arg^{201} were found (12); these cases may represent variants of MAS or may be the result of late somatic mutations.

Other genetic causes have been identified in the pathogenesis of AIMAH indicating that it is a heterogeneous disease. Bilateral adrenal nodules can occur in multiple endocrine neoplasia syndrome type 1 (MEN1). In the vast majority of MEN1 patients with adrenal lesions, there was no evidence of abnormal hormone secretion, but excess secretion of aldosterone or cortisol can occur. AIMAH or adrenal nodules have been reported in patients with familial polyposis coli and a mutation in the adenomatous polyposis coli (*APC*) gene and with hereditary leiomyomatosis and renal cell cancer disorders due to mutations in the fumarate hydratase gene (*FH*) on chromosome 1q42 (8,11).

Most initial cases of AIMAH appeared to be sporadic; however, family screening was not performed systematically. There are now several reports of familial cases of AIMAH with autosomal dominant transmission.

In familial AIMAH, a number of aberrant hormone receptors have been identified in individual families, including V1-V2- and V3-vasopressin, beta-adrenergic, combined V1-vasopressin and beta-adrenergic, and combined 5-HT4 and V1-V-2 vasopressin. The germ line transmission of the same receptors in all affected family members support a primary role of aberrant receptors in the pathophysiology of this type of AIMAH. The prevalence of familial forms of AIMAH is not known yet (1,8.11).

First degree relatives (> 25-30 yo) of patients with AIMAH should undergo screening for sub-clinical or clinical AIMAH. We suggest performing the 1-mg overnight dexamethasone test, taking into consideration underlying aberrant receptor effect (i.e., in upright posture if vasopressin receptor present or post prandially if GIP receptor present); those who do not suppress their plasma cortisol on the following morning below 1.8 μg/dl (50 nmol/L) should have an adrenal CT scan. Family members who are found to have hypercortisolism should also undergo evaluation for aberrant hormone receptors. Patients with AIMAH associated with genetic causes such as MEN 1 or polyposis coli have their familial screening for other associated pathologies.

Local ACTH Production and Other Paracrine Mechanisms

Increased adrenocortical expression of proopiomelanocortin/ACTH, serotonin or vasopressin has been described in some patients with AIMAH, suggesting that paracrine regulatory mechanisms may play a role in some cases (14,15). A recent study indicates that local ACTH production is very frequent in AIMAH and can increase in response to stimulation by the aberrant hormone receptors. Elevation of ACTH in adrenal vein samples of patients with AIMAH was found, but peripheral levels of ACTH remain relatively low compared to the degree of hypercortisolism. Relatively high intratumoral levels of ACTH irregularly distributed in some AIMAH cells that also express MC2R were found in such tissues. Administration of ACTH receptor antagonists could decrease cortisol production partially (15). This finding indicates that the terminology of ACTH-independent macronodular adrenal hyperplasia is inappropriate for this disease.

Therapy

Surgery

Bilateral adrenalectomy is uniformly effective in patients with AIMAH since this disorder is a primary adrenal disease. Surgical adrenalectomy is indicated in all patients with AIMAH and overt Cushing's syndrome who have no evidence of aberrant hormone receptors, or who have aberrant receptors that are not be amenable to medical therapy (1).

- In patients with moderately increased cortisol production (less than two-fold increase in urinary free cortisol levels), unilateral adrenalectomy often restores urinary free cortisol levels to normal. However, as the cell mass subsequently increases in the contralateral adrenal, a second adrenalectomy may become necessary (16,17).
- In patients with sub-clinical AIMAH and normal levels of urinary cortisol, the decision for therapy should be based on manifestations of cortisol excess such as hypertension, diabetes, osteoporosis, apparent brain atrophy or neuropsychological manifestations.
- In patients who are being monitored without adrenal surgery, annual CT scan and biochemical assessment are sufficient, as AIMAH is a benign process that has not been shown to become malignant (1).

Pharmacological Therapy

Pharmacological therapy is used in two settings in AIMAH. Adrenal enzyme inhibitors are sometimes given to patients with overt Cushing's syndrome to control cortisol secretion before surgery. In patients in whom aberrant hormone receptors have been identified, several potential therapies have been investigated as alternatives to adrenalectomy, including:

- Pharmacological blockade of post-prandial release of GIP with octreotide or pasireotide led to clinical and biochemical

improvement of Cushing's syndrome, but did not persist in the long-term, probably because of eventual desensitization of somatostatin receptors in GIP-secreting duodenal K cells (1,11,18).
- In catecholamine-dependent Cushing's syndrome and AIMAH, beta-adrenergic receptor antagonists were efficient in the long-term control of hypercortisolism (1,11,19).
- In LH/hCG-dependent AIMAH and Cushing's syndrome, suppression of endogenous LH levels with long-acting leuprolide acetate controlled steroid secretion and avoided bilateral adrenalectomy (1,7,11).
- When specific receptor antagonists for vasopressin, serotonin, GIP, or other aberrant receptors become available, a broader range of pharmacological therapies could become useful.

However, it is possible that despite complete blockade of the aberrant receptors, tumor regression does not occur, as other genetic events inducing proliferative gain-of-function mutations (other than aberrant receptors) have accumulated over time (11).

MAIN CONCLUSIONS

In recent years, several new findings have contributed to a better understanding of the heterogeneity of pathogenesis in AIMAH. Aberrantly expressed G-protein-coupled receptors in the adrenal cortex appear to play a central role in the hormonal hypersecretion and cell proliferation in a high proportion of patients with this disease. However, other molecular mechanisms, such as *gsp* or ACTH receptor mutations, and adrenal paracrine hormonal secretion can also be implicated in patients with AIMAH. Together, these studies have contributed to a more precise evaluation of patients with AIMAH, improving earlier diagnosis and offering new therapeutic and potentially preventive strategies.

CASES WITH QUESTIONS

Pertinent clinical cases will be presented to illustrate the presentation

DISCUSSION OF CASES AND ANSWERS

Included in the presentation

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When to Consider and How to Perform Case Detection Testing for Endocrine Hypertension

M21
Sunday, June 16
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

In approximately 5-10% of all patients presenting with hypertension there is an underlying cause such as endocrine, renal, vascular or neurological disease. Endocrine hypertension has emerged as an increasingly relevant form of secondary hypertension. Previously, endocrine hypertension was thought to be extremely rare and to account for only 0.5-1.0% of all causes of hypertension. Nowadays, with the advent of more reliable and sensitive diagnostic methodology, endocrine hypertension has been diagnosed much more frequently and has been estimated to be the most frequent cause of secondary hypertension with a prevalence of about 5-10% of all patients with hypertension. Apart from this quantitative aspect, a timely and correct diagnosis of endocrine hypertension is quite important for three reasons:

1. For some causes of endocrine hypertension, effective causal treatment is available and can cure the hypertension.
2. Beyond increased blood pressure, some causes of endocrine hypertension have severe deleterious cardiovascular and metabolic effects that are not associated to the hypertension but to increased hormonal activity.
3. Some kinds of endocrine hypertension may have devastating complications if not timely and properly diagnosed and treated.

Globally, the pathophysiological mechanisms of endocrine hypertension include:

- hormonal excess secretion by an adrenal tumor or hyperplasia
- deficiencies of key adrenal enzymes in hormonal synthesis
- mutations altering receptor or ion channel function

The following pathophysiologically based classification can be used as practical guidance *(Table 1)*:

For the diagnosis of endocrine hypertension, taking a thorough medical history and performing a careful physical examination remain indispensable.

Although many assays are available for biochemical testing, for proper appraisal of the diagnostic potential of these tests one should be aware that some of these tests are appropriate for screening purposes

TABLE 1.
Classification of endocrine hypertension

1. Mineralocorticoid hypertension
1a. Primary hyperaldosteronism
1. adrenocortical adenoma
2. adrenocortical hyperplasia
3. familial aldosteronism type I, II and III
1b. Pseudohyperaldosteronism
b. 11-β-hydroxysteroid dehydrogenase deficiency (licorice abuse, AME syndrome)
c. desoxycorticosterone excess (tumor, congenital adrenal hyperplasia)
d. cortisol excess (Cushing syndrome)
e. primary cortisol resistance
f. Liddle's syndrome
g. mineralocorticoid receptor mutation
h. pseudohypoaldosteronism II (Gordon syndrome)
2. Pheochromocytoma /paraganglioma
3. Thyroid dysfunction
4. Hyperparathyroidism
5. Acromegaly
6. Iatrogenic hormonal excess
AME: apparent mineralocorticoid excess

while others are suitable for confirming the diagnosis. In addition, as in many endocrinological disorders, dynamic testing is sometimes necessary to document autonomous hormone secretion. In daily clinical practice, many patients are on treatment with all types of medication and these may interfere with biochemical tests, either in an analytical, pharmacokinetical or pharmacodynamical way. This may result in false-positive and false-negative test results. Careful interpretation of test results may not only prevent missing a diagnosis but may also avoid unnecessary additional testing or redundant surgical procedures. Finally, imaging studies to locate an endocrine tumor should preferentially be carried out after obtaining proper biochemical evidence of excess hormone production.

BARRIERS TO OPTIMAL PRACTICE

- Most causes of endocrine hypertension are relatively rare (insufficient exposure of physicians)
- The pathophysiology of some types of endocrine hypertension is not well known by physicians
- Signs and symptoms of many forms of endocrine hypertension are quite non-specific
- There is lack of consensus on how endocrine hypertension should be analyzed
- Insufficient knowledge about the diagnostic performance of biochemical assays
- Cost-effectiveness of the different diagnostic strategies are insufficiently known
- Lack of concentration of these patients in expert centers for diagnosis and treatment

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to recognize the:

- Most relevant forms of endocrine hypertension and clinical clues that call for endocrine testing
- Optimal pre-test conditions, tests and sequence of biochemical and (functional) imaging
- Correct interpretation of diagnostic test results
- Available genetic tests and the indications for genetic testing

SUCCINCT REVIEW- STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

1. Mineralocorticoid hypertension

Mineralocorticoid hypertension is due to excess mineralocorticoid action, either by inappropriately high levels of aldosterone or by other compounds with mineralocorticoid action (e.g. desoxycorticosterone). The resultant retention of sodium and water will subsequently induce hypertension by increasing both circulating volume and peripheral vascular resistance. Associated biochemical features are a decreased or low-normal plasma potassium and metabolic alkalosis.

For the differential diagnosis of mineralocorticoid hypertension concurrent measurement of basal plasma aldosterone and plasma renin levels is the first step to distinguish primary hyperaldosteronism (PA) from pseudohyperaldosteronism *(Table 2)*. In PA, the primary abnormality is an increased aldosterone secretion with an ensuing suppression of renin secretion. In pseudohyperaldosteronism, another mineralocorticoid than aldosterone suppresses both aldosterone and renin secretion. In secondary hyperaldosteronism, the primary abnormality is increased renin secretion which is responsible for stimulation of aldosterone secretion. It becomes mainly manifest in clinical conditions with decreased renal perfusion like renal artery stenosis, heart failure and malignant hypertension. Secondary

TABLE 2. Plasma aldosterone and renin levels in mineralocorticoid hypertension

	Plasma aldosterone	Plasma renin
Primary hyperaldosteronism (PA)	High/increased	Low/suppressed
Pseudohyperaldosteronism	Low/suppressed	Low/suppressed
Secondary hyperaldosteronism	High/increased	High/increased

hyperaldosteronsim will not be discussed here further.

1a. Primary hyperaldosteronism (PA)
Thirty to 40% of all patients with PA harbour the classically described aldosterone-producing adenoma (Conn's syndrome). In 60-70% of the patients there is bilateral adrenal hyperplasia. Much more rare are adrenal cortical cell carcinoma and hereditary 'glucocorticoid-remediable' aldosteronism (GRA) as causes of PA.

Which patients need to be screened for PA?
Although it has been suggested previously that all new hypertensive patients should be screened for PA, there is no good evidence that this is cost-effective. It is more cost-effective to focus on those hypertensive patients who have an increased likelihood to have PA. As recommended by The Endocrine Society Clinical Practice Guideline the following patients should be screened *(Table 3)*:

How should patients be screened for PA?
Plasma potassium is an insensitive marker for first line screening for PA. In addition, several factors such as a salt-restricted diet, ACE inhibitors and A-II receptor blockers may mask a slight hypokalemia.

Screening for PA should include simultaneous measurement of plasma aldosterone and plasma renin activity or plasma renin concentration. The calculated plasma aldosterone/renin ratio (ARR) has been advocated to be used for screening purposes. Also the combined use of ARR and the absolute plasma aldosterone level has been proposed. The sensitivity and specificity of this test vary, depending on the used cut-off levels in the different studies. It is essential to take into account the type of laboratory assay and the used measurement units. The Endocrine Society Clinical Practice Guideline provides the cut-off values depending on assay and used measurement units and a cut-off of 20-40 $ng.dL^{-1}$ per $ng/mL^{-1}.h^{-1}$is most frequently used.

Since antihypertensive medication and plasma potassium may affect plasma levels of aldosterone and renin, these factors should be corrected or otherwise taken into account for proper interpretation of test results.

Blood for measurement of aldosterone and renin should be sampled mid-morning after being up for at least 2 hours and the sample should be drawn after the patient has been sitting for at least 5 minutes. No specific dietary instructions are necessary although patients should be instructed not to restrict salt intake. An eventual hypokalemia can mask an increased plasma aldosterone level and should therefore be corrected to at least 3.5 mmol/L before blood sampling.

Most antihypertensive drugs interfere with the renin-angiotensine-aldosterone system. In any case, mineralocorticoid receptor antagonists and diuretics should be stopped for at least 4-6 weeks before blood sampling. Betablockers, central sympatholytics, AII receptor blockers, and renin and ACE-inhibitors should be interrupted for at least 2 weeks. However, in daily clinical practice it is not always feasible to stop antihypertensive treatment. In that case there are several alternative drugs that can be used to control blood pressure: verapamil, a-adrenoreceptor blockers and hydralazine. Long-acting dihydropyridines are also devoid of significant effects on aldosterone and renin and can be used.

Other drugs like oral contraceptives may cause falsely elevated ARR when renin is measured as renin concentration. Also high

TABLE 3. Patients to be screened for primary hyperaldosteronism

• patients with moderate (stage 2) or severe hypertension (stage 3)
• hypertensive patients with spontaneous, even slight, hypokalemia
• hypertensive patients with an excessive hypokalemia on diuretic treatment
• hypertensive patients who resistant to antihypertensive treatment
• hypertensive patients with an adrenal mass (incidentaloma)
• hypertensive patients with a family history of early-onset hypertension
• hypertensive patients with a cerebrovascular accident < 40 years
• hypertensive patients who are first degree relatives of a patient with primary hyperaldosteronism

age and impaired renal function can cause a false-positive ARR due to the low plasma renin levels in these situations.

How should the diagnosis of PA be confirmed?
The diagnosis of autonomous hypersecretion of aldosterone needs to be confirmed since an increased ARR does not definitely prove the patient has primary hyperaldosteronism. According to The Endocrine Society Clinical Practice Guidelines there are several tests available to confirm the presence of PA:

1. Intravenous salt loading test (2 L NaCl 0.9% infusion for 4 hours in the recumbent position).
   Interpretation:
   plasma aldosterone levels after infusion: < 0.14 nmol/L (<5 ng/dl): no PA
   plasma aldosterone levels after infusion: > 0.14- <0.28 nmol/L (>5-<10 ng/dl): indeterminate
   plasma aldosterone levels after infusion: > 0.28 nmol/L (>10 ng/dl): PA present
2. Oral salt loading test (10 gr NaCL/day for 3 days so that Na+excretion is > 200 mEq/day).
   Interpretation:
   urinary aldosterone excretion (3e day): < 10 ug/day (<29 nmol/L): no PA
   >10 - <14 ug/day: indeterminate
   >14 ug/day (>40 nmol/d): PA likely
3. Fludrocortisone suppression test: 0.1 mg every 6 hours for 4 days with 6 gr/d NaCl extra.
   Interpretation:
   upright plasma aldosterone (4e day) at 10 am: > 0.17 nmol/L (>6 ng/dl): PA likely
4. Captopril challenge test: 25-50 mg captopril orally after sitting for 1 hour.
   Interpretation:
   plasma aldosterone 1-2 hours after captopril: > 0.33 nmol/L (>12 ng/dl) or ARR >12 (ng/dl)/(ng/ml/h): PA likely.

During all tests, potassium levels should be monitored and corrected to the normal range. Although there are differences in diagnostic accuracy of these tests, there is no unequivocal evidence to prefer one test over the other. The risk of these tests is minimal but sodium loading and fludrocortisone suppression test are contraindicated in patients with uncontrolled severe hypertension or compromised heart function.

How to locate the source of excess aldosterone secretion and to subtype PA?
The next crucial step is to locate the main source of excess aldosterone secretion since this determines the mode of treatment. A patient with unilateral aldosterone secretion by an adenoma or unilateral hyperplasia is an appropriate candidate for surgery (adrenalectomy) while someone with bilateral aldosterone secretion (bilateral hyperplasia) requires medical treatment (mineralocorticoid receptor antagonist).

CT scanning with slices of 2.5-3 mm of the adrenal glands can visualize small adenomas but cannot prove that an adenoma or an enlarged adrenal gland is the source of aldosterone secretion. CT scan can miss very small adenomas. MRI has no proven advantages over CT scanning. As shown previously, compared to AVS, CT scanning might result in incorrect therapeutic decisions (unjustified surgery or unjustified withholding surgery) in one of every three patients with PA. Yet, a CT scan should be the first step for subtyping because it can, based on the imaging characteristics, suggest that an adrenal mass is an adrenocortical carcinoma. A second reason is that the right adrenal vein can be localized very reliably by CT and this is very useful when proceeding to AVS.

One of the main recommendations of The Endocrine Society Clinical Practice Guideline is to perform AVS for subtyping PA for those patients who wish surgery when indicated.

A recent study showed considerable variability in used protocols and interpretation of AVS. Unfortunately there is no consensus on several methodological issues such as whether to use ACTH stimulation during AVS and whether the adrenal veins should be sampled simultaneously or sequentially. ACTH stimulation is supposed to minimize stress-induced variation in aldosterone secretion. Some experts suggest that ACTH stimulation also improves selectivity (indicating successful cannulation of the adrenal veins). A potential disadvantage of ACTH is an effect on

aldosterone secretion, thus increasing the risk of misclassification. Some studies have demonstrated impairment in diagnostic accuracy using ACTH stimulation while others did not. Despite the lack of definite consensus, one can say that when simultaneous sampling is performed one can refrain from ACTH stimulation but since the simultaneous technique is difficult and not available in all centers, the sequential technique with ACTH stimulation (bolus and continuous infusion) is a reasonable alternative.

Successful cannulation of the adrenal veins can be determined by calculating the adrenal vein cortisol / peripheral cortisol ratio. This is the so-called selectivity index (SI) and most centers use a cut-off for the SI of ≥2.

The operational measure for assessment of lateralization of aldosterone hypersecretion is the lateralization index (LI). This index, calculated from the aldosterone (A) and cortisol levels (C) in both adrenal veins, is defined as the ratio of the higher (dominant) over the lower (non-dominant) A/C ratio. Cortisol levels from adrenal venous blood are used for correction of the adrenal vein aldosterone levels because of potential dilution of the samples by non-adrenal blood. The criteria that are used for reliable interpretation of AVS vary widely, also depending on whether ACTH is used or not. A LI of ≥4 with ACTH stimulation and a LI of ≥2 without ACTH are most frequently used to document lateralization of aldosterone excess.

Apart from the LI, some studies have used contralateral aldosterone suppression (A/C ratio of the non-dominant adrenal vein < than the peripheral A/C ratio) as an additional criterium to define lateralization but this has not sufficiently been validated.

What are the indications for genetic testing?
Nowadays three different forms of familial PA are recognized. Familial PA type I (FH-I) is also known as 'glucocorticoid-remediable' aldosteronism (GRA) and hypertension becomes manifest at young age. This is due to a chimeric gene that results from unequal crossover between the genes *CYP11B1* and *CYP11B2*. The consequence is that aldosterone secretion becomes ACTH dependent. Although the diagnosis can be made by administration of dexamethasone, a definite diagnosis is made by mutation testing (long PCR). PA at young age, a family history of PA or a stroke at young age are indications for genetic testing.

For familial PA type II (FH-II) the molecular basis is still unknown but there is evidence for linkage to a region on chromosome 7 (7p21-22). Though no routine genetic testing is available, the diagnosis can be made when at least two first degree relatives have also PA. Recently familial PA type III (FH-III) has been described as a new form of hereditary PA in patients with severe PA. The gene mutated in FH-III is a gene that encodes for a potassium channel (*KCNJ5*) and is located on chromosome 11. Patients with severe PA in whom FH-I has been excluded are candidates for genetic testing. (*KCNJ5* sequencing).

1b. Pseudohyperaldosteronism
When both plasma aldosterone and renin secretion are suppressed the diagnosis of pseudo-hyperaldosteronism can be made and the following differential diagnosis should be considered.

Deficiency of the enzyme 11-beta-hydroxysteroiddehydrogenase type 2 (11-beta-HSD2) can be either hereditary or acquired and causes inhibition of the intrarenal conversion of cortisol into the biologically inactive cortisone. The high local concentration of cortisol in the kidney activates the renal mineralocorticoid receptor, thus causing water and salt retention and hypokalemia.

The "Apparent Mineralocorticoid Excess" syndrome (AME) is an autosomal recessive disorder and is characterised by 'loss of function' mutations of the gene that encodes for the enzyme 11-beta-HSD2. This syndrome features severe hypertension and intrauterine growth retardation and carries a high mortality at a very young age. A specific cause of acquired 11-beta-HSD2 deficiency is licorice abuse. The active compound of licorice is glycyrrhizinic acid which inhibits the enzyme 11-beta-HSD2. Stopping licorice abuse will completely restore blood pressure,

potassium and renin secretion. The diagnosis of 11-beta-HSD2 deficiency can be made by measuring the (tetrahydrocortisol+allo-tetrahydrocortisol)/tetrahydrocortisone ratio ((THF+alloTHF)/THC ratio) in urine while the AME syndrome can be confirmed by genetic testing.

Excess of desoxycorticosterone (DOC) can be caused by an adrenal tumor but this is very rare. The diagnosis is strongly suggested by an increased plasma DOC level in the presence of an adrenal tumor. In addition, excess DOC production can be caused by two rare forms of congenital adrenal hyperplasia: 11-beta-hydroxylase deficiency and 17-alpha-hydroxylase deficiency. Patients with these syndromes show also abnormalities in sexual development (genital ambiguity, delayed puberty, virilisation). In patients with 11-beta-hydroxylase deficiency the diagnosis can be confirmed by increased levels of DOC, 11-desoxycortisol and androgens. In patients with 17-alpha-hydroxylase deficiency the diagnosis can be confirmed by decreased levels of 17-alpha-hydroxyprogesteron and increased levels of DOC, corticosterone and 18-hydroxycorticosterone. Both diagnoses can be confirmed by genetic testing of *CYP11B1* and *CYP17*.

In primary cortisol resistance, inactivating mutations in the gene that encodes for the glucocorticoid-receptor cause a decreased number of these receptors or a decreased affinity of this receptor for cortisol. Due to the ensuing high ACTH levels, all ACTH-dependent steroids (cortisol, DOC) are increased and cause hypertension, water and salt retention and hypokalemia. In addition there might be signs of hyperandrogenism.

Cushing's syndrome. About 80% of patients with Cushing's syndrome have hypertension. There are several explanations for this, depending on whether or not there is ACTH-dependency. All hypertensive patients that have, even slight, clinical features suggesting Cushing's syndrome should be properly screened. As screening for Cushing's syndrome one of the following tests can be used:

1. 1 mg overnight dexamethasone suppression test
2. 24-hour urinary excretion of free cortisol (duplicate).
3. late night salivary cortisol measurement (duplicate)
4. 2 mg/d dexamethasone suppression test for 48-hours.

For further diagnostic work-up for Cushing's syndrome refer to The Endocrine Society Clinical Practice Guideline for the diagnosis of Cushing's syndrome.

Liddle's syndrome is an autosomal dominant disorder in which there are 'gain of function' mutations in the gene that encodes for the β or γ subunit of the epithelial sodium channel in the distal renal tubule. This results in an increased number of these sodium channels on the cell membrane with consequent increased sodium reabsorption and hypertension. Gene mutation testing establishes the diagnosis.

A mutation of the gene that encodes for the mineralocorticoid receptor induces an altered receptor specificity. Although the mineralocorticoid receptor retains its normal activation by aldosterone, it now can also be activated by hormones that normally lack this ability such as progesterone. The prevalence of this mutation is not exactly known. Young pregnant women with hypertension are candidates for genetic testing.

Pseudohypoaldosteronism type II (Gordon syndrome) is caused by gain of function mutations in WNK1 and WNK4. This results in an increased activity of the thiazide–sensitive sodium-chloride transporter in the distal collecting duct cells. The subsequent enhanced sodium and chloride retention may cause severe hypertension. Patients have hyperkalemia with suppressed renin and plasma aldosterone is about normal . The frank hyperkalemia, also due to inhibition of activity of the ROMK potassium channel by the mutated WNK, should arouse suspicion of this diagnosis. Genetic testing is necessary for a definite diagnosis.

2. Pheochromocytoma/paraganglioma

Pheochromocytoma/paraganglioma (PPGL) is a neuroendocrine chromaffin cell derived tumor and is responsible for hypertension in approximately 0.2-0.6.% of all hypertensives. Because it is potentially associated with catastrophic cardiovascular complications, it is

obvious that physicians test many hypertensive patients because they do not want to miss this diagnosis. However, not surprisingly, a definite diagnosis is made in only 0.3% of all patients tested for this tumor.

Pheochromocytomas are located in the adrenal gland in 80-85% of all cases, while the remainder of the catecholamine-producing tumors are located in extra-adrenal chromaffin tissue of the sympathetic chain (called paragangliomas). Paragangliomas in head and neck region are derived from parasympathetic tissue and usually do not produce catecholamines. Of all patients that present with an incidentally discovered adrenal mass, ±5% appears to have a pheochromocytoma. Malignancy develops in about 15% of all PPGL patients but this depends on the genetic background. Patients with specific genetic mutations such as those of the gene that encodes the enzyme succinate dehydrogenase subunit B, may develop metastatic disease in even 40% of the patients.

Essential to the diagnosis of PPGL is early recognition, based on knowledge of the variety of signs and symptoms. Most of the frequently occurring symptoms like headache, sweating, palpitations, and nausea are however non-specific. Pivotal for early diagnosis is however the recognition that these symptoms may have an episodic character; even hypertension is paroxysmal in about 35% of the cases. Paroxysms can be elicited by all kinds of physical or chemical stimuli like anesthetics, food, micturation, and some drugs. In addition, it should be recognized that many conditions that are associated with increased sympathetic nervous system activity may mimic a PPGL (e.g., panic disorder, migraine etc.). So establishing or ruling out the diagnosis of PPGL is sometimes fraught with difficulties.

Which patients should be tested for PPGL?

It is not indicated to screen all new hypertensive patients for PPGL since this is not cost-effective. Only those patients in whom there is, even slight, suspicion for a PPGL should be tested. The following clinical clues demand testing for PPGL *(Table 4)*:

TABLE 4. Clinical clues when to test for PPGL

• paroxysmal signs or symptoms of pheochromocytoma
• paradoxal blood pressure response to drugs or anesthesia
• an adrenal incidentaloma in a hypertensive patient
• hereditary predisposition of pheochromocytoma or paraganglioma
• any syndromic feature pointing to a hereditary syndrome

How to exclude or confirm a diagnosis of PPGL?

For proper interpretation of test results, preanalytical sampling conditions are important. Preferentially, measurements should be carried out in a fasting state to exclude any potential interference from dietary factors. In addition, the patient should be off any drug treatment that might interfere with the test results. One of the most relevant drugs here are tricyclic antidepressant drugs since they cause false-positive test results. However in daily clinical practice it is not always feasible to interrupt interfering drugs for sufficient time but one should at least be aware of potential interference when interpreting test results.

Ideally, blood samples for measurement of plasma metanephrines should be taken after supine rest for at least 20 minutes using an indwelling intravenous cannula. Although this is laborious it minimizes the risk of false-positive test results. A more practical alternative is to draw blood in the sitting position without prior rest. In case of increased results, the test should be redone but then after supine rest.

Measurements of free metanephrines in plasma (normetanephrine, metanephrine and 3-methoxytyramine) or fractionated metanephrines in 24-hour urine have a sensitivity that approaches 95-100% (*Table 5*). This high sensitivity is explained by the continuous intratumoral production of metanephrines. Upper reference limits for plasma normetanephrine range from 0.47 nmol/L in children to 1.05 nmol in patients older than 60 years. For plasma metanephrine there is a weak relationship with age and the upper reference limit is 0.35 nmol/L. Plasma

TABLE 5. Sensitivity and specificity of biochemical tests for diagnosis of pheochromocytoma

	Sensitivity (%)	Specificity (%)
Plasma free metanephrines	99	90
Plasma catecholamines	85	82
Urinary catecholamines	85-90	80-90
Urinary fractionated metanephrines	96-98	90
These data are based on several large scale studies in which the cut-off levels were different. In addition, it should be noted that the sensitivity values of all tests for familial pheochromocytoma are lower than that for sporadic pheochromocytomas. The reverse is the case for the specificity values.		

chromogranin A is not sufficiently sensitive to serve as an initial screening test.

An alternative method for blood testing is measuring metanephrines in a 24-hour urine collection. The diagnostic accuracy of urinary fractionated metanephrines is in fact as good as that of plasma free metanephrines but has the disadvantage that it is inconvenient for the patient and carries the risk of incomplete urine collections. There is no place anymore for measurement of urinary VMA excretion.

When plasma metanephrines are elevated more than fourfold the upper reference limit, proceeding to imaging is the next diagnostic step. In case of slightly increased plasma metanephrines (< 4x the upper reference limit), a clonidine-suppression test can be particularly helpful. A plasma normetanephrine of less than 0.61 nmol/L and a decrease in normetanephrine of more than 40% of the baseline value three hours after oral administration of 300 ug clonidine excludes a PPGL. When basal plasma normetanephrine is within the normal range, clonidine testing is not useful. The glucagon-stimulation test is obsolete since its diagnostic accuracy is poor. In addition, it is not without risk.

High-performance liquid chromatography (HPLC) with electrochemical or fluorometric detection or LC-MS/MS are currently the methods of choice for measuring plasma and urinary metanephrines.

How to locate a PPGL?

A contrast-enhanced computed tomography (CT) of the entire abdomen (including pelvis) provides the best initial method for localizing an pheochromocytoma because of its high spatial resolution. Magnetic resonance imaging is preferred over CT scan in patients with an allergy to contrast and in those patients in whom radiation exposure should be limited (pregnant women, patients with known germ line mutations). Ultrasound, despite being patient-friendly and cheap, has no place in the diagnostic work-up since it has an insufficient sensitivity.

The role of functional imaging is complex and not yet definitely clarified. In some patients functional imaging is not necessary: for instance, in a patient with a unilateral pheochromocytoma with predominant secretion of epinephrine or metanephrine and without a hereditary predisposition for PPGL, one can refrain from functional imaging. However in most PPGL patients, functional imaging is useful to document or exclude multifocality or metastatic disease.

If an abnormal mass is detected on CT scan in a patient with biochemically proven catecholamine excess, the widely available ^{123}I-MIBG (metaiodobenzylguanidine) scanning can establish whether that mass is chromaffin tissue or not. However, ^{123}I-MIBG uptake in tumor tissue can be blocked by several frequently used drugs (labetalol, antidepressants, calciumantagonists). These kinds of drugs may therefore be responsible for false-negative test results. Due to relatively poor sensitivity ^{123}I-MIBG scintigraphy has limited use in patients with metastatic PPGLs and in those with SDHx-related PPGLs. However, in patients with metastatic PPGLs in whom surgery is not an option, ^{123}I-MIBG scintigraphy can be useful since if positive, treatment with ^{131}I-MIBG may be considered.

Recent studies have suggested that several other PET scan-based diagnostic techniques like ^{18}F-fluorodeoxyglucose (18F-FDG), ^{18}F-fluorodihydroxyphenylalanine (^{18}F-FDOPA), and ^{18}F-fluorodopamine (^{18}F-FDA), perform better in some specific patient groups. For SDHx related paragangliomas, ^{18}F-FDOPA or somatostatin receptor imaging with ^{111}In-DTPA-pentetreotide is first choice while for patients with metastatic PPGL, ^{18}F-FDG-PET is the most important imaging modality.

Which patients should undergo genetic testing and which tests should be ordered?

In 30% of all PPGL patients a genetic mutation can be demonstrated. Nowadays, at least 10 different susceptibility genes have been described with *RET* (MEN-2 syndrome), *VHL* (Von Hippel Lindau disease), and *SDHD* and *SDHB* (familial paraganglioma syndromes) as the most important ones. In contrast, in apparently sporadic unilateral pheochromocytoma with a negative family history, no syndromic features and no metastases, the mutation rate is much lower.

There are two major reasons to consider genetic testing in a patient with a PPGL.

1. Some specific mutations such as those with mutations of the SDHB gene are associated with a high rate of metastatic disease, amounting to 40% or more of affected patients.
2. A genetic mutation in a proband will result in earlier diagnosis and treatment in his/her relatives for PPGL and other syndromic manifestations such as renal cell carcinoma in VHL disease.

Indications for genetic testing in a patient with PPGL include one or more of the following:

- Young patients (<50 yrs) with PPGL.
- Positive family history (based on family pedigree or identification of a PPGL susceptibility gene mutation in a relative).
- The presence of syndromic features of VHL or MEN-2.
- Multifocal or bilateral PPGL.
- Metastatic PPGL.

Genetic testing should be performed in accredited laboratories and genetic counseling should be available.

There are many algorithms to determine the sequence of genes to be tested.

- In patients with metastatic PPGL the first gene to be tested is *SDHB*
- In patients with head/neck paraganglioma the first genes to be tested are *SDHD*, *SDHB* and *SDHC*
- In extra-adrenal paraganglioma the genes to be considered first are: *SDHD*, *SDHB*, *SDHC*, *VHL*, *MAX*.
- In pheochromocytoma the genes to be considered first depend on the biochemical phenotype:
  1. Dopaminergic phenotype: *SDHD*, *SDHB*, *SDHC*
  2. Noradrenergic phenotype: *VHL*, if negative: *SDHD*, *SDHB*, *SDHC*, *MAX*
  3. Adrenergic phenotype: *RET*, if negative: *MAX*, *TMEM127*

3. Thyroid dysfunction related hypertension

Both hypofunction and hyperfunction of the thyroid are related to hypertension. The prevalence rates of hypertension in patients with hypothyroidism may be as high as 40%. Conversely, 3-4% of patients with hypertension have hypothyroidism.

In patients with hypofunction of the thyroid, diastolic blood pressure in particular is increased which is associated with an increased vascular resistance. In hyperthyroidism, nearly 25% of the patients have systolic hypertension associated with an increased cardiac output. Subclinical hyperthyroidism seems not to be associated with an increased blood pressure.

Although the prevalence of hyperthyroidism in new patients that present with hypertension is unknown, the threshold for testing thyroid function should be low since treatment of hyperthyroidism usually restores blood pressure completely.

4. Hyperparathyroidism

Hypertension is a common finding in primary hyperparathyroidism (10-70%) and it is likely that this is merely due to the effects of PTH than to that of calcium. This is based on the observation that patients with pseudohypoparathyroidism (having

low calcium and high PTH levels) have also hypertension as frequently as patients with primary hyperparathyroidism. Nevertheless, blood pressure level is not related to the serum calcium or parathyroid hormone levels. The prevalence rate of primary hyperparathyroidism in patients who present with hypertension is not known. Any other features of primary hyperparathyroidism (e.g. kidney stones) in a patient with hypertension demands for measuring plasma calcium and PTH.

5. Acromegaly

Nearly half of all patients with acromegaly exhibit hypertension which may be accompanied by cardiomyopathy or left ventricular hypertrophy. An increased sympathetic tone, an impaired endothelium-mediated vasodilation and sodium retention caused by growth hormone may all contribute to the development of hypertension. Successful and timely treatment of acromegaly usually improves the blood pressure level considerably.

6. Iatrogenic hormone excess

Several prescribed hormonal drugs may elicit hypertension as side-effect. In general blood pressure increases by approximately 5 and 3 mm Hg for systolic and diastolic blood pressure respectively during use of oral contraceptives (OC). Only 1% of all OC users will develop severe hypertension. The exact pathophysiological mechanism is unknown. Low dose estrogen OC have lower rates of hypertension. In women with a mild hypertension, use of OC is not contraindicated provided that blood pressure is checked at regular intervals. In contrast to the use of OC's, hormonal replacement therapy does not carry an increased risk of hypertension.

Finally, it is obvious that therapeutic use of corticosteroids or mineralocorticoid steroids may elicit hypertension. Treatment with these compounds obviates a regular check of blood pressure.

MAIN CONCLUSIONS

1. A careful medical history and physical examination are indispensable for a timely and correct diagnosis of endocrine hypertension. There are clearly defined indications to select those patients that benefit most from testing. Indiscriminate screening of all patients that present with hypertension for an underlying endocrine disorder might cause more harm than benefit and is therefore not indicated.
2. For most forms of endocrine hypertension, proper care must be given to optimal pre-test conditions for biochemical testing and imaging. For proper interpretation of test results, testing is preferred while off drug treatment where possible. Alternatively drugs are available to minimize drug interference. A biochemical diagnosis should be completed before proceeding to imaging.
3. For optimal patient outcome, interpretation of test results is paramount. This requires knowledge of the optimal cut-off values of biochemical tests to exclude or confirm the disease. Ideally, cut-off levels should be based on reference values established in each own laboratory.
4. The most useful initial tests for pheochromocytoma are measurements of metanephrines in either plasma or urine. All patients with positive test results need follow-up.
5. For primary aldosteronism, the most informative initial test is measurement of the plasma aldosterone/renin ratio (ARR). Establishing or ruling out the diagnosis in patients with an increased ARR requires a confirmation test such as salt loading.

CASES WITH QUESTIONS AND DISCUSSION OF CASES AND ANSWERS

Case 1

A 19 year-old female was referred because of recently diagnosed severe hypertension. The patient was treated by her family physician with 20 mg lisinopril and 5 mg amlodipine once daily. Despite this her blood pressure was 184/102 mm Hg, pulse rate 68 b/min. The patient insisted she was very compliant to her drug intake. She had no paroxysmal symptoms. Her medical history was uneventful, with no previous stroke and she was not known with previous renal disease. In her family her mother was treated for

hypertension. She denied any use of licorice and she did not smoke or use alcohol. Apart from her antihypertensives she used an oral contraceptive.

In the outpatient department, her blood pressure was 176/100 mm Hg with no orthostatic hypotension. BMI was 22.3 kg/m2. There were no signs of Cushing's syndrome and there was no apparent abnormal development of secondary sex characteristics. Examination of heart and lungs was normal.

Laboratory investigation: plasma Na+: 141, K+: 2.9, HCO3-: 31 mmol/L, creatinine: 76 umol/L. There was slight microalbuminuria. No cell casts in urinary sediment.

Echocardiogram: LVMI slightly increased. Abdominal ultrasound showed normal sized kidneys.

The 24-hour urinary excretion of creatinine was 12.1 mmol, sodium: 164 mmol, potassium: 68 mmol, free cortisol: 34 ug (n: <45), aldosterone: 6 ug (n: 2-20)

Plasma aldosterone was 9 pg/ml (n: 5-200) and plasma renin concentration was 4 mU/L (n: 5-75).

Questions:

1. ***Is it useful to do an adrenal CT scanning for excluding a Conn's adenoma?***
2. ***Is it useful to do testing for FH type I (GRA)?***
3. ***What are the most likely diagnoses?***
4. ***Is it useful to measure the urinary (THF +allo-THF)/THE ratio?***

The severe hypertension with target organ damage (increased LVMI and microalbuminuria) was likely to have an underlying cause given her young age and the poor response to medical treatment.

Based on the combination of hypertension, hypokalemia and metabolic alkalosis, it was reasonable to assume that this was mineralocorticoid hypertension. Since both plasma aldosterone and renin levels were low, a diagnosis of pseudohyperaldosteronism and not primary hyperaldosteronism was made and therefore a CT scan was not indicated at this stage. For the same reason, genetic testing for FH-type I (GRA) was not indicated.

The major initial disorders to consider for the differential diagnosis of pseudohyperaldosteronism with hypokalemia included Cushing's syndrome, desoxycorticosterone excess (tumor, congenital adrenal hyperplasia), and 11-beta-hydroxysteroid dehydrogenase (11-beta-HSD2) deficiency (licorice abuse, Apparent Mineralocorticoid Excess or AME syndrome).

There were no signs suggestive for Cushing's syndrome and this was supported by the normal 24-hour urinary free cortisol excretion. Plasma desoxycorticosterone was not yet measured but a normal sexual development made congenital adrenal hyperplasia unlikely, although not excluded. Finally the possibility of 11-beta-HSD2 deficiency had to be considered. For this the urinary (THF+alloTHF)/THC ratio was measured and it appeared to be elevated to 7.8 (n <1.1), indicating an impaired conversion of cortisol to cortisone. This suggested 11-beta-HSD2 deficiency, either due to licorice abuse or to the AME syndrome. A detailed food history made licorice abuse or other food products containing large amounts of glycyrrhizinic acid unlikely. Although it would be possible to measure glycyrrhitenic acid (the active metabolite of glycyrrhizinic acid) to prove or disprove abuse of glycyrrhizinic acid, mutation testing of the 11-beta-HSD2 gene was now ordered. Indeed, a pathogenic mutation in this gene could be demonstrated and was thus held responsible for the mineralocorticoid hypertension. The patient was successfully treated with sodium-restricted diet and epleronone.

Case 2

A 42 year-old male patient was referred because of a difficulty to treat hypertension and because of an increasing frequency and severity of episodic sweating and anxiety. The frequency of these episodes was 2-3 times a week, lasting for 20-30 minutes. The last few weeks, he sometimes also noticed nausea during these episodes. He hardly could do his work as engineer. He was since two years treated by a psychiatrist with clomipramine for depressive symptoms. The patient used 12.5 mg chloortalidon and 5 mg amlodipine once daily. His medical history was uneventful, apart from a deep vein trombosis six years

ago after knee surgery. In his family his obese brother was treated for hypertension and obstructive sleep apnoea syndrome. He did not smoke or use alcohol.

In the outpatient department his sitting blood pressure was 164/92 mm Hg, pulse rate 82 b/min and 144/86 mm Hg, pulse rate 96 b/min while standing. BMI was 24.6 kg/m2. There were no cutaneous signs indicating neurofibromatosis type I. He had slight pretibial pitting edema. Further physical examination was normal.

Laboratory investigation: plasma K+: 3.6, creatinine: 86 umol/L. There was no microalbuminuria. *EKG:* normal without signs of LVH.

Since the attending physician initially strongly considered the possibility of a pheochromocytoma, the following investigations were ordered: plasma free normetanephrine (NMN): 2.66 nmol/L (n<1.05 nmol/L); plasma free metanephrine (MN): 0.26 nmol/L (n< 0.35); plasma 3-methoxytyramine was normal. This increased plasma NMN prompted the physician to ask for an abdominal CT scan in this patient.

Questions:

1. Is it possible plasma NMN was elevated due to use of any of his drugs and should the CT scan be postponed until plasma metanephrines testing was repeated after interrupting for some time one of the drugs?

2. Which would be a useful next step?

- Order a 24-hour urine collection for measurement of metanephrines
- Order measurement of plasma chromogranin A
- Order a clonidine suppression test
- Order a glucagon stimulation test

The drug that would most likely be responsible for a false-positive test result of NMN is the tricyclic antidepressant clomipramine. Therefore it would be useful to stop this drug temporarily although this is not always feasible in all patients. If this drug would be the cause of a false-positive plasma free NMN the CT scan would have been redundant. In general, it is more effective to perform imaging after unequivocal demonstration of an increased catecholamine production.

After stopping all drugs for 10 days after consultation of his psychiatrist, the repeated laboratory results were as follows: *plasma normetanephrine (NMN):* 2.23 nmol/L (n<1.05 nmol/L); *plasma metanephrine (MN):* 0.22 nmol/L (n< 0.35). So plasma NMN remained elevated after stopping all drugs. With this persistently elevated plasma NMN level in the context of the suspicious symptoms, further testing was required to exclude or confirm a pheochromcytoma/paraganglioma.

A 24-hour urine collection for measurement of metanephrines could be done although it is unlikely to have an additional benefit over plasma metanephrines in this patient. Nevertheless, an ordered 24-hour urine collection showed also an increased NMN excretion with a normal MN excretion, strengthening the suspicion of a possible tumor. Plasma chromogranin A was not measured in this patient. Plasma chromogranin A has insufficient sensitivity to serve as screening test for catecholamine producing tumors. There might be a role for plasma chromogranin A as follow-up test since it might improve specificity.

Instead, a clonidine suppression test was done since this is able to discriminate between a chromaffin cell tumor and increased sympathetic activity as causes of an elevated plasma NMN. Measurement of plasma NMN before and 3 hours after administration of clonidine provides a nearly maximal sensitivity and specificity. Plasma NMN after clonidine decreased slightly but remained elevated to 1.96 nmol/L indicating a very high likelihood of the presence of a chromaffin cell tumor. Although glucagon testing has been done in the past to provoke a surge of catecholamine secretion in patients with normal baseline plasma catecholamines, it has nowadays been abandoned because of it has an insufficient sensitivity.

3. Which is the most likely localization of a chromaffin cell tumor in this patient?

The biochemical test results showed a

noradrenergic secretory pattern and this points more to a paraganglioma (extra-adrenal tumor) than to an adrenal tumor. Since most tumors are located under the diaphragm, the entire abdomen including the pelvic area should be visualized to search for a paraganglioma. In this patient, a contrast enhanced CT scan showed indeed an extra-adrenal para-aortic tumor of 3 by 3 cm, just below the diaphragm. Since extra-adrenal tumors are more frequently multifocal and develop metastatic disease more frequently than adrenal tumors, functional imaging such as ^{18}F-FDOPA or ^{18}F-FDG PET scanning are the best options in this patient.

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Pheochromocytoma & Paraganglioma Syndromes: Old and New Clues

M37
Monday, June 17
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Pheochromocytomas (Pheos) and Paragangliomas (PGLs) are rare neural crest-derived tumors arising in the adrenal medulla or in the sympathetic or parasympathetic paraganglia. The group of the sympathetic PGLs includes both the adrenal (Pheo) and the extra-adrenal (abdominal or thoracic) catecholamine secreting tumors (sPGLs) while parasympathetic PGLs, which are generally non-secreting, occur mostly in the head and neck region (HNPGL). PGLs and HNPGL can occur as sporadic or hereditary tumors. At present, about 35-40% of these tumors are due to germ-line mutations in susceptibility genes, thus making the Pheo/PGL the most heritable tumors so far known (1). Therefore, genetic analysis has become an important step in the management of patients with Pheo/PGL.

BARRIERS TO OPTIMAL PRACTICE

Still, the main clinical problem presented by pheochromocytomas/paragangliomas (Pheo/PGL) is the difficulty in their **diagnosis** because of the extreme variability of their clinical presentation (2). No signs and symptoms are specific enough to allow a diagnosis on clinical ground. It is well known that many Pheo/PGL are incidentally discovered as adrenal, abdominal, thoracic or cervical masses at radiology. The advancements achieved in the **genetics** of Pheo/PGL in the last decade have substantially changed the clinical approach to these tumors. Genetic analysis has become an important step in the clinical management of the patients (3) although the screening of the susceptibility genes may sometimes cause some difficulties to the clinicians. Additional major challenges for the clinician are the prediction of the of a Pheo/PGL after surgery and the management of patients with metastatic Pheo/PGL. Because of the rarity and the variability of these tumors, only recommendations from experts (4) and no guide-lines are at present available on the clinical management of these patients.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Define the best laboratory assays for the diagnosis of Pheo/ secreting PGL
- List the so far known susceptibility genes for Pheo/PGL
- Predict from the biochemical phenotype the genetic cluster to which a Pheo/ secreting PGL belongs
- Recognize the genotype/phenotype correlation of the familial Pheo/PGL
- Identify the risk factors for malignancy

SUCCINCT REVIEW- STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Genetics

Since a decade ago only 10% of Pheo/PGL were considered genetically determined. *(Table 1)* These are the tumors caused by mutations in *VHL*, *RET* and genes and are part of the corresponding syndromes, von Hipple-Lindau, MEN2 and Neurofibromatosis type 1, respectively. These tumors arise mostly in the adrenal and are bilateral, synchronous or metachronous, but very rarely they are the first clinical signs of the syndrome. Starting from year 2000, at least 7 additional new susceptibility genes were discovered (1). They

TABLE 1

Gene	VHL	RET	NF1	SDHB	SDHD	SDHC	SDHA	SDHAF2	TMEM127	MAX
Syndrome	Von Hippel Lindau	MEN2	Nerof.1	PGL 4	PGL 1	PGL 3	PGL 5	PGL2	U	U
Inheritance	AD	AD	AD	AD	AD/PT	AD	AD	AD/PT	AD	AD/PT
Associated Syndromic lesions	+++ HM/ RCC/ PL	100% MTC/ HP	100% NF/CS	+ GIST	+ GIST	no	no	no	no	no
Mean of age Pheo/ PGL at present-ation (yrs)	30	35	42	33	35	43	40	32	42	32
PHEO	++ (10-20%)	++ (50%)	+ (5%)	+	+	-	±		+++ (100%)	+++ (100%)
Bilateral PHEO	++	+++	++	±	±	-	-	-	++	++
sPGL	±	-	-	+	+++	++	±	++	±	-
HNPGL	±	-	-	+	+++	++	±	++	±	-
Multiple/ recurrent PHEO/ PGL	+++	+++	+++	++	+++	-	-	++	++	++
Bio-chemistry	N	A	A	N	N	N	N	-	A	N (A)
Malig-nancy	± 5%	± <5%	+ 9%	+++ 40%	± 5%	U	U	U	±	+ 10%

Legend:
U= Unknown; AD= Autosomal Dominant; PT=Paternal Transmission; HM= Hemangioblastoma; RCC= Renal Cell Carcinoma; PL= Pancreatic Lesions; MTC= Medullary Thyroid Carcinoma; HP= Hyperparathyroidism; NF= Neurofibromas; CS= café-au-lat spots; GIST= Gastrointestinal Stromal Tumor; sPGL= Secreting PGL; HNPGL= Head and Neck PGL; - absent; ± very rare; + rare; ++ frequent; +++ very frequent; N= Noradrenergic; A=Adrenergic

include the genes encoding the four subunits of the succinate dehydrogenase (SDHA, SDHB, SDHC and SDHD), the gene responsible for SDHA flavination (*SDHFA2*), and the more recently discovered genes *TMEM127* and *MAX*.

Mutations in the *SDHx* genes can cause either Pheo/sPGL or HNPGL. Sometimes tumors of both types are present in the same patient thus indicating that Pheo/PGLs and HNPGLs cannot be considered as two completely distinct groups (5). Among the SDHx genes, the more frequently mutated are *SDHB* and *SDHD*. The corresponding syndromes are named PGL4 and PGL1, respectively. PGL4 mostly presents abdominal sPGL characterized by the highest risk of malignancy. About 40 % of *SDHB* mutated tumors metastasize (6). PGL1 is characterized by the occurrence of multiple and/or recurrent HNPGLs, sometimes associated with Pheos or sPGL. Malignancy is rare (less than 5%). The responsible gene, *SDHD*, is maternally imprinted (silenced) and the tumors develop

only when the mutated gene is inherited from the father. Exceptions to this rule have been described in only three patients (7).

A paternal inheritance has been demonstrated also for the *SDHAF2* gene, responsible for the very rare PGL2 syndrome, characterized by single or multiple HNPGLs. Also PGL3, caused by *SDHC* mutations and PGL5, caused by *SDHA* mutations are very rare. PGL3 presents mostly single or multiple HNPGL but abdominal sPGL have also been reported. PGL5 is characterized by single tumors, generally abdominal sPGL or HNPGLs. Similarly to PGL1, PGL 2, 3 and 5 present a low risk of malignancy.

Interestingly, in the last years, germ-line mutations in the SDHx genes have been associated also to the occurrence of other solid tumors, among which GIST (8) and, more rarely, papillary thyroid or renal cell cancers.

Germ-line mutations of *TMEM127* have not been associated to a specific syndrome, so far. Mutation carriers develop Pheos, often bilateral (9).

Also for *MAX* mutation carriers a specific syndrome has not been described yet. They are affected by Pheos, often bilateral (10). Up to now, the study of the family pedigrees suggest a paternal transmission of the disease, similar to PGL1 and 2.

Clinical Picture & Diagnosis

Sympathetic PGLs (Pheo and sPGL) present signs and symptoms caused by the effects of increased catecholamine release which nevertheless is very variable. Therefore, blood pressure can range from normal to high. Hypertension, in turn, can be continuous, not different from essential hypertension, or present paroxysms, associated to other signs of adrenergic activation like tachycardia, sweating and pallor. Sudden death, myocardial infarction and cerebrovascular accidents may occur (11). Small Pheo/sPGL may be associated to a subclinical picture (12) and up to 20% of patients with a Pheo/sPGL may have normal blood pressure.

The diagnosis of Pheo/sPGL stems on laboratory assays demonstrating an increased release of catecholamines or their metabolites.

The recommended screening test for initial evaluation is the measurement of plasma free-metanephrines or urine-deconjugated differential metanephrines (13). In comparison with other biochemical tests such as vanilmandelic acid, plasma or urine catecholamines, metanephrines have higher sensitivity, ranging around 97-99%. The higher diagnostic accuracy of metanephrines is mainly due to their longer half-life and to their non-episodic production by the tumour cells where catecholamines are continuously converted to metanephrines by the high methyltransferase activity of the chromaffin tissue. The possibility of false negative results is negligible so that a normal level of plasma or urinary metanephrines makes the diagnosis of sPGLs unlikely.

Interestingly, genetics influence the biochemical pattern of Pheo/sPGL. According to their genetic profile, Pheo/sPGL can be divided into two clusters (14): cluster 1 includes *VHL* and *SDHx*-mutated tumors, characterized by an increase in norepinephrine, sometimes also dopamine. Cluster 2 includes *RET*, *NF1*, *TMEM127* and *MAX*-mutated tumors, characterized by an increase in epinephrine and often also in norepinephrine. Therefore, from a biochemical point of view, and considering the biosynthetic pathway of the catecholamines (dopamine, norepinephrine, epinephrine) tumors of cluster 2 appear more differentiated than tumors of cluster 1. Accordingly, tumors releasing dopamine and its metabolite methoxytyramine, have been shown to possess the highest risk of malignancy (15). Other risk factors for malignancy are *SDHB* germ line mutations, extra-adrenal localization and large tumor size. Nevertheless, diagnosis of malignancy stems only on the presence of metastases, i.e. presence of recurrences in organs devoid of chromaffin tissue such as liver, lungs, lymph-nodes, bones.

Parasympathetic HNPGLs do not generally secrete and they generally present as clinically evident or incidentally discovered cervical masses or are suspected for functional neurological impairment (dysphagia, deafness, anysochoria, etc.) caused by compression of cranial nerves (16).

Localization

Tumor biochemical phenotype may suggest tumor site as metanephrine releasing Pheos are located in the adrenals. 90% of Pheo/sPGL are located in the abdomen, in the adrenal or extra-adrenal sites while 10% are in the chest. Tumor localization is based on morphological and functional imaging (17). Computed tomography (CT) or magnetic resonance imaging (MRI) represent the best radiological approach for initial localization of Pheo/sPGLs. These procedures show high sensitivity (90-100%) but the specificity is not high enough, especially for small tumors, to unequivocally identify a mass as a Pheo/sPGL. Better specificity is offered by functional imaging. Historically, the most widely used nuclear medicine technique is 131I or 123I-metaiodobenzylguanidine (MIBG) scintigraphy. 123I-MIBG is preferred for its higher sensitivity, better quality images and lower radiation dose. Scintigraphic techniques allow a whole-body scan, thus permitting identification of extra-adrenal or multiple PGLs as well as metastatic sites. In case of negative MIBG other functional imaging studies with different tracers such as 18F-DOPA-PET and 18F-DA-PET can be recommended . Other options include 18F-deoxy-glucose (FDG)-PET which seems particularly useful in the localization of metastatic Pheo/sPGL, and specifically in metastatic SDHB mutated sPGLs.

HNPGLs are generally easily detected by MRI and do not need functional imaging. In any case, these tumors express somatostatin receptors at high density and therefore result positive at OctreoScan.

Genetic Testing

Because 35-40% of Pheo/PGL are genetically determined, genetic analysis and counseling, including an accurate family history, are strongly recommended (18). A careful clinical examination, looking for associated syndromic lesions, is also mandatory . It can also suggest a genetic testing algorithm thus offering a guide for a time and cost-effective genetic screening. Germ-line mutations are frequent in young patients, in patients with bilateral Pheos, multiple or recurrent Pheo/sPGL, multiple or recurrent HNPGL or the association of both. Genetic screening is useful for the patient, for the prediction of recurrences or early detection of associated syndromic lesions and for the family members to exclude or confirm the individual risk of developing the disease.

The finding of a novel mutation in a patient with an apparently sporadic Pheo/PGL has to be carefully evaluated and confirmed, if possible, by functional analysis before being considered pathogenic.

In the next future, the fast technical improvement in genetic assays will allow a contemporary screening of all the so far known susceptibility genes. In the meantime, it is up to the clinicians decide the best cost-effective genetic screening, starting from the phenotype of the single patient.

Therapy and Management

Laparoscopic **surgery** is the therapy of choice for **Pheo/sPGL** (19). Open access surgery is reserved for very large tumors or in case of tumor's invasion of surrounding tissues. A **medical** pre-surgical treatment with alpha-blockers and fluid administration is generally recommended in order to reduce surgical (acute hypertension, arrhythmias, pulmonary oedema) and post-surgical (hypotension) complications. Operative mortality is less than 1% when the procedure is carried out by an expert collaborative team (surgeon, anesthesiologist, endocrinologist). Patient's genetic profile may influence the surgical decision. In patients with a synchronous bilateral Pheo and in those with a high probability to develop a contralateral recurrence (VHL, RET, TMEM127 and MAX mutation carriers) an adrenal sparing surgery may be indicated in order to avoid chronic hypoadrenalism.

Clinical management of patients affected by **HNPGL** depends on many different factors such as age, general clinical conditions, PGL size and site, multiple localizations, presence of pre-existing cranial nerve deficits. In case of a solitary HNPGL which can be removed with a low operative risk (as for carotid body tumors), **surgery** may be considered whereas in case of high risk of nerve damage (as for vagal, jugular, tympanic PGL), or

embolization, a "wait and see" strategy or external **radiotherapy** may be preferable (20).

An additional major challenge is the therapy of **malignant**, which means metastatic, Pheo/PGL. At present, no effective therapy is available for their cure and their medical treatment is still a challenge (21). Debulking surgery of primary tumor is warranted in order to reduce morbidity caused by catecholamine excess and improve response to other treatments. Therapy of patients affected by malignant Pheo/PGL should be individualized according to the disease course. In some patients the progression of the disease is very slow and medical therapy limiting catecholamine release or actions can be sufficient for a long time. The most used therapy in progressive disease is radiometabolic treatment with beta-emitting isotopes coupled with meta-iodo-benzyl-guanidine (131I-MIBG) or somatostatin analogues (99Y-DOTA_TOC or 177Lu-DOTA-TATE). Their use is driven by the presence of the corresponding receptors. Somatostatin analogues are generally employed in malignant HNPGL. Unfortunately, radiometabolic treatment is never curative. In case of progression after radiometabolic therapy, chemotherapy with different agents or combination of them has been proposed. The most used regimen is a combination of cyclophosphamide, vincristine and dacarbazine (CVD). A trend toward a longer survival has been reported in some patients. It is possible to hypothesize that in the future, targeted medical therapy will be scheduled according to the genetic profile of the tumor (22). In fact, the two above-mentioned genetic clusters show different pathways activation: cluster 1 is characterized by overexpression of angiogenic factors and cluster 2 by increased activation of the kinase-signaling pathways. At present, targeted drugs such as the oral multitarget inhibitor sunitinib have started to be employed, especially in metastatic disease, and clinical studies are underway to define their role in the treatment of Pheo/PGL.

MAIN CONCLUSIONS

The diagnosis of Pheo/PGL is difficult due to the nonspecific clinical presentation, needs a high alertness by the clinicians and stems on laboratory results. The recommended assay is the differential measurement of plasma or urinary metanephrines. In the last 10 years genetic studies have demonstrated that the Pheo/PGL are the most heritable tumors so far known, as 30-40% of them are genetically determined. Genetics have now a relevant impact on clinical management of patients affected by Pheo/PGL. In fact, genetic profile influences the secretory pattern, the histochemical profile, the clinical presentation, the metabolic characteristics, the risk of malignancy, the intracellular pathways involved in tumor development and, very likely, it may offer, in the future, a potential tool to better plan targeted therapy in patients with metastatic disease.

CASES WITH QUESTIONS

Case 1

A 34 yr old Caucasian man presents with mild hypertension (BP: 150/93 mmHg) and a 4.5 cm left adrenal mass resulting highly vascular at MRI. His family history is negative. Laboratory assays shows: urinary metanephrine 45,0 mcg/24h (n.v. <330), urinary normetanephrine 3507,0 mcg/24h (n.v. < 395), urinary methoxityramine 320,0 mcg/24 h (v.n. <440). A total body 123I-MIBG scintigraphy shows a selective tracer uptake in the left adrenal. Neck sonography reveals a bilateral highly vascular mass at the left (2.0 cm) and right (1,7 cm) carotid bifurcation, both diagnosed as a carotid body tumor.

Questions:

1. ***Which Pheo/PGL familial syndrome most likely does this patient present?***
2. ***How is it possible to explain a complete silent family history?***
3. ***Which therapeutic procedure would you suggest?***
4. ***How high do you rate the risk of malignancy?***
5. ***Would you suggest additional exams to detect other types of tumor? If yes, which tumor?***

Case 2

A 17 yr old Caucasian girl presents with continuous hypertension, (165/98 mmHg), loss of weight, tachycardia (95 beats/min). Her family is composed by a 25 yr old brother, a 20 yr old sister, a 48 yr old mother and a 50 yr old father. They are all healthy. Her maternal grandmother died at the age of 41 for cardiac arrest during surgery for removal of the gallbladder. Laboratory results show normal urinary metanephrine (127.8 mcg/24h; n.v. < 330), very high urinary normetanephrine (7518.7 mcg/24h; n.v. < 395) and high metoxytyramine (1620.0 mcg724h; n.v. < 440) levels. An abdomen TC shows a highly vascular mass, 8.3 x 6.5 x 5.0 cm in diameter, near the aorta below the right kidney.

Questions:

1. ***Would you recommend a genetic screening in this patient?***
2. ***Which susceptibility gene would you suggest to screen for first?***
3. ***Would you suggest a total body scintigraphy?***
4. ***Would you suggest an MRI of the head/neck region?***
5. ***How high do you rate the risk for malignancy?***

Case 3

A 55 yr old Caucasian women complains of sudden headaches and palpitations. She is diagnosed with bilateral adrenaline and noradrenaline secreting pheos (3.7 cm in the right adrenal, 4.2 cm in the left adrenal). Her family history results not informative and at clinical examination no syndromic lesions are detected.

Questions:

1. ***Would you recommend a genetic analysis?***
2. ***Which susceptibility gene may most likely be responsible for her tumors?***
3. ***Which kind of surgery would you recommend?***

DISCUSSION OF CASES AND ANSWERS

Case 1

Answers:

1. The patient is most likely affected by a PGL1 syndrome due to a mutation in *SDHD* gene. The diagnosis is suggested by the presence of a bilateral HNPGL, in association with a pheochromocytoma showing a noradrenergic biochemical phenotype.
2. The *SDHD* gene is maternally imprinted and the syndrome is thus characterized by a paternal transmission. The patient has inherited the mutation from his father who, in turn, has inherited the mutation from his mother. If the *SDHD* mutation is transmitted via a female for some generations, the family history is silent.
3. A laparoscopic approach is suggested to remove the pheochromocytoma. A pre-surgical preparation with alfa-antagonists is recommended. No guidelines exist for the management of the two carotid body tumors. They might be removed by an expert head-neck surgeon but a wait-and-see strategy, with a radiological follow up might be adopted as well.
4. The risk of malignancy is low in PGL1.
5. An association between SDHB, SDHD mutated Pheo/PGL and GIST has been reported.

Case 2

Answers:

1. The young age of the patient is by itself a reason to suspect a germ line mutation and ask for a genetic screening. The sudden death of her grandmother during surgery may suggest the presence of an undiagnosed chromaffin tumor. The absence of any evidence of disease in the other members of her family can be explained by a low penetrance of the disease.
2. The *SDHB* gene should be screened for first. This decision stems on the extra-adrenal localization and on the biochemical noradrenergic phenotype of the PGL.
3. A total body scintigraphy is suggested to verify the possible presence of metastases. In fact, as explained below, the risk of malignancy is high.
4. In case of an *SDHB* mutation, an MRI of the head/neck region is suggested although in PGL4 the association of secreting PGL with HNPGL is much rarer than in PGL1.
5. The risk of malignancy is high even if the

genetic analysis does not detect *SDHB* mutations. In fact, the extra-adrenal localization, the large dimension, the biochemical noradrenergic/dopaminergic phenotype are all elements of suspect. The presence of a *SDHB* mutation would be an additional, confirmatory factor.

Case 3

Answers:

1. Genetic analysis is suggested by the presence of a bilateral Pheo.
2. Bilateral pheos are more often associated to VHL, RET, NF1, TMEM127 and MAX mutations. VHL can be excluded by the tumor adrenergic biochemical phenotype and NF1 by the silent clinical picture (no neurofibromas, no skin spots). MEN2 is possible but pheo is generally preceded by medullary thyroid carcinoma. MAX mutation is possible, although the biochemical phenotype of these pheos is often noradrenergic. The most likely mutated gene is *TMEM127*.
3. A laparoscopic, adrenal sparing, bilateral adrenalectomy should be recommended.

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Congenital Adrenal Hyperplasia From Adolescent to Adult

M45
Monday, June 17
1:00–1:45 PM & 3:00–3:45 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Congenital adrenal hyperplasia (CAH) is most commonly due to 21-hydroxylase deficiency. CAH due to 21-hydroxylase deficiency is now part of the newborn screening done in the United States. Early detection and early treatment have resulted in improved survival. Therefore, the treatment of adults with CAH is of great importance.

The management of CAH patients changes over the lifespan and is inherently age- and sex- specific. During childhood, management is aimed at achieving normal growth and development; while management of the adult is aimed at optimizing fertility, minimizing the virilization of females, and preventing long-term consequences such as osteoporosis, and metabolic syndrome.

BARRIERS TO OPTIMAL PRACTICE

Clinical symptoms in CAH are due to a combination of disease-related and treatment-related side effects. Both short-term and long-term complications may arise related to glucocorticoid and/or androgen excess. By consensus, hydrocortisone is the glucocorticoid of choice for children (1) but there is no consensus regarding the treatment of the adult CAH patient. Optimal therapeutic regimens are often difficult to achieve, and the transition from pediatric to adult care is a recognized challenge (2).

LEARNING OBJECTIVES

To identify issues in the transition of the CAH patient to adulthood, and to learn management strategies.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Diagnosis

Diagnosis of classic CAH is based on markedly elevated 17-hydroxyprogesterone (17-OHP) in the neonatal period or the first few years of life for males with classic simple virilizing CAH prior to neonatal screening. Although low early morning 17-OHP may rule out nonclassic (NC) CAH, a cosyntropin stimulation test is necessary to make a definitive diagnosis; 17OHP > 1,000 ng/dl (33 nmol/l) at 60 minutes is diagnostic of CAH due to 21-hydroxylase deficiency (1). Women with androgen excess may be misdiagnosed with NC CAH; thus it is important to establish the diagnosis through hormonal testing. CYP21A2genotyping may be performed for borderline cases. Genotyping should be done by an experienced laboratory because interpretation of results is often complex (3).

Therapy

Medical therapy for patients with classic CAH consists of glucocorticoid and mineralocorticoid replacement. Hydrocortisone is short-acting and therefore usually needs to be given thrice daily. A typical dose is 20-25 mg/day. Hydrocortisone likely has the least adverse effect on bone density, but should only be used in the highly motivated and compliant patient. Dexamethasone is long-acting and is usually given once daily, although rarely a patient requires twice daily dosing due to increased metabolism. A typical dose of dexamethasone is 375 mcg (range 250-500 mcg) daily. Dexamethasone is often used for

the patient who desires once daily dosing and for males with testicular adrenal rest (TART). Prednisone (5-8 mg per day) or prednisilone (4-6 mg per day) are given twice daily and are often used for sexually active females. Females with NC CAH desiring fertility are successfully treated with lower doses (i.e., prednisone 2 mg twice daily; total daily dose 4 mg). The lowest possible glucocorticoid dose should always be used. Some adults are able to decrease or discontinue fludrocortisone, although the majority of classic patients remain on fludrocortisone for life. Adult males with NC CAH do not require glucocorticoid treatment.

Medical Management and Challenges

Overtreatment (suppressed adrenal hormones) and undertreatment (hyperandrogenism) are commonly found in both pediatric and adult patients with CAH (4).

CAH patients are at risk for low bone mineral density (BMD) due to chronic glucocorticoid therapy. Most children with CAH have normal bone mineral density. However, low BMD is common amongst adults, and a high prevalence of vitamin D deficiency and insufficiency has been found in CAH (4). Thus, osteoporosis prophylaxis including physical activity and calcium and vitamin D supplementation should be implemented at a young age. Screening DEXA scans should begin in early adulthood.

In males, testicular adrenal rest (TART) is found in at least 50 percent of classic patients, but is not found in nonclassic patients. Ultrasound is the modality of choice for identifying TART. In males with classic CAH, a screening testicular ultrasound should be performed in childhood or adolescence and repeated once puberty is complete. If TART is present, intensifying glucocorticoid therapy is warranted with the use of a long-acting glucocorticoid (i.e., dexamethasone or prednisone) and testicular ultrasound monitoring should occur. If TART is not present, further evaluation for TART is not necessary unless infertility should occur.

TART may lead to obstructive azoospermia and infertility, which is sometimes reversible with higher dose glucocorticoid therapy (5). Longstanding TART can result in irreversible damage to testicular tissue. Although surgery for TART may be performed to relieve testicular pain and discomfort, it does not typically restore fertility, (6) and thus is not usually recommended. Men with classic CAH may also have hypogonadotropic hypogonadism due to inadequately controlled adrenal androgens and estrogens (7).

Females with CAH are at risk for infertility and irregular menses due to persistent or episodic increases in androgens and/or progesterone. Prenatal androgen exposure may also disrupt the hypothalamic-pituitary-ovarian axis. Ovarian adrenal rest occurs in females, but is difficult to visualize by conventional imaging. Insulin resistance may contribute to development of secondary PCOS.

Females desiring fertility require tighter control of adrenal hormones. This is true for both classic and nonclassic patients. Hydrocortisone or prednisone can be used in the female patient desiring fertility and during pregnancy; dexamethasone is not inactivated by placental 11β-hydroxysteroid dehydrogenase type 2 and therefore should NOT be used. The goal should be to maintain early morning 17-OHP < 800 ng/dl (24 nmol/l), with androstenedione in the normal range, and follicular phase progesterone <0.6 ng/ml (2 nmol/l).

Subfertility is common in women with nonclassic CAH. In addition, the rate of miscarriage in NC CAH has been shown to decrease with glucocorticoid therapy (8). Approximately two-thirds of women with NC CAH carry a classic gene, and thus genetic counseling is warranted (1). Females with nonclassic CAH who desire treatment for hyperandrogenism (i.e., hirsutism) but are not desiring fertility, may be treated with OCP's and an anti-androgen (i.e., spironolactone).

Other important issues in the management of the CAH patient include: glucocorticoid stress dose teaching for all classic patients and NC patients receiving glucocorticoid therapy; BP and plasma renin activity monitoring and recognizing that fludrocortisone dose may decrease with time; a surgical/gynecological evaluation in the adolescent/young adult

female with classic CAH - young adult women may require a second surgery or use of dilators to optimize sexual function; genetic counseling.

MAIN CONCLUSIONS

Management of the adult CAH patient should be individualized and is inherently age- and sex- specific. Laboratory evaluation should guide, not define, treatment. The desire for fertility, the presence of testicular adrenal rest (males) or female virilization, bone mineral density, and BMI should also help guide therapy. The goal should be to treat with the lowest possible glucocorticoid dose and to optimize the risk/benefit ratio for each patient. Improved transition from pediatric to adult care is needed and promises to improve patient outcome.

CASES WITH QUESTIONS

Case 1

A 17 year old female with classic CAH was born with ambiguous genitalia and was diagnosed with CAH at 4 days old based on a 17-OHP of 19,000 ng/dl (573.8 nmol/l). She was treated with hydrocortisone, fludrocortisone and salt during the first 2 years of life, and then salt was discontinued. Genital surgery was performed at 6 month of age. She had menarche at 14 years and has had irregular menses. She has reached her adult height. She will be starting college soon. On physical examination: BP 118/76, height 10th %, weight 50th %, BMI 23.3 kg/m2 . Pubertal status: Tanner 5 breasts and pubic hair. No hirsutism or striae. Her current regimen is hydrocortisone is 15.5 mg/m2/day (10 mg upon awakening, 5 mg mid-day, 10 mg at bedtime) and fludrocortisone 100 μg daily.

Laboratory evaluation at 8 a.m. prior to medication:

17-OHP	1150 ng/dl (35 nmol/l)
Androstenedione	190 ng/dl (5.7 nmol/l) (30-200 ng/dl)
Plasma renin activity	2.1 ng/ml/h (0.2-4.5 ng/ml/h)

Question:

What is the best plan for treatment as she transitions from adolescence to adulthood?

A) Continue on hydrocortisone, this patient has done well on hydrocortisone
B) Switch to a dexamethasone once daily to optimize compliance
C) Switch to dexamethasone and OCP
D) Switch to prednisone twice daily to optimize compliance

Case 2

A 16 year old male with classic CAH has reached his adult height. He presented at 2 years old with pubic hair and increased growth velocity and was diagnosed with CAH based on a 17-OHP of 7,200 ng/dl (217 nmol/l). He has been treated with hydrocortisone and fludrocortisone since diagnosis. On physical examination: BP 112/72, height 25th %, weight 25th %. Pubertal status: Tanner 5 pubic hair, testes 25cc bilaterally. His current regimen is hydrocortisone is 19 mg/m2/day (15 mg upon awakening, 5 mg mid-day, 15 mg at bedtime) and fludrocortisone 50 μg twice daily.

Laboratory evaluation at 8 a.m. prior to medication:

17OHP	5,710 ng/dl (172 nmol/l)
Androstenedione	570 ng/dl (5.2 nmol/l) (30-200 ng/dl)
Plasma renin activity	4.8 ng/ml/h (0.2-4.5 ng/ml/h)

Question:

What is the best plan for treatment as he transitions from adolescence to adulthood?

A) Continue on hydrocortisone
B) Switch to a dexamethasone once daily to optimize compliance
C) Switch to prednisone twice daily to optimize compliance

Question:

What additional tests should be done?

A) Testicular ultrasound
B) Check vitamin D level
C) DEXA
D) All of the above

Case 3

A 7 year old boy presents with pubic hair. He has been noted to have increased growth velocity. On physical examination: BP 100/60, height > 90th %, weight 90th %. Pubertal

status: Tanner 3 pubic hair, testes 2cc. Bone age 10 years 6 months. A cosyntropin stimulation test reveals a rise in 17-OHP from 450 ng/dL (13 nmol/l) to 6,790 ng/dl (205 nmol/l). He is started on hydrocortisone 10 mg/m2/day given thrice daily.

Question:
What is the best long-term plan for transition from adolescence to adulthood?

A) Continue on hydrocortisone, nonclassic patients are easily managed on short-acting glucocorticoid
B) Switch to a longer-acting glucocorticoid medication to optimize compliance
C) Discontinue hydrocortisone during puberty, nonclassic adult males do not require glucocorticoid therapy

Case 4
Question:
If this patient were female, how would the management change?

DISCUSSION OF CASES AND ANSWERS

Case 1
Answer:
A, C or D is correct and the regimen should be chosen based on patient preference and lifestyle. Dexamethasone should not be used without birth control in the sexually active young female because it is transferred to the fetus. The transition to adulthood should include a surgical/gynecological evaluation and genetic counseling. A baseline DEXA and vitamin D level are indicated. Glucocorticoid stress dose teaching should include self-administration of intramuscular Solu-cortef.

Case 2
Answer:
B or C is correct and the regimen should be chosen based on patient preference and lifestyle. Evaluation for TART is important in this patient.
Answer:
D. All of these screening tests are important and will help guide management.

Case 3
Answer:
C. NC males do not require treatment as adults.

Case 4
Answer:
The young adult NC female could be managed on hydrocortisone or prednisone, but should not require GC therapy throughout life. Many adult females with NC CAH are well controlled on OCP's and spironolactone. Glucocorticoid therapy may be needed if fertility is desired or in severe cases.

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Primary Aldosteronism: Diagnosis and Management

M56
Tuesday, June 18
11:15 AM–12:00 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Primary aldosteronism (PA) is much more common than previously thought, accounting for as many as 5-10% of hypertensives and 20% of those with drug-resistant hypertension (HT). Furthermore, aldosterone (aldo) excess is associated with the development of adverse cardiovascular (CV) and renal effects that are at least partly independent of its effects on blood pressure. Importantly, specific treatment of PA not only cures or improves the HT and any accompanying metabolic abnormalities, but leads to amelioration of the excess CV and renal damage and CV morbidity seen in these patients compared to those with primary (essential) HT. As a result, Endocrine Society guidelines have recommended wider screening for PA in an effort to maximize detection of patients who may benefit from optimal, specific management.

BARRIERS TO OPTIMAL PRACTICE

- Numerous confounding factors (including body position, time of day, diet, gender and medications) can affect aldo and renin levels and complicate interpretation of test results unless they are controlled for or their effects at least taken into account
- Withdrawing interfering medications can take time and may entail substantial risk in some cases.
- Protocols for confirmatory testing vary widely in their complexity and reliability
- CT adrenal scanning lacks reliability for distinguishing unilateral from bilateral forms of PA
- Although adrenal venous sampling (AVS) is reliable, it is invasive and often difficult to perform and interpret
- Currently employed assays for renin and aldo lack precision and reproducibility
- Spironolactone can cause sex steroid-related side effects
- Use of eplerenone for PA is not subsidized in most countries.

LEARNING OBJECTIVES

- As a result of participating in this session, learners should be able to recognize:
- The importance of screening for and diagnosing PA
- Who should be screened and how
- Why confirmatory testing is important and how it should be undertaken
- Why AVS is critical in subtype differentiation, and how rates of success can be improved
- How to interpret complex data from AVS procedures
- Why subtype differentiation is critical to optimal management
- How to make decisions on surgical or medical approaches to management

SUCCINCT REVIEW- STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Screening

Who should be screened for PA?

The Endocrine Society guideline recommends the case detection of PA in patient groups with "relatively high prevalence of PA" including patients with moderate, severe, or resistant HT; HT and spontaneous or diuretic-induced hypokalemia; HT with adrenal incidentaloma; or HT and a family history of early-onset HT or cerebrovascular accident at a young age

(<40 years) which is encountered in families with the rare, inherited, glucocorticoid-remediable form of PA; and, given that PA exists in familial forms, all hypertensive first-degree relatives of patients with PA. Some have argued, however, for screening of all hypertensives (i.e. even those with mild HT who lack hypokalemia or a significant family history) on the basis that (1) the longer the diagnosis is missed, the more likely patients will suffer irreversible consequences of HT and aldo excess, and the less likely their HT will respond to specific surgical or medical treatment; and (2) screening before commencement of medications avoids the difficulties of ARR interpretation associated with the confounding effects of drugs on aldo and renin concentrations.

How should patients be screened?

While the ARR is generally considered the most reliable means of screening for PA, its interpretation is not straightforward. Although renin/angiotensin is the main regulator of aldo production, other important regulators (e.g. K+ and ACTH) and rates of hepatic blood flow are also influential. This helps explain why renin and aldo do not always move strictly in parallel in response to physiological manoeuvres and certain medications. Thus false positive or negative ratios may occur and need to be avoided where possible.

A. Preparation for ARR measurement
1. Hypokalemia is corrected, after measuring plasma K+ in blood collected slowly using a syringe and needle, avoiding fist clenching during collection, waiting ≥10 sec after releasing the tourniquet, and ensuring separation of plasma from cells within 30 min.
2. Patients are encourage to liberalize (rather than restrict) sodium intake.
3. Medications which significantly affect the ARR are withdrawn: ≥2 weeks before testing for beta-blockers, clonidine, methyldopa and NSAIDs which cause false +ves, ≥2 weeks for ACE inhibitors, angiotensin receptor blockers and dihydropyridine calcium blockers which cause false -ves; and ≥4 weeks for diuretics (including spironolactone and eplerenone) which also cause false negatives.
4. Where necessary to maintain HT control, other antihypertensive medications which have lesser effects on the ARR, such as verapamil slow-release (with or without hydralazine), prazosin or doxazosin and/or methyldopa are commenced.
5. Do not withdra w contraceptive agents unless confident of an effective alternative.

B. Conditions for collection of blood
1. Blood is collected mid-morning, after the patient has been ambulant for ≥2 h and seated for ≥5mins.
2. Blood is collected carefully to avoid stasis and hemolysis [see (A) 1) above].

C. Factors to take into account when interpreting results
1. Gender (females have higher ratios)
2. Advanced age (over 65 years; also associated with higher ratios)
3. Time of day, recent sodium intake, posture and length of time in that posture
4. All medications
5. Method of blood collection including any difficulty
6. Concentration of potassium
7. Renal function
8. Phase of menstrual cycle in women

The problem of assay reliability

Highly reproducible assays are essential for the diagnosis and management of PA. There are concerns about the accuracy and reproducibility of both renin and aldo assays currently in use. A major step forward has been the development of new, high-throughput mass spectrometric methods of aldo measurement which have proven highly reliable within the clinically relevant range. Because of the critical role of validated assay techniques and the innate variability of both aldo and renin, a single ARR should not be relied on to guide management decisions. Before deciding that PA is highly likely or highly unlikely, the ratio should be repeated until confident it is indeed raised, meanwhile adjusting medications and conditions of collection if indicated. The next step, a definitive test

involving salt loading, is not entirely risk-free in patients with severe HT or reduced CV or renal function. The most commonly used cutoff values for the ARR and the potassium and aldo values required for a positive screen will be discussed.

Confirmation of PA

Fludrocortisone suppression testing (FST)

Plasma aldo is measured during 4 days administration of fludrocortisone acetate (0.1 mg 6 hourly), slow release NaCl (1800 mg thrice daily with meals), a high salt diet, and sufficient oral slow-release KCl (given 6 hourly) to maintain normokalemia. Failure of upright plasma aldo to suppress to <6 ng/dL (<165 pmol/L) by day 4, despite suppression of renin (<8 mU/L), and in the absence of a rise in ACTH (inferred from cortisol) between 7 and 10am which may have prevented aldo suppression, confirms PA. The complexity of this protocol is a potential limitation to its widespread use.

Saline suppression testing

Plasma aldo is measured at the end of an IV infusion of 0.9% saline (usually 2 L over 4 hours). Levels regarded as diagnostic for PA vary from >5 to >10 ng/dL (>140 to >280 pmol/L). This approach requires only a brief outpatient visit, but has been found by some investigators reported to be less sensitive than FST and probably carries a higher risk of provoking heart failure in severely hypertensive and/or elderly patients.

Oral salt loading

Urinary aldo levels are measured following oral salt loading (sufficient to achieve a urine sodium excretion of over 200 mmol/d). As with the FST, patients are given enough KCl supplementation to maintain normokalemia. A 24 h urinary aldo level of >12 μg/d (>33 nmol/d) on the third day is regarded as diagnostic.

Captopril challenge testing

Patients receive 25–50 mg captopril orally after sitting or standing for at least 1 h. Blood samples are drawn for measurement of PRA, plasma aldo, and cortisol at time zero and at 1 or 2 h after challenge, with the patient remaining seated during this period. Plasma aldo is normally suppressed by captopril (>30%). In patients with PA, it remains elevated and PRA remains suppressed. Differences may be seen between patients with APA and those with IHA, in that some decrease of aldo levels is occasionally seen in IHA. There are reports of a substantial number of false-negative or equivocal results

Subtype Differentiation

If confirmatory testing is positive, further investigations are directed towards determining the subtype of PA, as the treatment of first choice for each subtype differs.

Genetic testing of peripheral blood for the "hybrid gene" is diagnostic for glucocorticoid-remediable PA (familial hyperaldosteronism type I or FH-I), and has virtually supplanted biochemical methods (for example, demonstration of marked, persistent suppression of plasma aldo during several days of dexamethasone administration). The great majority of patients with PA, however, will test negative for the hybrid gene, leaving the more difficult task of separating the unilateral varieties from bilateral PA.

Adrenal CT scanning is usually able to detect aldo-producing carcinomas because of their relatively large size (usually >3 cm) but frequently misses aldo-producing adenomas (APAs, which have an average size of ~1 cm) and may be frankly misleading as it cannot distinguish these from non-functioning nodules, which are relatively frequent (~4%) in the general population. Similar limitations apply to adrenal magnetic resonance imaging, and adrenal selenocholesterol scanning fails to detect most small tumors.

Adrenal venous sampling (AVS) is the only dependable way to differentiate bilateral from unilateral PA. Some centers therefore perform this procedure in all patients with PA (other than those with FH-I). To avoid effects of posture and diurnal variation on steroid levels, sampling should be performed in the morning after overnight recumbency, and stress should be minimized. The AV to peripheral venous (PV) cortisol gradient is used to judge whether cannulation has been successful. In

most centers, gradients of ≥2.0 or ≥3.0 are taken to indicate successful cannulation. If AVS is performed with ACTH stimulation however (in an attempt to avoid fluctuations in steroid secretion), the cutoff is usually ≥5.0 Calculation of the aldo/cortisol ratio for each AV and PV sample corrects for differences in "dilution" of AV with non-AV blood. If the AV aldo/cortisol ratio on one side is ≥2 times higher than the simultaneous PV ratio, with a ratio ≤ peripheral on the other side, the study is considered to show lateralization, indicating that unilateral adrenalectomy should cure or significantly improve the HT. Some centers rely instead on comparing the aldo/cortisol ratio on one side with that on the other, with side to side ratios of ≥4 usually taken to indicate lateralization.

Success rates for adrenal venous cannulation in AVS vary widely and urgent measures are required to improve them in centers experiencing sub-optimal results. The level of expertise and experience of the proceduralist and close liaison with the treating team are critical. Pre-AVS CT localization of the adrenal veins, intra-procedural cortisol measurement and highly reliable assays also improve accuracy and success.

Treatment

Because aldo has deleterious effects on the CV and kidneys independent of effects on BP, excess aldo must be reduced or its effects adequately blocked at the mineralocorticoid receptor (MR) or antagonized at the epithelial sodium channel it activates. Unilateral adrenalectomy for unilateral PA results in cure of HT in 50-60% of patients and improvement in all the remainder. For other patients with PA, treatment with MR blockade (spironolactone 12.5-50 mg/day or eplerenone 25-100 mg/day) or with antagonism at the sodium channel (amiloride 2.5-20 mg/day) is usually effective, but regular monitoring of electrolyte concentrations and renal function is required to avoid potentially dangerous side effects of hyperkalemia and azotemia due to overtreatment. Spironolactone is the most effective, but, through blockade of androgen receptors, can cause gynecomastia and reduced libido in males and painful, lumpy breasts and menstrual irregularities in females, side effects which should be absent with the more specific but weaker MR antagonist, eplerenone. Patients with the rare FH-I usually show excellent blood pressure responses to glucocorticoids given in low doses (e.g. dexamethasone 0.25-0.5 mg/day) which do not cause Cushingoid side effects, but can also be treated effectively by mineralocorticoid receptor blockade.

MAIN CONCLUSIONS

- PA should be sought because it is common and has adverse cardiovascular effects that result both from hypertension and from non-BP-dependent effects and which are ameliorated by specific treatment.
- PA should be considered in all hypertensives, but especially those with moderate, severe, or resistant HT; HT and spontaneous or diuretic-induced hypokalemia; HT with adrenal incidentaloma; or HT and a family history of early-onset HT or cerebrovascular accident at a young age (<40 years) which is encountered in families with the rare, inherited, glucocorticoid-remediable form of PA; and, given that PA exists in familial forms, all hypertensive first-degree relatives of patients with PA.
- Confirmatory testing is important as it allows patients in whom PA can be definitively excluded to be spared invasive further testing (and especially AVS).
- AVS is the only reliable means of differentiating unilateral (surgically correctable) from bilateral (usually medically treated) PA. Success rates can be optimized by high throughput, restricting the procedure to 1-2 dedicated radiologists per center, offering AVS, using contrast CT to localize the adrenal veins prior to AVS, and using point-of-care cortisol measurement.
- Correct interpretation of AVS requires that successful cannulation of each adrenal vein be confirmed by comparing AV with peripheral venous cortisol levels, and that adrenal/cortisol ratios for each adrenal vein be calculated and compared with peripheral.
- Subtype differentiation is critical to optimal

management as unilateral adrenalectomy leads to profound improvements in BP control, degree of target organ damage and quality of life in patients with unilateral disease and to a substantially greater degree than for medical treatment in those with bilateral disease.

CASES WITH QUESTIONS

History

A 60 yr female with a 30 year history of HT was referred after her BP levels, previously well controlled, became more difficult to control over the preceding 12 months. At the time of presentation she was taking perindopril 4mg daily, prazosin 2mg twice daily and furosemide 20mg daily. There was no history of urinary tract disease, heart disease or strokes, recent headaches, palpitations or sweating episodes. There was a strong family history of HT affecting her father, father's sister and mother's nephew.

On Examination

Not obese or Cushingoid. HR 82 bpm and regular, BP 190/96 recumbent and 180/106 upright in clinic and 142-165/70-80 seated at home. JVP, apex beat, heart sounds, chest and abdominal examinations normal. No radio-femoral delay, no renal or carotid bruits and pedal pulses normal.

Initial Investigations

Na+ 138, K+ 3.8, Cl- 101, HCO3- 27, Urea 5.6, Creat 80 umol/L, 24h urine protein and albumin normal, ECG normal, Echo LVMI 97g/m2 (normal <100).

Further Investigations (Seeking Endocrine Causes)

Renal DTPA and renal artery duplex U/S normal, 24hr urinary catecholamines & metanephrines normal, plasma aldo 20.2 ng/dL, plasma renin activity 1.5 ng/ml/h, aldo/renin ratio 13.5 (normal <20). Six weeks after changing medications to verapamil S/R 120 mg twice daily, hydralazine 12.5 mg twice daily and prazosin 1 mg twice daily, plasma aldo was 29.7 ng/dL, plasma renin activity 0.5 ng/ml/h and the aldo/renin ratio 59.4 (normal <20).

Fludrocortisone suppression testing (FST) showed *(Table 1)*:

The long PCR test for the hybrid gene causing glucocorticoid-remediable PA was negative. A CT adrenal scan was reported not to show an adrenal mass lesion. Adrenal

TABLE 1

Day	Sample	Aldo (ng/dl)	Renin (ng/ml/h)	K+ (mmol/l)	Cortisol (nmol/l)
Basal	0800h Recumbent	14.0	0.2	3.6	512
	1000h Upright	34.0	0.6	3.6	420
Day 4	0800h Recumbent	8.6	<0.1	3.9	391
	1000h Upright	32.9	0.3	4.0	314

TABLE 2

	ALDO (ng/dL)	CORTISOL (ugdL)	CORTISOL AV/PV	ALDO/CORTISOL RATIO
Right AV1 Peripheral	410.9 54.0	659.9 16.1	41.0	0.6 3.4
Right AV2 Peripheral	667.6 56.0	453.5 17.7	25.6	1.5 3.2
Left AV1 Peripheral	4300 64.8	264.7 19.8	13.4	16.2 3.3
Left AV2 Peripheral	34525 50.0	1153 19.2	60.0	29.9 2.6

venous sampling was performed *(Table 2)*:

Treatment

She underwent left laparoscopic adrenalectomy, yielding a 1.6 cm adenoma, and resulting in cure of her HT and biochemical cure of PA (confirmed by post-operative FST).

Questions:

1. ***Was screening for primary aldosteronism indicated in this patient?***
2. ***What are the effects of her original medications on measurement of renin and aldo?***
3. ***How do you interpret the results of the fludrocortisone suppression test?***
4. ***How do you interpret the results of the adrenal venous sampling procedure?***
5. ***What is your diagnosis?***

DISCUSSION OF CASES AND ANSWERS

1. Current indications for screening for PA in a hypertensive patient include (1) the presence of hypokalemia, (2) drug-resistant HT; (3) adrenal incidentaloma and (4) any patient in whom you are considering the possibility of secondary HT. Some argue, however, that a case can be made for screening virtually all hypertensives. This patient had drug-resistant HT.
2. Perindopril (by reducing angiotensin II and negative feedback to the juxta-glomerular cells) and furosemide (by promoting Na+ excretion) both raise renin. Perindopril lowers aldo by reducing angiotensin II. Any tendency of furosemide to cause hypokalemia also lowers aldo. Hence both drugs tend to lower the aldo/renin ratio and cause false negatives (as in this case).
3. Failure of day 4 upright aldo to suppress to <6.0 ng/dL despite suppression of renin to <1.0 ng/mL/h, while normokalemic and in the absence of a morning rise in cortisol which excludes a rise in ACTH that may have prevented aldo suppression, has confirmed PA.
4. Adrenal venous sampling is the "gold standard" for separating unilateral from bilateral disease that is critical for medical or surgical management decision making. Different institutions may employ different sampling methods. In our institution, we perform the procedure in the morning after overnight recumbency. We collect at least two samples from each adrenal vein with simultaneous collection of peripheral venous samples (without ACTH stimulation). A mean adrenal venous aldo/cortisol ratio of at least 2.0 times that in the peripheral vein, in combination with a mean ratio on the other side that is no higher than peripheral (contralateral suppression), fulfills our criteria for lateralization. In this case, results were consistent with good lateralization to the left adrenal.
5. The correct diagnosis is left aldo-producing adenoma.

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Clinical Management of Adrenocortical Carcinoma

M2
Saturday, June 15
3:00–3:45 PM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Adrenocortical carcinoma (ACC) is a devastating tumor for either patients or their families because of short life expectancy and severe impact on quality of life, which is severely affected by metastatic progression, associated endocrine syndromes and treatment-related side effects. The fact that ACC has a first peak of incidence in young children and frequently occurs in women of childbearing age makes the management of this aggressive tumor even more challenging. In addition, currently available treatments of advanced ACC have limited efficacy and relevant toxicity that concurs to reduce quality of life.

Due to the rarity of ACC, with a reported annual incidence of 0.5–2 cases per million population, progress in the development of treatment options beyond surgery has been limited. Up to now, no personalized approach of ACC therapy has emerged, apart from plasma level - guided mitotane therapy, and no simple targetable molecular event has been identified from preclinical studies. Moreover, pathological and clinical criteria for risk stratification of ACC patients need to be implemented and the identification of prognostic and predictive biomarkers has to be actively pursued.

BARRIERS TO OPTIMAL PRACTICE

ACC is an infrequent tumor, thus it is difficult to get adequate experience on its management outside reference institutions.

Management of ACC patients is challenging and demanding because physicians have to deal with either oncological issues, concerning tumor progression and metastatic development, or endocrinological issues, related to tumor secretion or specific treatment (mitotane effects on the endocrine system).

Moreover, ACC has a heterogeneous behavior with a broad spectrum of biological aggressiveness and the treatment plan should be tailored accordingly, although we have still initial and incomplete knowledge on the factors predicting patient outcome.

Treatment of ACC is multi-modal, including surgery (often repeated), mitotane, cytotoxic agents, interventional radiology procedures, radiotherapy, and should be delivered by a multidisciplinary team within centers with adequate facilities.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Understand the management strategies of ACC patients following surgery
- Understand the management strategies of ACC patients with advanced disease

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Background

Surgery aiming at complete removal of ACC is the only potentially curative approach and has the most important impact on patient's prognosis. However, studies reported a disappointingly high rate of recurrence of 70-85% after apparent radical extirpation of ACC with high proliferation index or locally advanced disease. This observation makes a strong case for post-operative adjuvant approaches in ACC management.

The adrenolytic drug mitotane has been widely used for treating advanced ACC since the sixties and is still considered the reference treatment for advanced, inoperable ACC. Furthermore, the use of mitotane as an adjunctive measure has become increasingly popular after we showed that adjuvant mitotane treatment was associated with a significant reduction in the risk of recurrence and death in a large series of patients with ACC. Given its retrospective nature, however, the study could not provide a definitive demonstration of efficacy.

Despite the limited level of evidence available, adjuvant mitotane therapy is accepted by most authorities in the clinical setting of an elevated risk of recurrence. However, implementation of collaborative prospective randomized studies is crucial to finally prove the benefit of adjuvant mitotane treatment in patients with ACC after complete resection. To this aim, our center is currently coordinating a prospective randomized study –the ADIUVO trial (NCT00777244)- which is currently recruiting at different European and North-American centers.

Adjunctive approaches other than mitotane (i.e. cytotoxic drugs) have been infrequently reported in the literature. There is an ongoing debate on the role of adjunctive radiotherapy to prevent local recurrence. However, this technique does not seem able to prevent distant recurrences and in my opinion should be used in association with mitotane.

Patient Selection for Adjuvant Mitotane

Recent data suggest that the proliferation activity of the tumor is the most important factor predicting risk of recurrence following complete (R0) surgery. Assessment of the proliferation index Ki-67 is the best way to assess proliferation, despite some problems to harmonize Immunohistochemical readings among different pathologists. In an European multicentric study, a threshold value at 10% was found to separate patients at good or worse prognosis with a HR of recurrence of 1.042 per each % increase.

Resection status is another established adverse risk factor, being Rx (unknown), R1 (microscopically positive margins) and R2 (macroscopically positive margins) associated with progressively reduced recurrence-free survival.

Stage III disease may also portend to an unfavorable prognosis, particularly when a venous thrombus in the renal or caval vein is present. The rare stage IV ACC that may be completely resected should be considered in the high risk category. Weiss score is not a clearly predictive of recurrence *(Table 1)*.

Monitored Mitotane Treatment

Nowadays, the concept of monitored mitotane treatment, with regular checks of drug levels to adjust dose, has been clearly established as a standard of practice. Mitotane monitoring is readily available across Europe, where it is provided as a free service by the company distributing mitotane (info@lysodren-europe.com). Mitotane monitoring is the key to guide dose adjustments to target mitotane concentrations that have been associated with a therapeutic effect. Indeed, plasma mitotane levels >14 mg/l have been found to predict tumor response and improved survival in

TABLE 1 – ENSAT staging system of ACC (Fassnacht et al., 2009)

ENSAT	TNM	Definition
I	T1, N0, M0	Tumor ≤ 5 cm
II	T2, N0, M0	Tumor > 5 cm
III	T1-T2, N1, M0 T3-T4, N0-N1, M0	Lymphnode involvement or infiltration of adjacent tissues or renal and/or caval vein thrombosis
IV	T1-T4, N0-N1, M1	Metastases

TABLE 2 – Practical guidelines to adjuvant mitotane treatment.

• Start with 1 g daily and increase mitotane dose every 4-7 days up to 8-10 g daily, or the maximum tolerated dose. Give mitotane in split doses with meals or snacks.
• Accommodate mitotane schedule to patient's tolerance aiming at serum mitotane concentrations of 14-20 mg/l (therapeutic levels).
• Check mitotane levels every 4-8 weeks to adjust dosage until reaching target levels.
• At target, clinical assessment, biochemical and hormonal evaluation, and monitoring of mitotane levels every 3-4 months, or in case of significant side-effects. Adjust mitotane dose according to circulating levels and tolerability.
• In case of slight unwanted effects, continue mitotane and treat symptoms (e.g., nausea, diarrhea).
• In case of moderate side effects, step down to the previously tolerated dose and use symptomatic therapy.
• In case of severe side effects, discontinue mitotane and institute specific treatment. Duration of treatment stop depends on clinics and mitotane levels. After interruption, restart with a lower dose.

patients with advanced ACC. Preliminary results of our group demonstrated that the concept of a therapeutic impact of plasma mitotane concentrations is applicable also to disease-free patients who are treated adjuvantly.

In my practice, I start mitotane as soon as possible after surgery, in any case within 3 months. Although a high-dose regimen is able to provide therapeutic plasma concentrations of mitotane more rapidly, I am more cautious with dose escalation *(Table 2)*. A high-dose regimen requires an intensive follow-up and may be more frequently associated with side effects, while our schedule is better tolerated with less impact on the quality of life, and is easier to manage in an outpatient setting.

Mitotane is a toxic drug and unwanted effects are observed in almost all patients, but toxicity is usually mild and tolerable, if managed properly. The most common unwanted effects are gastrointestinal manifestations (nausea and diarrhea) that appear early, independently on mitotane levels. They can be managed with temporary dose reduction, or delay of dose increments, and symptomatic therapy. Elevation in GGT levels is an universal finding that is not actually troublesome unless values are exceedingly elevated. Clinically significant liver toxicity is characterized by a marked increase in transaminases and bilirubin, but is infrequently observed in the absence of predisposing conditions. Central neurologic toxicity is more closely associated with elevated mitotane concentrations (>20 mg/l) but subtler symptoms, such as memory impairment or attention deficit, may be observed in some patients at lower drug concentrations. A great individual variability in the susceptibility to mitotane-related unwanted effects is apparent for causes that are still unknown. Because of the adrenolytic effect of mitotane, all patients should receive glucocorticoid replacement to prevent adrenal insufficiency (*Table 3*). Steroid doses are typically higher than in Addison's disease, due to an enhanced metabolic clearance rate of glucocorticoids induced by mitotane. An inadequate treatment of adrenal insufficiency increases mitotane-related toxicity, particularly gastrointestinal side-effects, and reduces tolerance. Mineralocorticoid supplementation is not mandatory in all patients because the zona glomerulosa is partly spared by the toxic effect of mitotane. Moreover, mitotane affects thyroid and gonadal function by mechanisms that are still to be completely elucidated. Mitotane administration is associated with low FT4 levels without a compensatory rise in TSH, an effect that becomes apparent early in the course of treatment prompting thyroxin replacement. In women, gonadal function is usually preserved and most female patients have regular cycles; some women develop ovarian cysts and olygomenorrhea with possible vaginal bleedings. Conversely, in men mitotane treatment frequently causes sexual dysfunction, due to inhibition of testosterone secretion. Sex steroid replacement may become necessary to treat erectile dysfunction in some patients but may worsen

TABLE 3 – Hormone replacement during adjuvant mitotane treatment.

• Start glucocorticoid replacement at initiation of mitotane treatment and use higher doses than usual (50-70 mg hydrocortisone – 75-100 mg cortisone acetate, or even larger daily doses).
• Glucocorticoid replacement is monitored best clinically, since assessment of serum or urinary cortisol is confounded by analytical problems. ACTH levels give only a clue of over- or under-replacement.
• Look for clinical and biochemical signs of mineralocorticoid deficiency in the long-term; give fludrocortisone if needed.
• Look for hypogonadism in long-term treated men assessing clinical symptoms and free testosterone. Total testosterone may be normal due to the mitotane-induced increase in SHBG. Replace testosterone in the event of erectile dysfunction or impotence.
• Gynecomastia may be simply due to the estrogenic effect of mitotane and is worsened by testosterone replacement.
• Low FT4 levels associated with normal TSH are frequently observed. Replace thyroxine when FT4 levels are below normal.

gynecomastia. DHT treatment may be associated with less gynecomastia.

A general measure to deal with mitotane toxicity is to step down to the previously tolerated dose, or discontinue temporary the drug in the event of severe manifestations. However, well-informed and motivated patients are able to cope with side effects and maintain compliance to treatment. To accomplish this task, it is important to establish a close patient–physician relationship to induce and maintain adherence to treatment. Patients seek advice frequently, also because their local physicians are unfamiliar with mitotane use and its attendant complications, and it is necessary to give a timely counseling to keep patients on treatment. The optimal duration of therapy remains undefined. Since most ACC recurrences after complete resection occur within 5 years from primary surgery, I consider such a period as a landmark, if compliance with treatment does allow. Anyway, I do not consider discontinuing mitotane before 2 years of treatment. *(Table 3)*

Strategies for Management of Acc Patients With Advanced/Metastatic Disease

Mitotane is by far the most studied agent in ACC and the only FDA and EMEA approved drug in advanced ACC. When used as monotherapy, objective responses were reported in 13% to 33% of cases with duration of 2 to 190 months. Various dosages of the drug were used, ranging from 3 to 20 grams per day. Greater objective response rates ranging between 55% - 66% have been observed in patients whose plasma mitotane levels were between 14 and 20 mg/L, the so called therapeutic concentrations (see before). Time to reach therapeutic concentrations has been shown to last from 1 to 6 months after mitotane initiation and sometimes is never obtained. This time-lag between initiation of treatment and full activity is of concern when treating rapidly progressive disease and is beyond the rationale of combining mitotane with classic cytotoxic agents. For management of mitotane therapy and attendant toxicity see the previous chapter.

Mitotane has been claimed to reverse the P-glycoprotein (Pgp) protein expression which may influence the cell clearance of drugs like doxorubicin and etoposide, thus providing further rationale for combination regimens. However, side effects of mitotane (see before) are enhanced by concomitant chemotherapy. Mitotane is also a strong inducer of liver enzyme activity including the CYP3A4, thus enhancing degradation (and possibly reducing activity) of a number of drugs metabolized by this system (i.e., sunitinib and other targeted therapies).

Experience with cytotoxic chemotherapeutic agents in ACC is limited. Over the last 15 years, only 11 prospective studies employing single agent chemotherapy have been published. Response rates ranged from 7% to 54%, with high variability in the response criteria. Cisplatin-containing regimens have

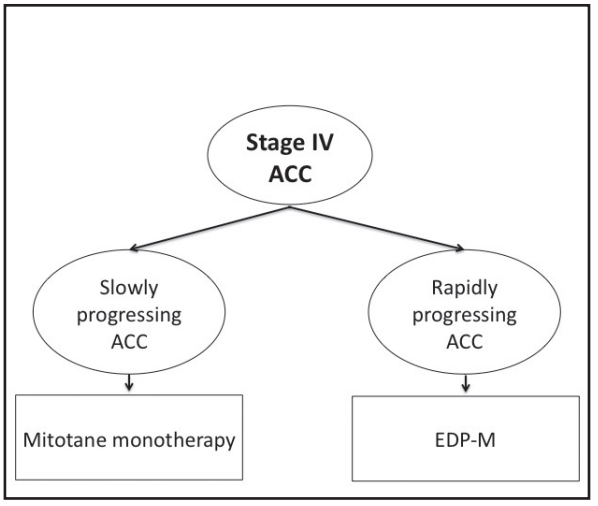
been the most frequently used and possibly the most active.

The FIRMACT phase III trial, which is the first phase III ever published in the field of ACC, compared the Berruti and Khan protocols who reported the highest objective response rates in the literature: 36% with streptozotocin-mitotane (S-M) and 55% with etoposide-doxorubicin-cisplatin-mitotane (EDP-M), respectively. Although no statistically substantial increase in overall survival was documented in patients receiving EDP-M as the first-line therapy, significantly better response rates and progression-free survival rates were achieved with EDP-M in comparison with S-M. The rate of serious adverse events was comparable. Of note, the results of the second-line regimens replicated the rates observed with the first-line therapy. Since EDP-M was superior to S-M in terms of progression-free survival either as first-line or second-line therapy, the crossover design may have attenuated its advantage on overall survival.

However, in 2012, the benefit of combining mitotane to other cytotoxic drugs remains to be demonstrated as well as the anti-tumour effect of agents like etoposide or doxorubicin. In parallel, it is well known that combining mitotane with other cytotoxic agents increases the rate of side effects. In such a context, a new protocol is required in order to justify the combination of four drugs and its attendant toxicity. Moreover, results of the FIRMACT with a median survival of about 14 months cannot be considered as satisfactory and new therapeutic options are needed.

Prognosis in advanced or metastatic ACC patients is poor, the 5-year overall survival being <15%, however, advanced ACC shows a remarkable heterogeneity and long survival has been reported in patients with oligometastatic and slowly progressive disease. Recent progress in stratification of prognosis of advanced ACC has been obtained. A number of metastatic organs ≤ 2 and a Ki-67 value ≤ 20% are markers of a better prognosis among stage IV ACC, and may be useful to identify patients amenable of treatment with mitotane monotherapy. The combination with locoregional therapies such as radiofrequency ablation and liver chemoembolization is recommended. In case of rapidly progressing or life-threatening extensive metastatic disease and/or radiological progression under mitotane, cytotoxic chemotherapy is indicated. In such cases, EDP-M is recommended as the first-line therapy for ACC requiring cytotoxic therapy. In patients unfit for the EDP-M regimen, P-M may be a plausible alternative. *(Figure 1)*

FIGURE 1: Strategies for Managing Stage IV ACC Patients



MAIN CONCLUSIONS

At San Luigi Hospital, patients at high risk of recurrence following surgery (Rx or R1 resection; Ki-67 > 10%) are recommended adjuvant mitotane treatment, while the remainders are encouraged to enter the ADIUVO trial. Adjuvant mitotane is commenced as soon as possible after surgery, using a "low-dose" start-up regimen because it is more feasible in an outpatient setting and implies less intensive follow-up. Adjuvant mitotane is continued for 4-5 years. Imaging evaluation with thorax-abdomen-pelvis CT is done every 3 months for the first 2 years and then at longer intervals.

Patients with stage IV ACC are offered first-line mitotane therapy if the disease burden is limited and there is no evidence of fast progression, or progression to mitotane therapy despite attainment of therapeutic concentrations. In the remainder cases, EDP-M is recommended. Imaging evaluation

with thorax-abdomen-pelvis CT is done every 2-3 months in most cases.

CASES WITH QUESTIONS

Case 1

A 12 cm adrenal mass is incidentally discovered in a 37-yr-old men. Hormonal assessment is negative. Surgery is macroscopically radical and histology concludes for ACC, Weiss score 5, Ki-67 35%.

What is the more appropriate post-operative management?

A) Follow-up with imaging assessment every 3 months
B) Mitotane
C) EDP-M
D) Radiotherapy to the tumor bed

Case 2

A 72-yr-old lady is diagnosed with adrenal-dependent Cushing's syndrome due to a 5 cm adrenal tumor. She undergoes laparoscopic adrenalectomy and pathological report is R0 resection, Weiss score 4, Ki-67 8%.

What is the more appropriate post-operative management?

A) Follow-up with imaging assessment every 3 months
B) Mitotane
C) EDP-M
D) Radiotherapy to the tumor bed

Case 3

A 45-yr-old lady underwent removal of a 20 cm adrenal mass 26 months ago. At a scheduled imaging assessment, 3 metastatic liver lesions (35 mm, 22 mm, 15 mm) are detected.

What is the more appropriate management?

A) Radiofrequency ablation (RFA)
B) Mitotane
C) EDP-M
D) S-M

Case 4

In a 23-yr-old man, multiple lung and liver metastases are detected 6 months after removal of a 8 cm adrenal mass (Weiss score 8, Ki-67 50%).

What is the more appropriate management?

A) Radiofrequency ablation (RFA)
B) Mitotane
C) Etoposide-Doxorubicin-cisPlatin-Mitotane (EDP-M)
D) Streptozotocin-Mitotane (S-M)

DISCUSSION OF CASES AND ANSWERS

Case 1

My choice is adjuvant mitotane treatment, since this tumor may be classified in the high risk category (elevated Ki-67, stage III). In this clinical setting, there is evidence that adjuvant mitotane may decrease the risk of recurrence. EDP-M is too toxic to be employed in an adjuvant setting and has no substantial evidence for this use. Adjuvant radiotherapy may decrease the risk of local recurrence but not of distant metastases. It could be used in combination with mitotane.

Case 2

My choice is follow-up with no treatment, since this tumor may be classified in the low risk category (low Ki-67, stage I). In this clinical setting, the potential benefit of adjuvant mitotane may be carefully weighted with toxicity and the risk-benefit ratio is unclear. Moreover, the advanced age of the patient makes more likely non-compliance to mitotane and its attendant side effects. For the other options see discussion of case 1.

Case 3

My choice is mitotane monotherapy, since this stage IV ACC may be classified in the less aggressive category (long recurrence-free interval, only one metastatic site). EDP-M may be reserved in case of progression to mitotane monotherapy. Further rationale to this choice comes from the observation from the FIRMACT trial that EDP is more active in patients whose mitotane levels are elevated. RFA may be used concomitantly with mitotane.

Case 4

My choice is EDP-M, since this stage IV ACC may be classified in the aggressive

category (short recurrence-free interval, multiple metastatic sites, elevated Ki-67). Results of the FIRMACT trial suggest that EDP is more active than S-M. Owing to the latency of mitotane to attain the therapeutic concentrations and full efficacy, this option does not seem adequate for such a rapidly progressive tumor.

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BONE

Osteoporosis: Side Effects of Therapies

M26
Sunday, June 16
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

There are about 2 million osteoporotic fractures each year in the USA, and with an aging population, there likely will be more in years to come. In treatment trials, most medications for osteoporosis decrease fracture risk by about 50%. Thus, diagnosis of osteoporosis/fracture risk and appropriate treatment should lead to fewer fractures, large savings of money, and even fewer deaths, especially if hip and vertebral fractures are averted. Treatment of the chronic condition of osteoporosis is also chronic, yet we do not know the optimal method of long term management. Treatment with oral bisphosphonates requires about 75-80% of doses to be taken in order to demonstrate fracture risk reduction. There is evidence that concern about side effects leads to poorer adherence to long term treatment. We know the most about bisphosphonates because they are the class of drugs used most frequently in osteoporosis, but other FDA-approved treatments (denosumab, teriparatide, raloxifene, calcitonin) also have potential side effects, only some of which will be discussed. Many of the side effects were not discovered until hundreds of thousands of patients used the various medications for extended time periods. There is very limited randomized controlled trial information from which recommendations can be made.

BARRIERS TO OPTIMAL PRACTICE

- Lack of data on optimal long term treatment of osteoporosis
- Media emphasis on side effects and lawyer ads
- Lack of evidence-based guidelines

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- List the important side effects of bisphosphonates
- Know methods to avoid or minimize some side effects
- Understand the limitations of the long term data
- Be familiar with potential side effects of drugs other than bisphosphonates
- Use an approach to long term management of osteoporosis

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Mild or Avoidable Side Effects with Bisphosphonates

Esophageal Irritation and Cancer

- Avoid oral bisphosphonates in patients with severe GERD, Barrett's, esophageal motility disorders
- Have patients take meds properly (make them recite method)
- Get GERD under control first
- Recent meta-analysis: no increase in esophageal carcinoma
- Consider using intravenous preparations

Bone and Joint Pain: Unexplained, low incidence

Eye pain, Uveitis: Recent studies suggest not a problem.

Hypocalcemia

- Check serum calcium and albumin, especially before I.V. bisphosphonates
- Check 25-OH vitamin D level

- Provide adequate calcium ~ 1000 mg/day in diet; more is not needed
- Provide adequate vitamin D: Bring level up to 30 ng/ml

Worsening Renal Function
- Check serum creatinine, eGFR at baseline and periodically
- Alendronate minimum eGFR = 35, risedronate 30
- Consider denosumab
- Good hydration, slower infusion of I.V. bisphosphonates

Acute Phase Reaction
- Very unusual with oral bisphosphonates
- Mostly after first dose of I.V. bisphosphonates
- Adequate hydration; no need to fast
- Use acetaminophen or other OTC meds for flu-like syndrome

Atrial Fibrillation
- Probably not a real concern but patients with osteoporosis are of similar age as those with A Fib
- Meta-analyses: Variable results, mostly negative
- Possible higher incidence of Afib in cancer patients on higher doses

More Serious Side Effects

Skin Rashes
- From mild skin rashes to toxic epidermal necrolysis - rare

Osteonecrosis of the Jaw
- Exposed bone in mandible or maxilla, usually after dental procedure
- Complete dental work, especially invasive procedures/extractions first
- After healing, start bisphosphonate
- For patient on bisphosphonates, ADA recommends continuing even if an invasive procedure is planned.
  - Good dental hygiene for all
  - Role of antibiotics not settled but often used
  - Chlorhexidine mouth washes
  - Generally responds to conservative Rx
  - 6 Cases in Denosumab FREEDOM trial
  - Bisphosphonate incidence: 1/10,000-1/100,000

Atypical Femoral Fractures
- Fractures are in femoral shaft and cause a fall
- Probably occur in patients not on anti-resorptives
- Exact incidence unknown but found with bisphosphonates, denosumab

ASBMR Definition 2010-Major Features (required for dx):
- From distal to lesser trochanter to proximal to supracondylar flare
- Associated with little or no trauma
- Transverse or short oblique configuration
- Non-comminuted
- Complete fractures extend through both cortices and may be associated with a medial spike
- Incomplete fractures involve only lateral cortex

ASBMR Definition 2010-Minor Features (not required):
- Localized periosteal reaction of lateral cortex
- Generalized cortical thickness increase in femoral diaphysis
- Prodrome: dull pain in groin or thigh
- Bilateral fractures and symptoms
- Delayed healing
- Co-morbidities: Low vitamin D, hypophosphatasia, RA
- Drugs: Bisphosphonates glucocorticoids, PPIs

ASBMR will likely make small changes in the definition. An update from the Task Force is in preparation.

Incidence
- Varies, depending on population and definition
- Recent Study (Dell): 1.78/100,000 person years on bisphos. < 2 years
- Typical fracture incidence 463/100,000 person years
- 38.9/100,000 person years on bisphosphonates 6-8 years
- 107.5/100,000 person years on bisphosphonates > 10 years

Relative Risk (from recent meta-analysis by Gedmintas et al)
- Overall Relative Risk (RR): 1.70
- Overall RR from Case-Control Studies: 11.12
- Overall RR from Cohort Studies 1.52
- RR in studies using ASBMR definition: 11.78

Who gets AFF?
- Some evidence for young active women with osteopenia
- In some series, women of Asian ethnicity are at higher risk
- AFF has occurred in men
- AFF reported with bisphosphonates and denosumab

How to avoid AFF
- Use anti-resorptives in patients at increased fracture risk
- Bisphosphonates for 3-5 years
- Assess patients' risk at end of Rx period
  - Overall evaluation
  - Medications: Glucocorticoids, PPIs, ADT, aromatase inhibitors, etc.
  - DXA
  - Re-calculate FRAX
- Treat those who continue to be at higher risk
- Drug holiday for those whose risk has improved
- New ASBMR Task Force recommendations in preparation

Side Effects from Other Osteoporosis Medications

Raloxifene

Increased thromboembolic events
Worsening of vasomotor symptoms

Calcitonin

Nasal irritation
Cancer ?

Teriparatide

Nausea
Muscle Cramps
Hypercalcemia
Hypercalciuria
No evidence for increased incidence of osteosarcoma
- Avoid in patients at risk for osteosarcoma
- Young patients
- Radiation to bone
- Paget's disease

Stimulation of osteoblasts
- I avoid in patients with prostate cancer (no data)

Denosumab

Both ONJ and AFF have been reported but incidence not established.

In clinical trials, serious infections were more common in those patients receiving denosumab compared to placebo (4% vs. 3.3%) and new malignancies were also more common in denosumab patients (4.8% vs. 4.0%). Long term safety remains to be established by post-marketing surveillance.

Calcium and Vitamin D

Subjects for a separate MTP!!!!

MAIN CONCLUSIONS

All drugs have side effects, some of which can be minimized. Knowledge of the side effects helps in planning long term management of osteoporosis.

CASES WITH QUESTIONS

Case 1

A 72 year old man had a fracture of the patella, leading to a bone mineral density that showed osteoporosis of the spine and hip. Risk factors included tobacco abuse and COPD, alcohol abuse, poor dietary calcium, and omeprazole. He was started on alendronate and 500 mg of elemental calcium daily. He returned for a visit 3 months later and seemed to be taking alendronate properly and regularly, but one month later he returned complaining of a pruritic rash on his left leg as well as pruritus without rash on his arms. The rash appeared to be related to the days he took alendronate. It would wane and then get worse again when he took the next week's dose.

Is the rash likely to be due to alendronate?

It is not always easy to be sure, but careful questioning led to the conclusion that the rash was probably related to alendronate.

If the rash is related to alendronate, does that preclude using another bisphosphonate?
Interestingly, there are case reports that patients could switch to another bisphosphonate. It is even possible that the rash is due to the binders used in a given pill.

Would you give intravenous bisphosphonate to someone who has had a rash from oral bisphosphonate?
I don't have any good data, but I would not. Maybe I would try an oral bisphosphonate again. If the rash is more than erythematous papules, I would be less inclined to challenge the patient again.

What are your alternatives to bisphosphonates in cases like this?
If this patient were a woman, you could consider raloxifene. Many experts believe that data supporting calcitonin for osteoporosis is not particularly strong. Denosumab would be a reasonable choice for this patient, and indeed this patient was switched to denosumab for the next two years without problem.

What are the severe skin reactions to osteoporosis drugs?
While mild erythematous rashes have been reported with bisphosphonates, more severe skin disorders have been noted to occur in < 1/10,000 patients. DRESS (drug rash with eosinophilia and systemic symptoms), SJS (Stevens Johnson Syndrome), and TEN (toxic epidermal necrolysis) have been reported: SJS and TEN for bisphosphonates. While strontium ranelate is not available in the U.S., DRESS and TEN have been reported in Europe, and some American patients are buying strontium citrate as an over the counter "supplement."

Case 2
This 58 year old woman has been on an oral bisphosphonate for 5 years. She underwent normal menopause at 51. She was not a smoker but was 5'4" tall and weighs 120 lbs. Bone density 5 years ago: spine T-score -2.9, femoral neck -1.8. At present, spine T-score is -2.8 and femoral neck -1.8. She is health conscious and can describe the correct method of taking her medication. She does aerobic exercises 4 days a week and resistance training twice a week. She reads about the side effects of bisphosphonates and is concerned about them, although she has had no GI side effects and no dental issues. She gets adequate dietary calcium and takes a multivitamin with 400 units of vitamin D daily.

Which laboratory tests would you consider at this time?
Answer: 25 (OH)-vitamin D, 24 hour urine calcium, bone resorption markers (CTX). There is some evidence that vitamin D should be > 30 ng/ml for the best response to bisphosphonates. The 24 hour urine calcium, particularly if it was not done before, might signal malabsorption or hypercalciuria. The CTX should be low, and if not it could mean poor absorption of drug or non-adherence.

What is her FRAX score, assuming no RA and no parental history of hip fracture?
Answer: 10 year hip fracture risk: 0.8%, any major fracture 7.4%

What about her spine? The T-score is -2.8, not really changed from baseline?
Answer: FRAX uses femoral neck only. She remains at higher risk for spine fracture and for other osteoporotic fractures.

The patient is a young active woman who has already taken bisphosphonates for 5 years. Isn't she a prime candidate for atypical femoral fractures?
Answer: Yes. This is a real dilemma.

What are your options?
Answer: There are several options. Obviously you will correct her vitamin D and investigate her gut (test for celiac disease) if her urinary calcium is surprisingly low. If her CTX is not suppressed, it may help in your discussions about taking the medication correctly and regularly. Assuming all her tests are normal, one option is to continue therapy, based on her continued low bone density. A second would be to change to an intravenous bisphosphonate or denosumab or raloxifene. More specific data about the patient and her wishes would

help in choosing a substitute therapy. Another choice would be to prescribe teriparatide for 2 years. This would likely improve her spine considerably. Then at two years you would have to decide whether to start an anti-resorptive, and perhaps odanacatib will also be available at that time. Finally, you could just keep her on her present conservative regimen (dietary calcium, vitamin D, and exercise) and reassess her in two years, including a repeat DXA. There is no right (or easy) answer, but we will discuss the pros and cons of each choice.

Case 3

A 78 year old man with COPD requiring glucocorticoid tapers two or three times a year and chronic inhaled glucocorticoids has osteoporosis. He also has GERD, which is not under good control with omeprazole twice daily. He also has diabetes mellitus with neuropathy and falls. His spine bone density is +2.1 and his femoral neck T-score is -2.6. He continues to smoke. Because of his GERD, he never received oral bisphosphonates. Renal function, vitamin D, and serum calcium were all acceptable. So, the patient received intravenous zoledronic acid 5 mg I.V. over 15-20 minutes. He had been counseled on the potential acute phase reaction.

The patient returned to the Bone Clinic one year later. He stated that he felt "awful" for 2 weeks, with muscle and bone pain, subjective fever, and headache. "Whatever you gave me, I don't want to have again!"

What happened?

Answer: The acute phase reaction is most common and worst in patients who have not had any exposure to oral bisphosphonates. In addition, bone pain is a known complication of bisphosphonates, mechanism unknown. Whether this patient was well hydrated at the time of infusion and whether he took some acetaminophen before the infusion, we cannot know for sure.

What do you do now?

Answer: The patient refuses, correctly, to try bisphosphonates again, although the chance of the acute phase reaction is lower with the second infusion. On the other hand, we know little about more subacute bone pain, noted in some patients, even with oral bisphosphonates.

One alternative is denosumab. It is a potent anti-resorptive, in one study more potent than alendronate. It is convenient because it is given as a subcutaneous injection every 6 months. So, it does not increase the pill burden for this patient, and if he comes to the Clinic, we can be sure he gets treated. It has downsides, of course. It is more expensive, and there is much less long term experience with this medication. To my knowledge, bone pain has not been reported with denosumab, but I am interested in whether audience members have heard of this in their practices.

An alternative for this patient is teriparatide, although it can cause muscle cramps that might remind the patient of what he suffered with zoledronic acid. It is expensive and given as a daily subcutaneous injection for up to 2 years. For patients with considerable exposure to glucocorticoids, it may be a superior choice. Whether this patient would accept a daily injection of a substance that must be kept cold is not clear. Of course, at the end of 2 years we will have to make choices again. In addition, teriparatide is particularly good for the spine, and his bone density there cannot be interpreted because of obvious artifacts.

A final alternative might be to refer the patient to Gastroenterology to see if better control of his GERD is possible. Then, maybe an oral bisphosphonate challenge can be given to see if he has a recurrence of bone pain.

DISCUSSION OF CASES AND ANSWERS

Included with questions.

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Strontium ranelate is not available in the USA, but some patients with osteoporosis are self-medicating with strontium citrate, available in stores that sell vitamins and supplements. Little is known about the efficacy and safety of strontium citrate; this article provides a tool that may help.

Vitamin D Deficiency: Metabolic Consequences

M52
Monday, June 17
1:00–1:45 PM & 3:00–3:45 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Vitamin D is not just for preventing rickets and osteomalacia. Recent findings primarily in animal studies but also in a number of epidemiologic studies and a few clinical trials indicate that adequate vitamin D levels are important for a wide variety of physiologic and pathologic processes including cancer prevention, controlling hormones such as parathyroid hormone, insulin, FGF23, and renin, and regulation of the immune response. 25 Hydroxyvitamin D (25OHD) levels above 10ng/ml may suffice to prevent rickets and osteomalacia, but these levels are not sufficient to provide for these more recently discovered clinical benefits or fracture prevention. The recent report from the Institute of Medicine (IOM) concluded that a level of 20ng/ml was adequate for maintenance of skeletal health in the general population, but that the evidence was insufficient to make recommendations for the nonskeletal actions of vitamin D. On the other hand the Endocrine Practice Guidelines Committee, with a focus less on the general population than on the patients we see in our practices recommended levels of 25OHD above 30ng/ml. This makes a big difference in terms of the numbers of individuals whom we would define as vitamin D deficient needing treatment. Both groups acknowledge the inconsistencies and incompleteness in the data on which these recommendations are based. Moreover, the troublesome lack of consistency of the vitamin D assays contributes to the problem. Given the potential role of vitamin D in a wide range of physiologic processes, establishing a safe and effective target level of vitamin D confidently measured is an important goal to reach.

BARRIERS TO OPTIMAL PRACTICE

- Consensus has not been achieved on the optimal level of serum 25OHD for vitamin D sufficiency or the amount of vitamin D supplementation that should be recommended to achieve the optimal level. This is likely to vary depending on age and other morbidities, but such considerations have not received much study. The IOM has made age adjusted recommendations for vitamin D supplementation and adequate serum levels of 25OHD based on data focused on the skeletal actions of vitamin D, but did not find the evidence sufficient to make recommendations for the nonskeletal actions, which may require higher doses. Moreover, levels adequate for the general population may be inadequate for patients with various morbidities.
- The assays used for measuring 25OHD in blood vary not only between assays but between laboratories using the same assay, making the setting of a universal target level problematic.
- The data supporting the importance of adequate vitamin D levels for prevention/treatment of a number of conditions associated with vitamin D deficiency are based primarily on animal studies and epidemiologic surveys, with few randomized double blind prospective trials. Existing data are in many cases inconsistent.
- Compliance with any medication that needs to be taken for many years and which has no obvious immediate effect on the subject's sense of well-being is problematic.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Understand the basic metabolism and mechanisms of action of vitamin D, including its pleiomorphic actions in multiple tissues
- Recognize the differences between vitamin D3 and vitamin D2 and how those differences impact therapy
- Assess the quality of the data supporting the current recommendations for serum 25OHD levels, and know where the gaps in our knowledge exist regarding optimal vitamin D levels.
- Determine the appropriate means of achieving vitamin D sufficiency with supplementation, while appreciating some of the pitfalls regarding monitoring those levels.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

The multiple actions of vitamin D

Skeletal health: A number of studies have been conducted to determine whether vitamin D supplementation prevents fractures. Bischoff-Ferrari et al. [1,2] recently published a meta-analysis of randomized controlled trials (RCT) examining the efficacy of vitamin D supplementation on fracture prevention with or without supplementary calcium in subjects over 65 years old. These studies included non-vertebral fractures (12 RCTs, 42,279 subjects) or hip fractures (8 RCT, 40,886 subjects). Studies using 400 IU vitamin D per day or less did not show benefit, a conclusion also recently reached by the USPSTF, whereas those studies using more than 700 IU vitamin D per day showed a significant reduction (approximately 20%) in fractures. Part of this reduction may come from increased bone mineral density in those receiving vitamin D supplements, but part of the benefit may also come from an improvement in neuromuscular function and a decreased risk of falling [3].

Hormone secretion: 1,25(OH)2D regulates the production and secretion of a number of hormones, which in some cases feedback on the renal production of 1,25(OH2D3. Vitamin D deficiency has been linked to a variety of diseases resulting from either over or under secretion of such hormones, providing a physiologic basis for the importance of this regulation.

1. Parathyroid hormone (PTH). 1,25(OH)2D inhibits the synthesis and secretion of PTH [4] and prevents the proliferation of the parathyroid gland. 1,25(OH)2D also upregulates the calcium sensing receptor (CaR), which by sensitizing the parathyroid gland to calcium inhibition provides an additional means by which 1,25(OH)2D (and calcium) regulates PTH production and secretion. Hyperparathyroidism is a feature of vitamin D deficiency and contributes to bone loss; thus, PTH levels are a useful marker to follow when vitamin D supplementation is initiated to correct vitamin D deficiency.
2. Insulin. 1,25(OH)2D stimulates insulin secretion, presumably by regulating calcium flux, although the mechanism is not well defined. Pittas et al. [5] published a meta-analysis of studies demonstrating a link between vitamin D deficiency and type 2 diabetes mellitus (DM), and a study demonstrating that vitamin D and calcium reduced the number of prediabetics from developing frank diabetes [6].
3. Fibroblast Growth Factor 23 (FGF23). FGF23 is produced primarily by bone, in particular by osteoblasts and osteocytes. 1,25(OH)2D stimulates FGF23 production [7]. A number of diseases are caused by overproduction or underproduction of FGF23 leading to abnormalities in vitamin D metabolism and phosphate handling. At this point the role of FGF23 in vitamin D deficiency per se has not been carefully examined, although in chronic kidney disease, elevated FGF23 levels may contribute to the osteomalacia frequently observed.
4. Renin. The juxtaglomerular cells of the kidney as well as the heart produce renin, a protease that converts angiotensinogen to angiotensin I, which is subsequently converted to angiotensin II, a major regulator of aldosterone production and

vascular tone. Mice lacking the ability to produce or respond to 1,25(OH)2D (CYP27B1 null, VDR null, respectively) have increased renin production leading to increased angiotensin II, hypertension, and cardiac hypertrophy [8]. The negative regulation of renin/angiotensin by 1,25(OH)2D may explain the inverse correlation between hypertension and heart disease with 25OHD levels observed in epidemiologic studies, but randomized controlled trials with vitamin D as treatment of hypertension have been disappointing [9].

Regulation of immune function: The potential role for vitamin D and its active metabolite 1,25(OH)2D to modulate the immune response rests on the observations that VDR are found in activated dendritic cells, macrophages, and lymphocytes; that these cells produce 1,25(OH)2D (i.e. express CYP27B1); and that 1,25(OH)2D regulates the proliferation and function of these cells [10]. Two forms of immunity exist, each regulated by 1,25(OH)2D.

1. Adaptive immunity. The adaptive immune response involves the ability of T and B lymphocytes to produce cytokines and immunoglobulins, respectively, to specifically combat the source of the antigen presented to them by cells such as macrophages and dendritic cells. Vitamin D exerts an overall inhibitory action on the adaptive immune system. This may be useful in the management of autoimmune diseases [11] and transplanted organs [12] as shown in animal studies and some epidemiologic studies with type 1 diabetes mellitus and multiple sclerosis.
2. Innate immunity. The innate immune response is the first line of defense against invading pathogens. The response involves the activation of toll-like receptors (TLRs) in polymorphonuclear cells (PMNs), monocytes and macrophages as well as in a number of epithelial cells including those of the epidermis, gingiva, intestine, vagina, bladder and lungs [13]. TLRs are transmembrane pathogen-recognition receptors that interact with specific membrane patterns (PAMP) shed by infectious agents that trigger the innate immune response in the host [14]. Activation of TLRs leads to the induction of antimicrobial peptides and reactive oxygen species, which kill the organism. Among those antimicrobial peptides is cathelicidin. The expression of this antimicrobial peptide is induced by 1,25(OH)2D in both myeloid and epithelial cells, cells that also express CYP27B1 and so are capable of producing 1,25(OH)2D needed for this induction. It is through this mechanism that vitamin D may be essential for resistance to a number of infections including tuberculosis [15].

Regulation of proliferation and differentiation: The proliferation and differentiation of many different cell types is controlled at least to some degree by vitamin D and its metabolites. As such, the role of vitamin D in the prevention and/or treatment of conditions where such regulation goes awry has received considerable attention. Much of the interest has focused on cancer prevention and treatment. 1,25(OH)2D has been evaluated for its potential anticancer activity in animal and cell studies for several decades. The list of malignant cells that express VDR is now quite extensive. However, data from prospective trials with vitamin D and its metabolites for the prevention/treatment of cancer are limited. A prospective 5 yr trial with 1100 IU vitamin D and 1400-1500 mg calcium showed a 77% reduction in cancers (multiple types) after excluding the initial year of study[16]. In this study, vitamin D supplementation raised the 25OHD levels from a mean of 28.8ng/ml to 38.4ng/ml with no changes in the placebo or calcium only arms of the study. However, this was a relatively small study in which cancer prevention was not the primary outcome variable. Trials with 1,25(OH)2D and its analogs for the treatment of cancer have been disappointing and limited by hypercalciuria.

Therapeutic considerations

What is vitamin D sufficiency?

Serum 25OHD levels provide a useful surrogate for assessing vitamin D status, as the conversion of vitamin D to 25OHD is

less well controlled (i.e. primarily substrate dependent) than the subsequent conversion of 25OHD to its active metabolite 1,25(OH)2D. 1,25(OH)2D levels, unlike 25OHD levels, are well maintained until the extremes of vitamin D deficiency because of the secondary hyperparathyroidism, and so do not provide a useful index for assessing vitamin D deficiency at least in the initial stages. Historically, vitamin D sufficiency was defined as the level of 25OHD sufficient to prevent rickets in children and osteomalacia in adults. Levels of 25OHD below 10ng/ml (or 25nM) are associated with a high prevalence of rickets or osteomalacia. Although there is currently no consensus for the optimal levels, the recent recommendations from the IOM state that levels of 25OHD above 20ng/ml are sufficient [17]. Although that recommendation is based primarily on prospective clinical trials regarding skeletal health, other experts point out that this level may be too low for the nonskeletal actions of vitamin D [18].

Vitamin D treatment strategies.
Adequate sunlight exposure is the most cost effective means of obtaining vitamin D. Whole body exposure to enough UVB radiation or sunlight to provide a mild reddening of the skin (minimal erythema unit) has been calculated to provide the equivalent of 10,000 IU vitamin D_3. Duration of exposure depends on skin pigmentation and intensity of the sunlight. A 0.5 minimal erythema dose of sunlight (i.e. half the dose required to produce a slight reddening of the skin) or UVB radiation to the arms and legs, which can be achieved in 5-10 min on a bright summer day in a fair skinned individual in Boston, has been calculated to be the equivalent of 3000 IU vitamin D_3. However, concerns regarding the association between sunlight and skin cancer and/or photoaging have limited this approach, perhaps to the extreme, although it remains a viable option for those unable or unwilling to benefit from oral supplementation. Current recommendations from the IOM for daily vitamin D supplementation include 400 IU for infants, 600 IU for children and adults 1-70 yo, and 800 IU for adults older than 71 [17]. Upper limits range from 1000 IU in infants to 4000 IU in older children and adults. These are recommendations for the general population and would not apply to those with malabsorption of vitamin D or alterations in its metabolism. A number of studies have demonstrated that for every 100 IU vitamin D_3 supplementation administered on a daily basis for four or more months, 25OHD levels rise by 0.5-1ng/ml. Thus to increase a patient's 25OHD level from 10ng/ml to 20ng/ml, the supplementation would need to be 1000-2000 IU per day. 700-800 IU appears to be the lower limit of vitamin D supplementation required to prevent fractures and falls in the elderly [1-3], but the levels of vitamin D required to forestall most of the other presumed benefits of vitamin D are not established. Nor is it clear at what age an individual should start being concerned about maintaining an optimal 25OHD level. Unfortified food contains little vitamin D with the exception of wild salmon and other fish products such as cod liver oil. Milk and other fortified beverages typically contain 100 IU/8oz serving. The 25OHD level after a single 50,000 IU dose of D_2 returns to baseline by 2 wks, whereas a comparable dose of D_3 results in elevated 25OHD levels for over 1 month. However, when given on a daily basis 25OHD levels are well maintained with adequate levels of either form of vitamin D. Therefore, if vitamin D_2 is used, it needs to be given at least weekly. Toxicity due to vitamin D supplementation has not been observed at doses less than 10,000 IU per day (the IOM report limits the highest safe dose to 4000 IU), although such doses are seldom required except in situations in which the vitamin D is poorly absorbed (malabsorption syndromes). Toxicity manifests as hypercalcemia and hypercalciuria, leading to renal failure as a result of nephrocalcinosis and nephrolithiasis and neurologic symptoms including coma.

MAIN CONCLUSIONS

UVB stimulation of vitamin D_3 production in the skin is the major source of vitamin D—very little is found in the diet except in some fatty fish. Vitamin D_2 comes from the UVB radiation of plants and is handled somewhat differently than vitamin D_3 by the body.

Nearly all cells in the body have receptors

for the active form of vitamin D, $1,25(OH)_2D$, indicating that vitamin D has the potential to regulate many physiologic processes beyond that of bone mineral metabolism, although RCT data supporting an important role for vitamin D in these nonskeletal effects are limited.

The IOM expert panel indicated that 20ng/ml 25OHD levels for the general population was sufficient at least for the skeletal effects, and this level was achieved by 97.5% of the US population. However, most of the world's populations outside the USA, people of color, and many patients have 25OHD below 20ng/ml.

30ng/ml or higher has been proposed by the Endocrine Practice Guidelines Committee as a reasonable target especially for older individuals and patients, a level considered safe by the IOM (up to 50ng/ml), and one that can generally be achieved by doses of 800-2000 IU/day.

Assays for 25OHD are still variable but getting better as they become better standardized

CASES WITH QUESTIONS

Case 1

A 60 year old white male enters your office with a complaint of low back pain. His primary physician ordered a lateral spine which showed diffuse osteopenia, degenerative changes primarily in the lumbar spine, and the question of mild compression fractures in T6 and L1. DEXA measurements were then obtained of the spine and hip which documented the osteopenia. You are asked to see the patient to help manage the osteoporosis. The back pain is not severe, is not associated with neurologic problems, but is starting to interfere with routine activities around the house. There is no history of trauma to the back. The patient gives a 40 pack year history of cigarette smoking, but quit 5 years ago. He drinks socially now, but was a heavy drinker during his time in the service. He gives no history for malabsorption, but avoids dairy products because they give him gas. He is a bit of a couch potato, and does not spend much time outside. Your initial physical examination finds an overweight male (BMI 30) in no acute distress, but with some stiffness and pain on flexion of the back.

What lab tests should be ordered?

The serum calcium and phosphorus come back at 9.1 and 2.9, respectively. 25OHD comes back as 15ng/ml. Twenty four hour urine calcium is 95mg, with creatinine of 1600mg. What additional information do you need? What is the approach to treatment?

Case 2

A 75 year old white female is referred to you with the tentative diagnosis of normocalcemic hyperparathyroidism. She was screened by her physician with DEXA, and a T score of -2.5 was noted in the lumbar spine. The physician sent off a PTH and serum calcium: the PTH was 120 pg/ml (upper limits of normal 65pg/ml) but the serum calcium was 9.4 mg/dl. The physician contemplated sending the patient to the local ENT surgeon for parathyroidectomy, but decided to get your opinion first. You obtain a history of a 3 inch loss of height over the past 20 years and a recent rib fracture after falling against the dining room table. The patient had a mild stroke a few years ago, and although she has fully recovered, she developed a seizure disorder for which she takes phenytoin. The patient lives alone, and doesn't get out much because of "arthritis" and some gait imbalance for which she uses a walker around the house. She cooks for herself, but her appetite is poor. Physical examination shows kyphosis and tenderness to fist percussion over the thoracic spine, with some pain on compression of the ribs. Mild symmetric weakness is noted in the proximal musculature.

What further tests do you want?
How should this patient be treated?

DISCUSSION OF CASES AND ANSWERS

Case 1

This patient most likely has osteoporosis, but the accurate determination of BMD using AP DEXA is obscured by the DJD in the spine—common in males of this age. A lateral DEXA of the spine and/or qCT could be ordered to document the expected low

BMD. The next question is the etiology of the osteoporosis. The history provides several possibilities. Heavy smoking and alcohol consumption could lead to osteoporosis. The lack of dairy products, lack of sunshine, and obesity all suggest vitamin D deficiency supported by the low 25OHD and reduced CaXP product even though both Ca and P values are within the normal range. The low urine calcium also supports the diagnosis of vitamin D deficiency. Although the low 25OHD would appear to confirm this diagnosis, the possibility that the patient has liver disease with reduced production of the carriers of vitamin D metabolites in blood, namely vitamin D binding protein (DBP) and albumin, should lead to measurement of LFTs including albumin (DBP measurements are not widely available). PTH also serves as a good marker for vitamin D deficiency and should be measured in this case. Liver disease per se is associated with osteoporosis, and generally is not improved with vitamin D when the "free" 25OHD levels are normal despite low total levels is in the situation of a low DBP and albumin level. Assuming that vitamin D deficiency is established, the use of oral vitamin D supplements to bring his level to 30ng/ml is indicated. Because of the obesity this will likely require on the order of 2000 IU/day. The rule of thumb I use is for every 1ng/ml of 25OHD elevation desired, provide 100 IU vitamin D/day. That would calculate out to 1500 IU/day in this patient, but given the obesity the patient will likely require more than that indicated by this rule of thumb.

Case 2

This patient has osteoporosis/osteomalacia. Although the high PTH indicates hyperparathyroidism, the mid normal serum calcium suggests that this is secondary rather than primary, and as such PTX is not indicated. A number of findings in the history and physical point to vitamin D deficiency and osteomalacia, rather than garden variety osteoporosis. These include the history of anticonvulsant use (which increases the catabolism of vitamin D metabolites) and the bone tenderness and proximal muscle weakness on physical exam. A low serum phosphorus, low 25OHD and low urine calcium confirm the diagnosis. The patient should be treated with vitamin D and calcium to restore her 25OHD levels to approximately 30ng/ml and her urine calcium to levels between 100-200mg/24hr. Her requirements for vitamin D may exceed those suggested by the rule of thumb discussed for case 1 because of the ongoing use of phenytoin.

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Risk Assessment Monitoring Bone Markers/Osteoporosis

M39
Monday, June 17
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Osteoporosis is a major public health problem and its prevalence is increasing especially as populations age. In Canada, as in many other parts of the world, approximately one in three or four women and one in five or six men, will suffer from an osteoporotic fracture during their lifetime. The morbidity and mortality associated with hip fractures has considerable medical, social and financial implications. But these fragility fractures are to some extent preventable. However, one has to identify those at risk in order to prevent the first and subsequent fragility fractures. A particular landmark publication by a working group of the World Health Organization in 1994 was the development of a diagnostic classification of osteoporosis based on bone density. This defined osteoporosis in a postmenopausal woman as a BMD of -2.5 or less compared to the young adult norm expressed as a T-score of -2.5 or lower. This value roughly corresponded with the fraction of the population sustaining fragility fractures although the majority of fragility fractures do not occur in women with a T-score at this level (i.e., while the fracture rate is highest among those with the lowest BMD the number of fractures is greatest in those with a nonosteoporotic BMD—simply because more of the population are in that category). The evaluation of persons suspected of having osteoporosis has evolved because the disease typically causes symptoms only when fractures have occurred, and the diagnosis was often made late. The development of tools such as bone mineral densitometry (BMD) especially in the spine and hip has allowed identification of individuals at risk of fragility fractures before the first fracture occurs. However, there has been a paradigm shift in the prevention and treatment of osteoporosis and fractures. The focus now is on preventing fragility fractures and their negative consequences rather than simply treating a low bone mineral density, which is viewed as only one of several risk factors for fragility fracture (albeit an important one). The WHO classification defining osteoporosis according to BMD, despite its merits, proved to be somewhat limiting for a number of reasons not the least of which was that it placed undue emphasis on the importance of BMD as a risk factor for osteoporotic fractures while obscuring the complexity of fracture risk which is due to many other factors. While not in any way negating the importance of bone mineral density, given that certain clinical factors increase the risk of fracture independent of bone mineral density, it is important to take an integrated approach and now to base treatment decisions on the absolute risk of fracture. Thus, appropriate interventions to prevent fractures need to accurately identify those at risk and therefore most likely to benefit from treatment. Unfortunately, many of those who sustain a fragility fracture are neither appropriately assessed nor treated. Many guideline recommendations have therefore focused on the assessment and management of women and men at high risk for fragility fractures. Because low BMD is only one (albeit, a very important one) of several risk factors for fracture, different societies and official bodies have developed guidelines and fracture risk assessment tools

(e.g., FRAX) adopting a system for ten-year absolute fracture risk assessment. In addition to try and better identify those at higher fragility fracture risk, biomarkers of turnover have also been measured although they are not yet officially incorporated into the different fracture risk models. However, in some situations they are being used for follow-up although not for diagnosis.

BARRIERS TO OPTIMAL PRACTICE

Despite the high prevalence of fragility fractures in different populations and the knowledge that fractures predict future fractures, an unacceptably low proportion of patients who have fractured receive appropriate assessment and therapy to prevent further fractures. A number of factors exist which act as barriers to optimal practice. The disparity between fragility fracture occurrence and the lack of subsequent osteoporosis management has been identified as the postfracture osteoporosis care gap. Until recently, many practitioners have not been concentrating on those at highest risk, i.e., the post-fragility fracture population.

LEARNING OBJECTIVES

Bone densitometry

- Understanding predictive power of bone densitometry technologies
- Performance overview of predictive power of densitometric methods
- BMD (and other predictors) predict fracture risk in vivo
  - Combination with clinical risk factors
  - Combination with (vertebral) fracture status
  - Combination with biomarkers
- Interpretation of risk estimates

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, TERAPY, AND/OR MANAGEMENT

Fracture Risk Assessment: BMD And Risk Factors

- The gradient of risk, i.e. increase in fracture risk for specific change in BMD depends on the technique used and the site measured. The relative risk increases by about 1.5-3.0 per SD decrease in BMD
- T-score has a different prognostic significance at different ages
- About half of fractures occur in postmenopausal women with low bone mass
- The combination of BMD with other risk factors improves the risk assessment (previous fracture, low body mass index, parental history of hip fracture, glucocorticoid treatment, current smoking, excessive alcohol intake, secondary causes of osteoporosis) and will allow us to identify postmenopausal women at higher risk
- Intervention thresholds should be based on fracture probability rather than on any particular level of BMD
- Treatment will be more efficiently targeted for those patients who will receive the greatest benefit

Many different osteoporosis guidelines including those in 2010 from Osteoporosis Canada use an integrated risk assessment (based on BMD and other risk factors) which allow the development of a treatment model to stratify women and men older than 50 years into fracture risk groups. These categories align with treatment implications: low risk (less than 10% 10-year fracture probability), moderate risk (10-20% 10-year fracture probability) and high risk (greater than 20% 10-year fracture probability). The computer based algorithm FRAX developed at the WHO Collaborating Centre for Metabolic Bone Diseases at the University of Sheffield in the UK provides models for the assessment of fracture probability in men and women. The approach uses easily obtained clinical risk factors to estimate 10-year fracture probability. The tool uses sex, age, body mass index, prior fracture, parental hip fracture, prolonged glucocorticoid use, rheumatoid arthritis (or other secondary causes for osteoporosis), current smoking, alcohol intake (more than 3 units daily) and bone mineral density of the femoral neck either as an absolute number or a T-score. Fracture risk discrimination using the WHO Fracture Risk Assessment Tool with BMD is better than the tool without bone mineral density or with bone mineral density alone. The relationship between BMD and fracture risk has been calculated in a large

number of studies. One of the earliest and still the most useful is the meta-analysis by Marshall et al of some of the earlier studies that document the fracture risk gradient. BMD is clearly the most readily quantifiable predictor of fracture risk for those who have not yet suffered a fragility fracture (although as already said it is not the only risk factor). But for each standard deviation of BMD below a baseline level, either peak bone mass or mean for the reference population of the person's age and sex, the fracture risk approximately doubles. The FRAX model has been calculated for different countries with country specific data. Thus, it is recommended that in the absence of a FRAX model for a particular country a surrogate country should be chosen based on the likelihood that it could be representative of the index country that will be used in the FRAX model for fracture assessment.

Recently official position statements have been developed by ISCD and IOF with respect for FRAX. Certain important questions have been addressed:

1. BMD at skeletal sites other than femoral neck for FRAX input. The official position is that measurement other than BMD or T-score at the femoral neck by DXA are not recommended. The FRAX algorithm was calibrated for use with femoral neck BMD based upon the strength of the association with subsequent fractures (particularly hip fractures) in the FRAX derivation cohorts and the availability of a standardized young adult reference database (NHANES III white female for calculation of T-scores). Lumbar spine BMD is also strongly associated with future fracture risk especially spine fractures but is not incorporated in the FRAX algorithm. (A method described by Dr. William Leslie for incorporating lumbar spine density when it is lower than femoral neck density will be presented during the workshop.) The procedure is based upon the difference (offset) between lumbar spine and femoral neck Tscores.
2. How useful is FRAX without BMD? The official position taken is that FRAX with BMD predicts fracture risk better than clinical risk factors or BMD alone, but that FRAX without BMD is appropriate when DXA facilities are not readily available. In sensitivity analyses, the positive predictive value and number needed to treat were always better for the combination than either BMD or clinical risk factors alone across all ages studied. Two separate Canadian studies have demonstrated the ability of FRAX with or without BMD to predict hip fractures and major osteoporotic fractures. Despite the good predictive value of FRAX to identify fracture risk in treatment naïve patients, it is not appropriate to use FRAX to monitor treatment response. At present, many clinicians do use BMD measurements and/or biochemical markers (see below) to determine the response to treatment. Having a tool that quantifies the risk for fracture following treatment would indeed be useful, however, more research is necessary to define treatment response and to determine if changes in FRAX scores truly reflect the treatment response. Thus, it is important to determine whether changes in the FRAX scores truly reflect changes in the risk for fracture and the actual fracture incidence in treated patients. Finally, the evidence that the rate of bone loss maybe an independent risk factor for fracture is still somewhat controversial and for that reason the rate of bone loss has not yet been included as a FRAX risk factor. The current official position is that unless compelling and consistent data emerge of a relationship between rate of bone loss and fracture risk that is independent of the final BMD it is not appropriate to incorporate rate of loss in the FRAX algorithm.

Different organizations have different thresholds and recommendations for treatment based on fracture risk assessment.

NOF recommendations: www.nof.org/professionals/Clinicians_Guide.htm

Healthcare providers should consider FDA-approved medical therapies in postmenopausal women and men age 50 and older based on the following:

A hip or vertebral (clinical or morphometric) fracture

- T-score ≤ -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes.
- Low bone mass (T-score between -1 and -2.5 at the femoral neck or spine) and a 10-year probability of a hip fracture ≥ 3% or a 10-year probability of a major osteoporosis-related fracture ≥ 20% based on the US-adapted WHO algorithm.
- Clinician's judgment and/or patient preferences may indicate treatment for people with 10-year fracture probabilities above or below these levels.

Canadian guidelines algorithm: Papaioannou A, et al. CMAJ 2010:182;1864-1873

Bone Turnover Markers Objectives

- What are bone turnover markers (BTMs)?
  - How do we measure them?
- Have they been validated?
- What are they usually used for?
- What are the goals for treatment monitoring?
  - Anti-catabolic treatments
  - Anabolic treatments
- Practical considerations in the use of BTMs

While BMD by DXA is one of a number of factors that quantify fracture risk, bone turnover markers (BTMs) are emerging as promising tools in the assessment and management of osteoporosis. They provide dynamic information regarding skeletal status that is independent from and often complementary to BMD measurements. In the past, BTMs were primarily reserved for research, however, with recent refinements in methodology and clinical measurement, the clinical data linking BTMs to fracture risk and the use of BTMs is increasing in clinical practice. Perhaps the greatest challenge for the adoption of BTMs within the clinical setting is the potential variability. It is, therefore, essential to understand the pre-analytical and analytical variability and employ an appropriate strategy to minimize them. A variety of pre-analytical factors influence

FIGURE 1

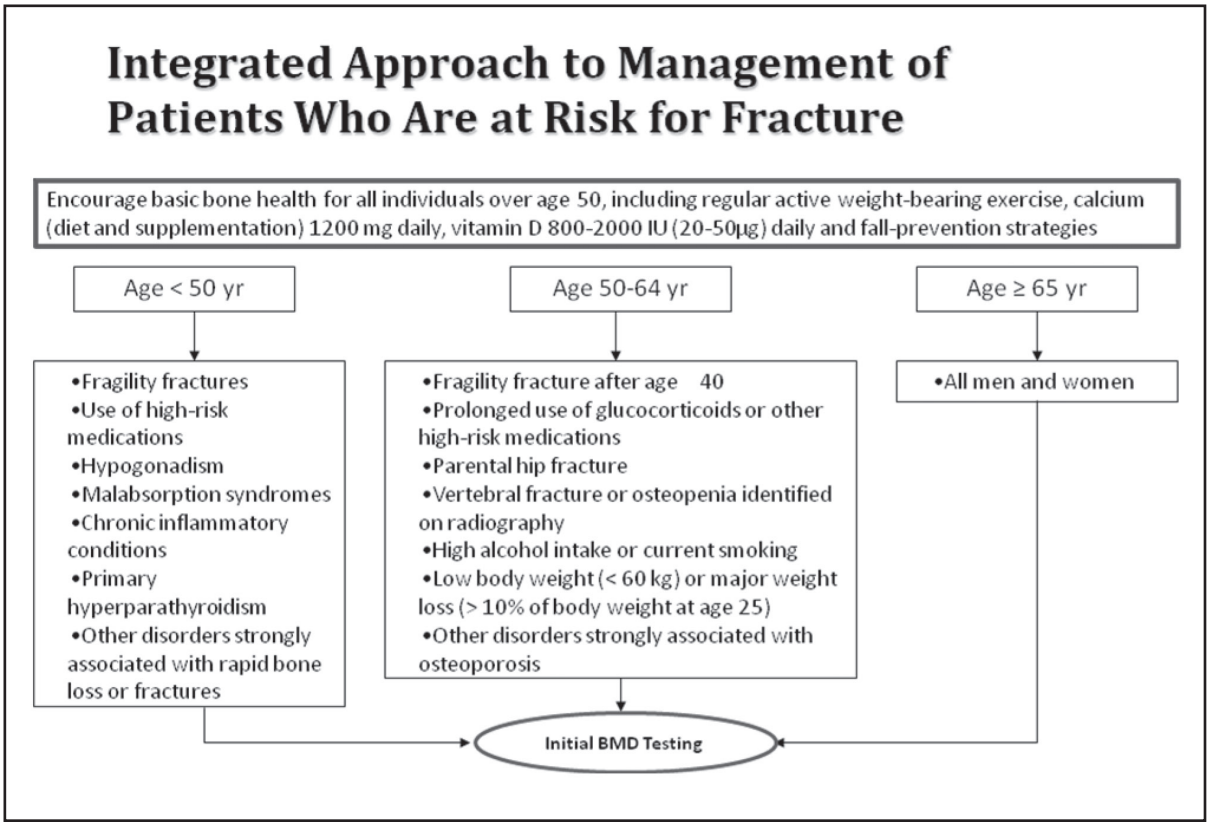


FIGURE 2

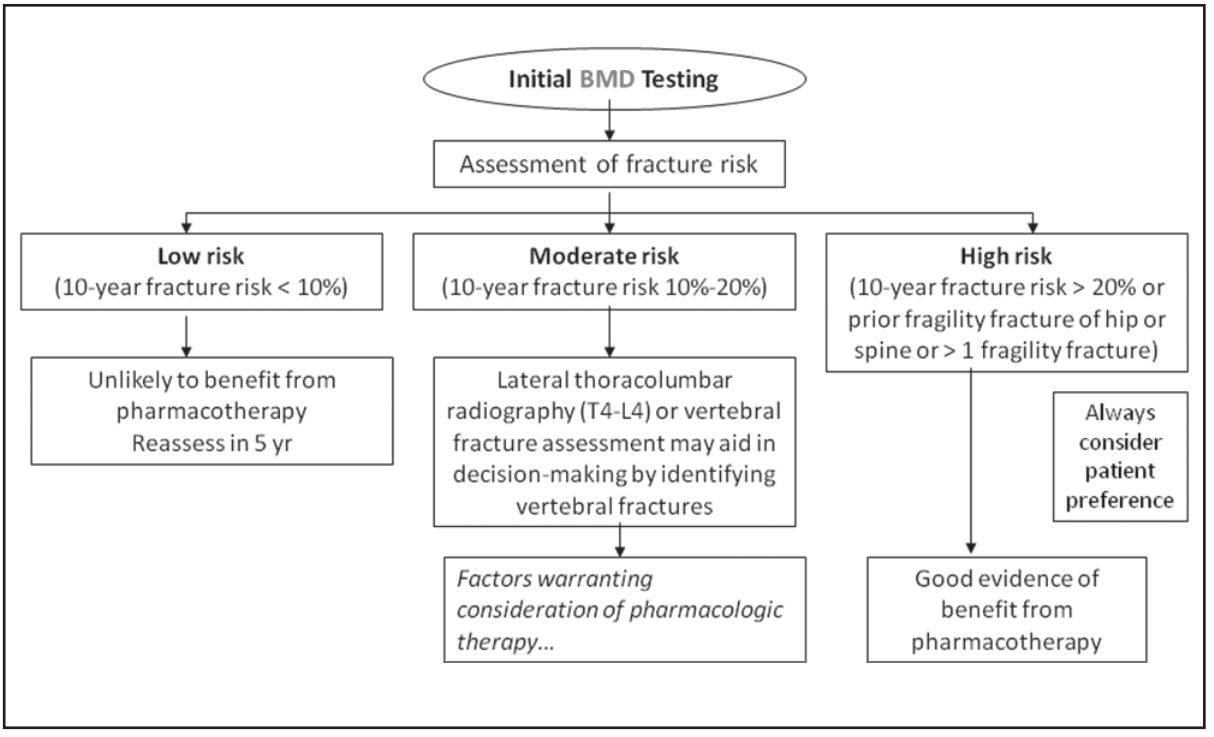


FIGURE 3

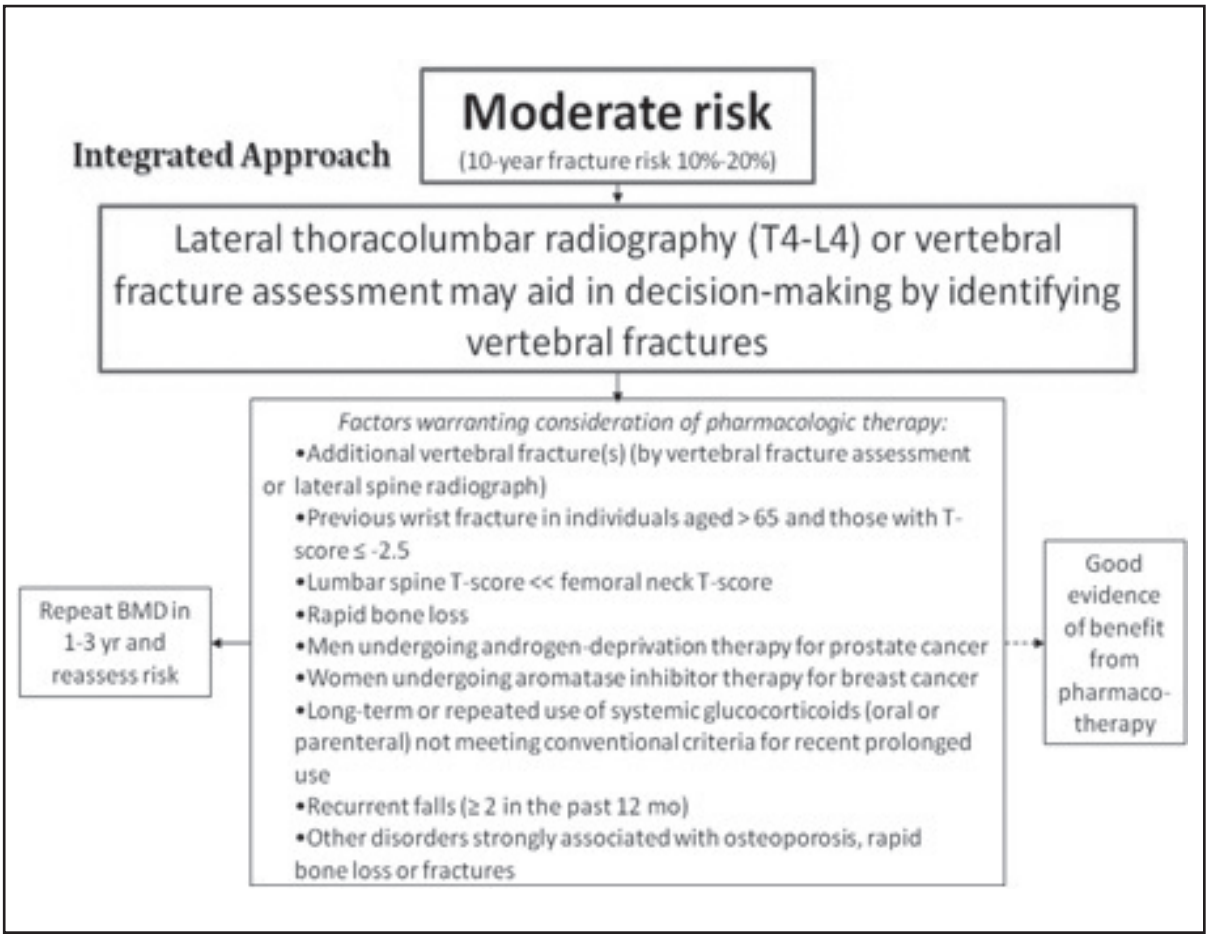


FIGURE 4

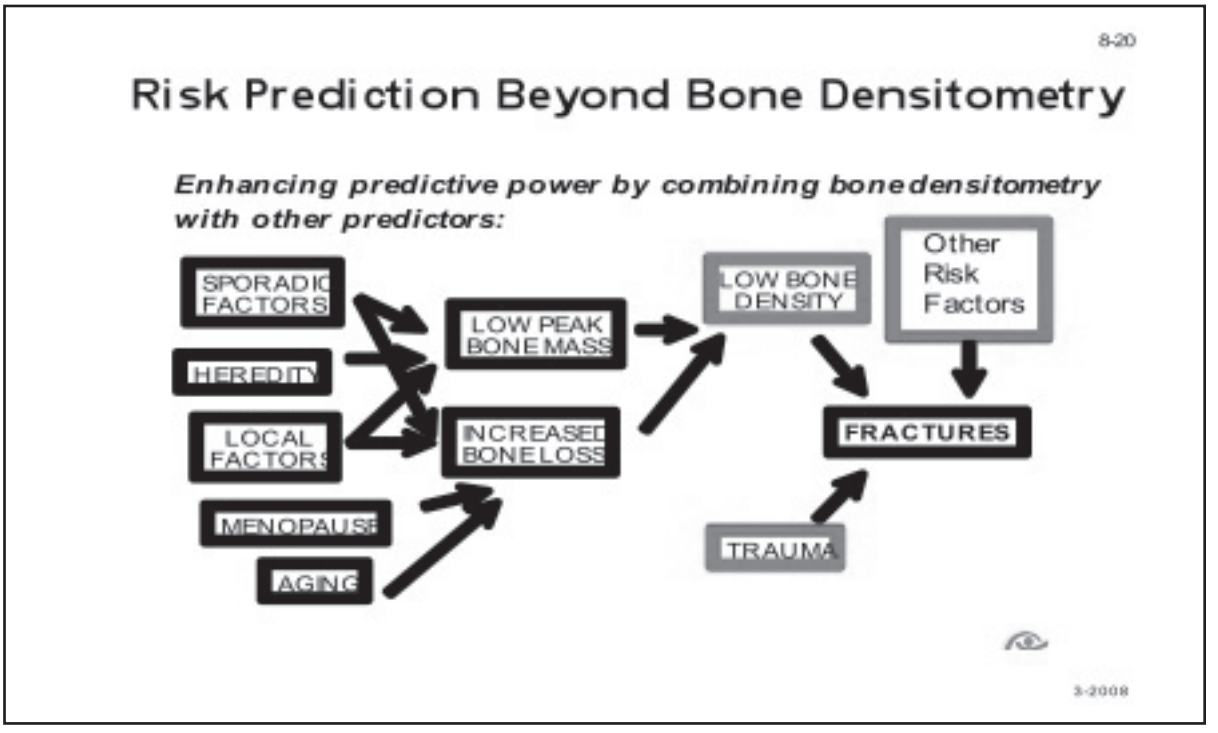


FIGURE 5

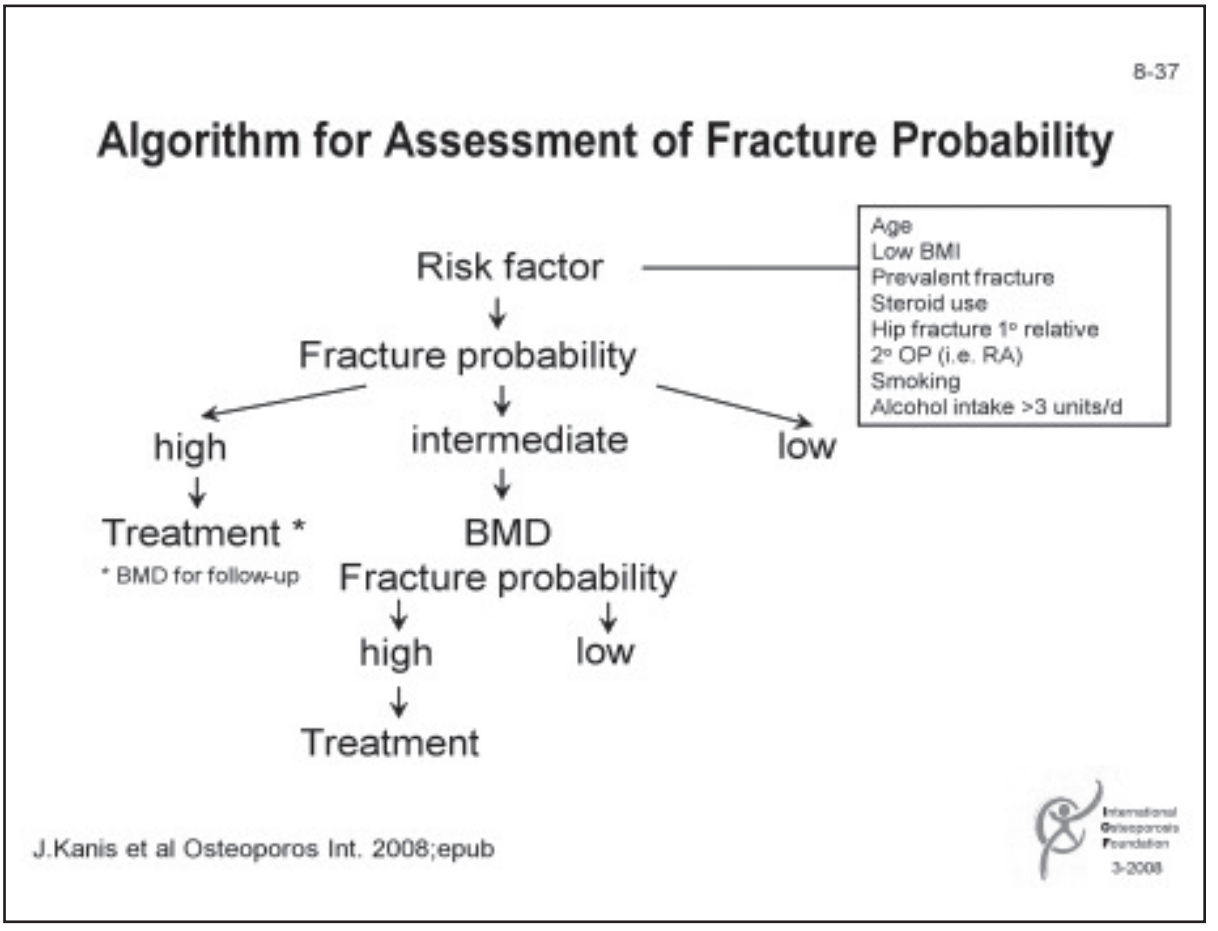
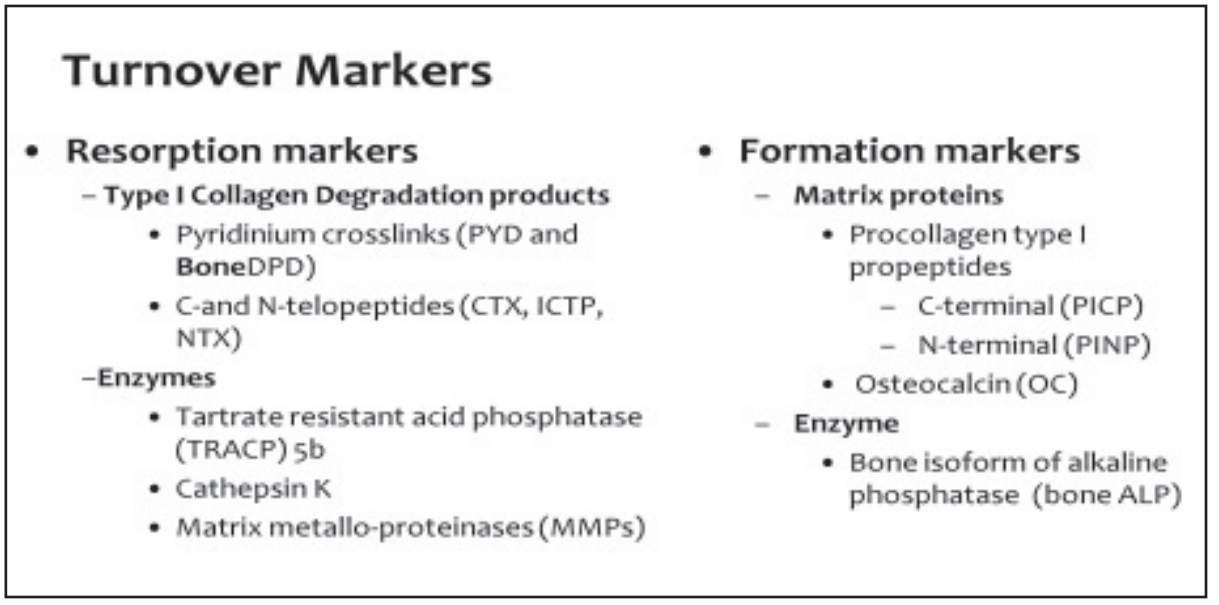


FIGURE 6



BTM concentrations and thus their variability when measured. These include food intake, growth, sex, seasonal changes, circadian and menstrual variations, exercise habits, recent fractures, age, immobility and diseases that cause secondary osteoporosis. Most BTMs show a circadian rhythm peaking in the early morning with a trough in the afternoon and evening. This variability has been reported to be greater for resorption than for formation markers. Since the skeleton is responsive to mechanical loading, this has to be taken into account when assessing BTMs. A single session of exercise can increase BTM concentration by 15-40% for up to 72 hours depending upon the intensity and duration of the exercise. Conversely, immobility known to lead to rapid losses in bone mass can substantially increase resorption markers. *Figure 6* shows the different types of markers of resorption and formation.

BTMs are valuable for assessing the dynamic nature of bone. When paired with static BMD data, BTMs may enhance the estimation of the future risk of fracture and may independently provide a tool for the monitoring of therapy. The two most commonly measured turnover markers are serum C-telopeptide as a resorption marker and bone specific alkaline phosphatase as a formation marker although N-terminal pro-collagen type 1 propeptide (P1NP) is becoming more popular. It has low diurnal variability and stability at room temperature. Moreover, its circulating levels are not significantly influenced by food intake and consequently patients do not need to be fasting. P1NP is primarily metabolized by the liver and its clearance is unaffected by renal dysfunction.

Alkaline phosphatase is a ubiquitous ecto-enzyme, which catalyzes the hydrolysis of monophosphate ester groups. The potential advantages for using ALP in clinical practice include sample stability, low biological variability (less than 10%), lack of renal function concern and very low diurnal variability.

For bone resorption markers, the C-telopeptide crosslink of type 1 collagen is favored. Serum CTX concentrations have been shown to have a large circadian variation that can be diminished by fasting. They are strongly influenced by food intake so samples really need to be taken at the same time of day and in a fasting state. The serum CTX has shown large decreases after initiation of bisphosphonate or other anti-resorptive therapy, e.g., denosumab.

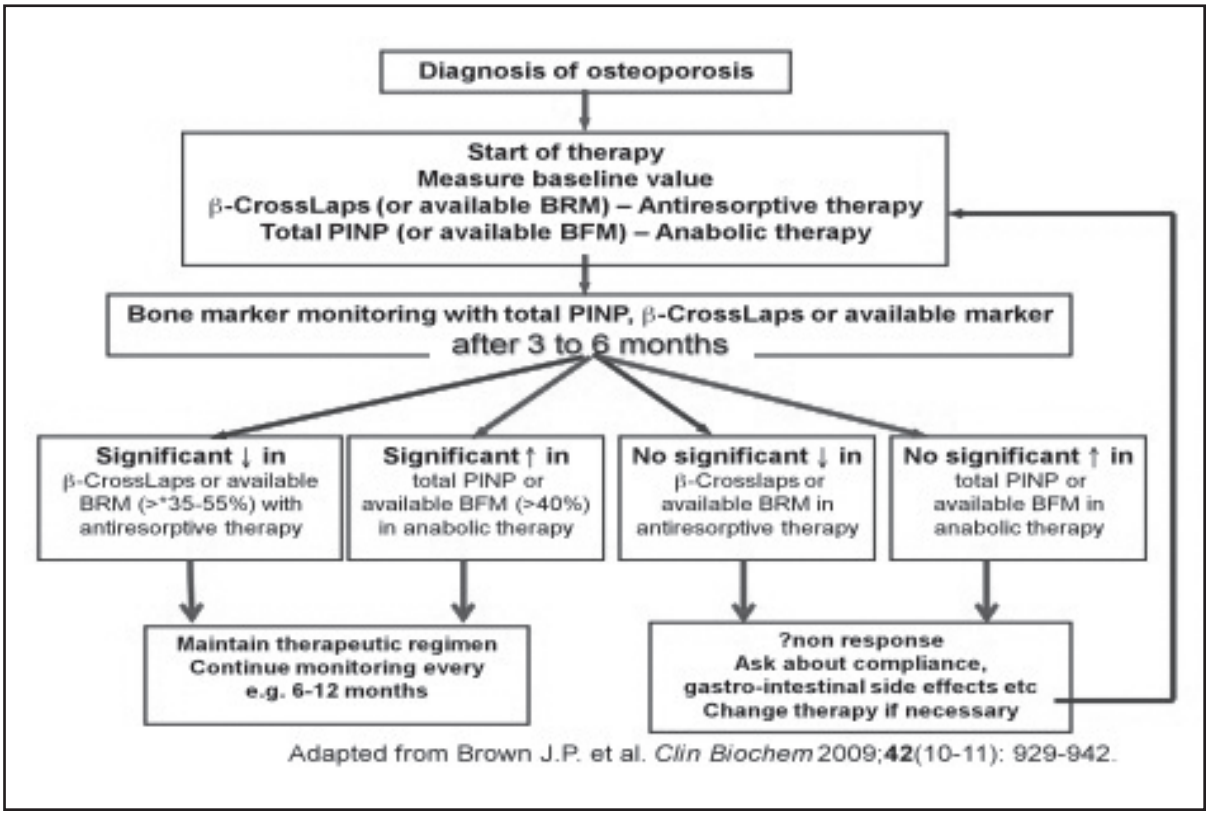
Clinical Use of Bone Turnover Markers

While population studies consistently report increased levels of BTMs in groups of

women with postmenopausal osteoporosis and inverse relationships between BMD and BTM concentrations particularly in the elderly, BTMs cannot be used to diagnose osteoporosis in an individual. Prospective studies investigating the relationship between baseline BTM and future fracture risk have yielded some inconsistent results. However, a number of prospective population based studies have reported that increased levels of resorption markers are associated with an approximate two-fold increased risk of fracture (vertebral and non-vertebral) compared to women with normal BTM levels. In estimating the 10-year absolute risk of hip fracture, the combination of one elevated resorption marker (CTX) with an osteoporotic BMD or history of previous fracture resulted in a higher risk prediction than that identified with low BMD alone.

Theoretically, baseline levels of BTMs could be used to guide treatment decisions. In women with low remodeling rates with low levels of resorption markers, one might favor an anabolic agent over antiresorptive therapy. Several studies have indeed found a significant association between the level of bone remodeling and the BMD response to anti-resorptive agents. However, most clinical trials have shown that the anti-fracture efficacy of osteoporosis therapies is largely independent of the baseline turnover. More data are therefore needed to guide treatment decisions and estimate treatment responses and at the moment BTMs are not yet recommended for that purpose. Monitoring of response to therapy and postmenopausal osteoporosis is however possible. Measurement of BMD by DXA is the most widely used surrogate marker for response to antiosteoporotic therapy. However, using BMD to determine therapy response may take one to two years. In contrast, clinical trials of various anti-resorptive therapies have reported a rapid decrease in bone resorption markers within weeks after initiation of therapy plateauing after between three to six months. In post hoc analyses of several clinical trials early reductions in bone turnover markers predicted long-term fracture reduction. Moreover, with

FIGURE 7



Adapted from Brown J.P. et al. *Clin Biochem* 2009;**42**(10-11): 929-942.

anabolic therapy, e.g., parathyroid hormone, one can assess the response by measuring bone formation markers which rise early compared to bone resorption markers which increase later, giving rise to the so-called anabolic window.

Despite their relatively high variability both pre-analytically and analytically, the differences in BTMs between those with normal and elevated turnover are generally greater. This characteristic allows for the use of BTMs to identify persons at high risk for bone loss and presumably subsequent fracture. Furthermore, the use of BTM to monitor the efficacy of osteoporosis therapies does hold promise and may indeed enhance adherence to antiosteoporosis therapy although this has not yet been conclusively proven.

Websites with useful data for physicians, including slide kits, guidelines, algorithms etc., are as follows: www.nof.org, National Osteoporosis Foundation; www.shef.ac.uk/NOGG, National Osteoporosis Guideline Group; www.iofbonehealth.org, International Osteoporosis Foundation;

www.osteoporosis.ca, Osteoporosis Canada; www.bonekey-ibms.org, International bone and mineral society; www.ISCD.org, International Society for Clinical Densitometry.

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4. Websites Useful data for physicians including slide kits, guidelines, algorithms etc.

Male Osteoporosis

M24
Sunday, June 16
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Osteoporosis occurs in both men and women but the diagnosis and treatment of osteoporosis in men has received significantly less attention from both the research community and from clinicians. While the incidence of fragility fractures at most anatomic sites, including the hip, is about one third in men compared to women, mortality after hip fracture is 2-3 times greater, approaching 20-30% in men (1-3). Despite the large impact of osteoporosis in men, only a small minority (<10%) of male patients are treated with an approved anti-osteoporosis medication, even after experiencing a hip fracture (2, 4). Improvements in the care of these patients will require sustained educational initiatives aimed at both physicians and patients.

BARRIERS TO OPTIMAL PRACTICE

- Lack of appreciation of the scope of the clinical problem.
- Lack of familiarity with current recommendations for screening and treatment.

LEARNING OBJECTIVES

- Be familiar with the prevalence and consequences of male osteoporosis.
- Understand the contributions of clinical factors to fracture risk and the influence of hypogonadism to skeletal health.
- Assess the efficacy of both antiresorptive and anabolic therapies in male osteoporosis.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

As discussed above, osteoporosis in men is an under-diagnosed clinical entity that carries vast public health ramifications. Just as in women, the most important method of assessing fracture risk in men is the measurement of bone mineral density (BMD) by dual x-ray absorptiometry (DXA). Additionally, the online FRAX tool, which estimates 10-year hip and major osteoporosis fracture risk can be used in men and has become a part of the treatment recommendations published by various expert committees (http://www.shef.ac.uk/FRAX/tool.jsp). Based on the current WHO definition of osteoporosis (T-score ≤ -2.5 using a male data base), is has been estimated that 3-6% (1-2-million) of American men over 50 have osteoporosis and 28-47% (8-13 million) have osteopenia (5). Factors that contribute to osteoporosis in men (other than advancing age which is the most important contributor) include low body mass index, smoking, excessive alcohol use, corticosteroid use, hypogonadism, and diabetes (6).

Given this wide prevalence of osteoporosis in men, the National Osteoporosis Foundation currently recommends that all men over 70 and men between the ages of 50-70 who have additional risk factors for osteoporosis be screened by bone mineral density DXA measurements of the hip and spine, though actual practice patterns are not nearly approaching that degree of intensive screening (NOF guidelines can be found at: http://www.nof.org/files/nof/public/content/file/950/upload/523.pdf).

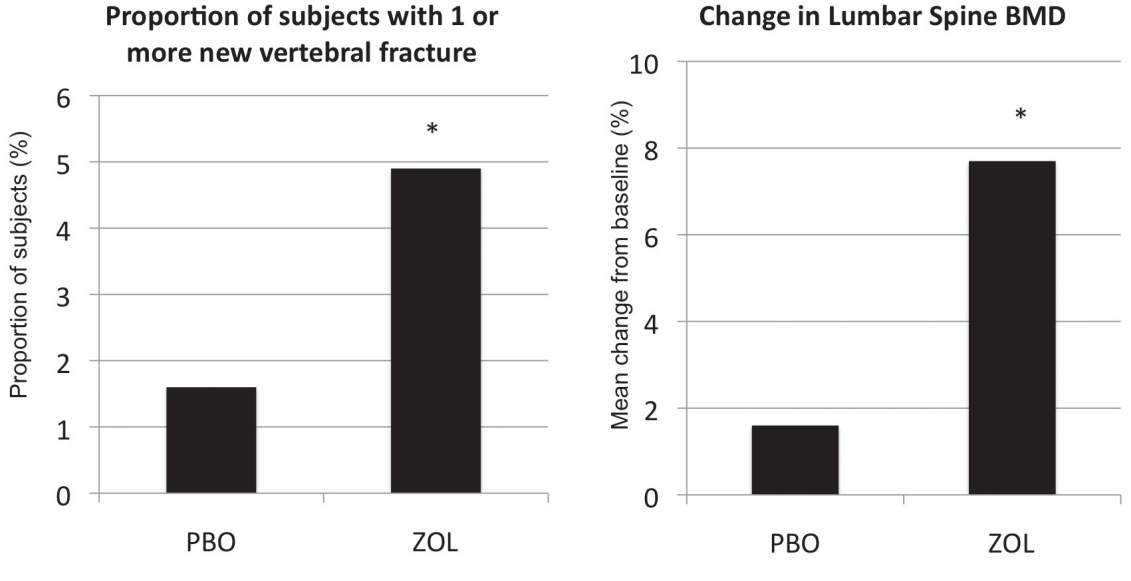
Of the various clinical risk factors connected to male osteoporosis, the role of hypogonadism in male osteoporosis has received special

attention over the past decade. Specifically, research has focused on the potential skeletal impact of the natural decline in gonadal steroid production that occurs with aging. While both epidemiologic and experimental studies have suggested that estrogens are likely the predominate gonadal steroid regulator of bone health in adult men, the measurement of testosterone remains the most useful method of assessing gonadal steroid sufficiency as a specific estrogen deficient state (independent of androgen deficiency) has not been defined. Furthermore, because the level of testosterone deficiency at which bone health is compromised is undefined, clinical trials assessing the effects of testosterone replacement on bone mineral density have used inconsistent definitions of hypogonadism. This inconsistency has resulted in the conflicting results and continued controversy regarding the skeletal efficacy of testosterone replacement in aging hypogonadal men.

For example, in a randomized controlled trial of 103 older men with baseline testosterone levels less than 475 ng/dl receiving either topical testosterone or placebo for three years, the group receiving testosterone failed to demonstrate greater increases in spine bone mineral density than the placebo group (primary endpoint). While a subgroup analysis of this study did suggest that men with the lowest baseline testosterone levels may have experienced some BMD benefit, the clinical significance of this post-hoc finding remains uncertain (7). In contrast, in a 3-year study of men with more significant hypogonadism (n=70), treatment with parenteral testosterone at slightly greater than replacement doses did increase BMD significantly (8). There are no dedicated fracture trials of testosterone replacement in men and the role of testosterone replacement in the treatment of hypogonadal bone loss remains undefined, especially in the context of the safety issues surrounding androgen replacement in the elderly.

FIGURE 1

Figure 1: *Boonen et al. NEJM 2012:* 24-month double-blind RCT of 1199 men aged 50-85 with primary or hypogonadism-associated osteoporosis assigned to receive placebo or zoledronic acid 5 mg yearly.



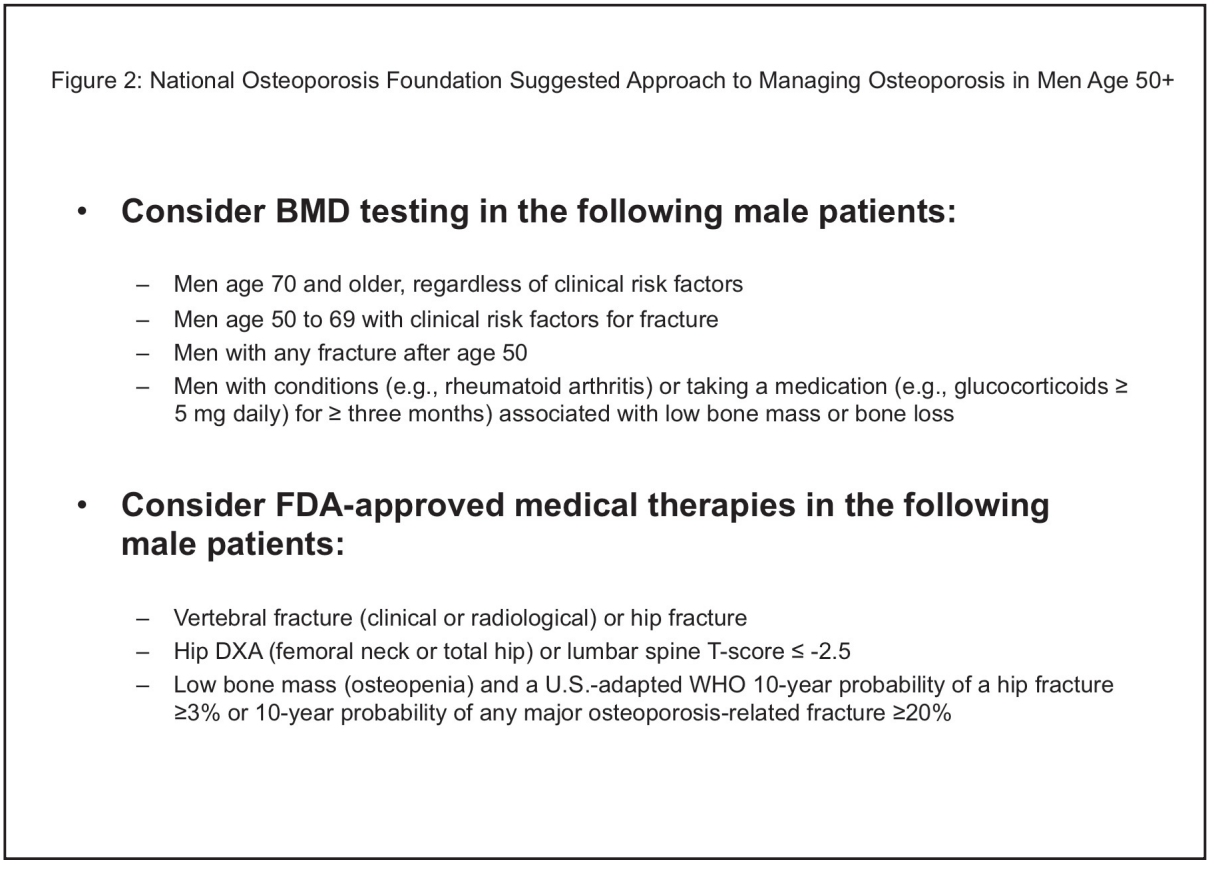
There are currently several therapies that are FDA-approved for the treatment of osteoporosis in men. With the exception of zoledronic acid, where a recent study demonstrated that treatment reduces morphometric vertebral fractures, none has been studied in large enough numbers to adequately assess fracture reduction (9). All of these agents, however, have been shown to increase bone mineral density to a similar degree as postmenopausal women and the effect appears to be independent of preexisting hypogonadism. This holds true not only for the antiresorptive agents studied (alendronate, risedronate, ibandronate, zoledronic acid, denosumab), but also for teriparatide (9-14).

Given that there are no comparative efficacy trials in men, treatment decisions should likely be made on the basis of cost and tolerability. Current guidelines from both the National Osteoporosis Foundation and the Endocrine Society recommend that treatment should be initiated in all men in whom DXA-derived BMD T-score (gender-matched) is less than -2.5 at the femoral neck, total hip, or spine and in all men 50 years and older who have T-scores between -1 and -2.5 if their FRAX-derived 10-year hip fracture risk is exceeds 3% or their 10-year major osteoporosis-related fracture risk exceeds 20% (15).

MAIN CONCLUSIONS

Despite its large impact on public health, osteoporosis in men is an under-recognized, under-diagnosed, and under-treated entity. Excellent diagnostic screening tests and fracture risk assessment tools are widely available for the motivated clinician and effective, well-tolerated, therapy is available for those at increased risk of fragility fracture. Because it still unclear if testosterone replacement alone is sufficiently efficacious in the setting of concomitant osteoporosis and hypogonadism, specific antiresorptive or anabolic therapy should be initiated in all men at elevated risk of fracture independent of whether testosterone replacement is being used for other indications.

FIGURE 2



CASES WITH QUESTIONS

Case 1

ID/CC: 41 year-old WM, extreme sports enthusiast, who is referred for multiple spinal fractures.

HPI: Generally healthy until 3 years ago when, while skiing in Utah, had a "head-over-heels" fall resulting in T7 and T10 compression fractures.

PMH: Previous fractures T11 and T12 in his early twenties (also while skiing). Multiple rib fractures, sternum, hand, related to mountain biking, skiing, during his 30s.

He denies seizure disorder or anticonvulsant use, nephrolithiasis, known thyroid, parathyroid, hepatic, or renal disease, known hypogonadism. He was an avid milk drinker as a child and still drinks 2 glasses/day. He reports a normally timed puberty.

MEDS: CaCO3 1200 mg QD, 1 MVI QD

FH: Mother was diagnosed with OP in her late 70s (no fractures)

He has no FH of hypercalcemia, nephrolithiasis, or other endocrine disease.

SH: Married with 2 children (last one born 12 months ago). He works as an executive in large Boston-area financial company. He has 2 drinks/day and an occasional cigarette/cigar . He continues ski, cycle, runs, lift weights.

PE: 6 feet, 178 pounds, normotensive.
Normal appearance (not Cushingoid).
No rash or pigment changes.
Normal beard development and muscle mass.
Normal thyroid.
Slight kyphosis in mid-thoracic region.
Testes 20 cc bilaterally.

DATA:
Normal electrolytes (Cr = 1.0)
Ca/Phos/Alb = 9.1/3.1/4.4
TSH =0.80
PTH = 21 pg/ml
25-D = 29.3 ng/ml
Testosterone = 385 ng/dl
Normal SPEP
24-hour urine #1: Total volume = 3110 ml, Cr = 1775 mg, Ca = 390 mg
24-hour urine #2 Total volume = 2395 ml, Cr = 1600 mg, Cortisol = 35 mcg
Urinary NTX = 38 nmol BCE/mmol Cr

Questions:
What are the next diagnostic steps? Is a bone biopsy indicated? Should empiric therapy be started? Which medication should be used?

Case 2

73 year-old WM fell on ice and fractured left femoral neck. He is referred after completing rehabilitation.

PMH: +hypertension, +COPD (no oral glucocorticoid use).

He denies seizure disorder or anticonvulsant use, nephrolithiasis, known thyroid, parathyroid, hepatic, or renal disease, known hypogonadism. Rare dairy intake. He cannot recall if his puberty was normally timed.

MEDS: albuterol, lisinopril.

FH: He has 2 sisters, both of whom have experienced height loss and have documented osteopenia by DXA.

SH: Retired accountant. Non-smoker, no ETOH

ROS: Prior to his fall, he reports that he felt generally well, though he has been experiencing a decrease in libido and overall energy in past several years.

PE: 5 feet 9 inches, 155 pounds.
Normal appearance (not Cushingoid).
Normal thyroid.
Testes 15-20 cc bilaterally.

DATA:
Normal electrolytes (Cr = 1.2)
Ca/Phos/Alb = 9.0/3.3/4.0
TSH =1.80
PTH = 59 pg/ml
25-D = 19 ng/ml
Testosterone = 205 ng/dl
Testosterone (repeated) = 267 ng/dl
LH = 7.2
PRL = 8
24-hour urine: Total volume = 1310 ml, Cr = 1300 mg, Ca = 174 mg

Questions:
What are the next diagnostic steps? Is a pituitary MRI indicated? Should the patient be treated with testosterone replacement alone? Should the patient be treated with a bisphosphonate alone? Should the patient be treated with both testosterone and a bisphosphonate?

DISCUSSION OF CASES AND ANSWERS

Cases discussions will be interactive with particular emphasis on identifying areas that are not addressed with robust randomized controlled trials.

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Hyperparathyroidism: Diagnosis and Medical Therapy

M29
Sunday, June 16
1:00–1:45 PM & 3:00–3:45 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM.
The most common clinical presentation of modern day primary hyperparathyroidism (PHPT) is asymptomatic hypercalcemia that is detected by routine biochemical screening. Classical PHPT was characterized by symptoms and signs that reflected the effects of increased PTH secretion and hypercalcemia, known as "bones, stones, abdominal moans and psychic groans." However, the introduction of the multichannel serum autoanalyzer in the 1970s led to the recognition of a cohort of individuals with asymptomatic hypercalcemia, in whom evaluation led to the diagnosis of PHPT. The term "asymptomatic primary hyperparathyroidism" was introduced to describe patients who lack obvious signs and symptoms referable to either excess calcium or parathyroid hormone. In the United States and in most parts of the world, the asymptomatic phenotype of PHPT has replaced classical PHPT.

BARRIERS TO OPTIMAL PRACTICE.
Although classical features of PHPT are not typically seen today, asymptomatic PHPT can be associated with other characteristics involving the skeleton and the kidney. Additional organ systems may be involved, leading to cardiovascular and neuropsychological manifestations. Although parathyroidectomy is indicated in all patients with overt clinical symptoms, there is controversy over the need to treat those patients who are diagnosed in the absence of clear symptomatology.

LEARNING OBJECTIVES.
As a result of participating in this session, learners should be able to:
- Review features of asymptomatic PHPT and the criteria for parathyroidectomy
- Review medical treatment options for PHPT

STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT.
Diagnosis:
The biochemical hallmarks of PHPT include elevated serum calcium levels in the presence of elevated or inappropriately normal levels of PTH. All nonparathyroid causes of hypercalcemia are associated with levels that are suppressed. In asymptomatic individuals, the differential diagnosis of hypercalcemia and abnormal PTH levels include other causes such as drug-associated PHPT or familial hypocalciuric hypercalcemia. Advances in PTH measurement techniques, involving second and third generation PTH assays, can help with diagnosis. It is now recognized that specific diagnostic criteria characterize the newly recognized phenotype of normocalcemic hyperparathyroidism.

Therapy:
Criteria for parathyroidectomy include: serum calcium 1 mg/dl about the upper limit of normal; estimated golmerular filtration rate <60 ml/min; T-score < 2.5 at any site or fragility fracture; age younger than 50 years.

Pharmacologic therapy has been studied in mild PHPT, although no drugs are approved for use specifically in patients with asymptomatic PHPT. Estrogen and raloxifene modestly lower serum calcium levels while bisphosphonates have been associated with

improvements in bone density. Cinacalcet, which is approved for severe PHPT and parathyroid cancer, normalizes serum calcium.

MAIN CONCLUSIONS

Asymptomatic PHPT is the most common type of PHPT in many parts of the world. Most of the patients do not evolve to become overtly symptomatic. Data are available on treatment indications and options for those with asymptomatic disease.

CASES

Cases to be presented at session

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Idiopathic Osteoporosis in Premenopausal Women

M53
Tuesday, June 18
11:15 AM to 12:00 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Osteoporosis is most commonly diagnosed in postmenopausal women and older men. However, premenopausal women may present with either low bone mass or fractures and few data exist to guide their management. Although idiopathic osteoporosis (IOP) in premenopausal women is rare, such patients often present challenges in diagnosis and management.

BARRIERS TO OPTIMAL PRACTICE

- Lack of data on significance of low bone mineral density (BMD) measurements in premenopausal women
- Lack of awareness of the clinical significance of low trauma fractures in premenopausal women
- Lack of clinical trial data on treatment of osteoporosis in premenopausal women

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- To understand the significance and causes of low BMD in premenopausal women
- To understand the microstructural, remodeling and bone material property characteristics of bone in women with IOP
- To understand the principles of management of osteoporosis in premenopausal women with secondary osteoporosis and IOP

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Diagnosis and Etiology of Osteoporosis in Premenopausal Women

In postmenopausal women, osteoporosis is defined as a BMD of the spine, hip, or forearm more than 2.5 SD below the young adult mean (T-score ≤-2.5), with or without the presence of a low trauma fracture; osteopenia refers to T scores between -1.0 and -2.5. In premenopausal women, T scores should not be used to categorize BMD, the term "osteopenia" should not be used at all, and the term "osteoporosis" should be used judiciously.

Z scores, which compare a young woman's BMD to the mean of an age-, gender-, and ethnicity-matched reference population, should be used instead of T scores to categorize BMD measurements. Based on the definition of a Z-score, which encompasses 95% of the normal population, 2.5% of premenopausal women will have a Z-score < 2.0. A Z score that is ≤-2.0 should be designated "low bone density" or "below expected for age".

The term "osteoporosis" should be avoided in premenopausal women with isolated low BMD measurements, because the degree to which isolated low BMD measurements predict short-term (5-10 year) fracture incidence in young women is unknown. In addition, the clinical significance of isolated low BMD measurements is uncertain. Some premenopausal women with small skeletons may appear to have low BMD, because DXA scanners cannot distinguish between small bones and less dense bones. Thin premenopausal women may have low BMD because their skeletons are adapted to carrying lower loads. They may also have low BMD because they have genetically determined low peak bone mass. It is generally assumed

that such women have normal bone quality (normal trabecular and cortical volumetric BMD and microarchitecture and stiffness or strength), although there are no data to support this assumption.

On the other hand, during adolescence, certain life style choices (excessive alcohol, tobacco exposure, low calcium intake, physical inactivity) or an underlying illness or exposure to certain medications (glucocorticoids, Depo-Provera) may interfere with peak bone mass acquisition. Such secondary causes of osteoporosis, which may also cause excessive bone loss after adolescence, may be associated with abnormal bone quality, although again there are few data. Lactation is associated with losses of 3-10% at the spine and hip over the first 3-6 months with recovery after weaning over the next 12-18 months. Therefore, BMD measurements should not performed for at least a year after pregnancy or lactation, during this period of transient loss and recovery.

Routine BMD screening of premenopausal or perimenopausal women is not recommended unless there is a history of fragility fracture(s), or conditions or medications associated with low bone mass or bone loss (estrogen deficiency, glucocorticoids, etc.). Premenopausal women with a low trauma fracture or Z score ≤-2.0 should have a thorough history, physical examination and laboratory evaluation to identify potential secondary causes of bone loss, such as renal or liver disease, hyperthyroidism, hyperparathyroidism, Cushing's syndrome, early menopause, other disorders associated with estrogen deficiency, such as anorexia, celiac disease and other forms of malabsorption, idiopathic hypercalciuria, or connective tissue disorders.

TABLE 1: Secondary causes of osteoporosis in premenopausal women

• Anorexia nervosa
• Gastrointestinal malabsorption (eg. celiac disease, postoperative states)
• Vitamin D and/or calcium deficiency
• Hyperthyroidism
• Hyperparathyroidism
• Cushing's syndrome
• Hypogonadism
• Hypercalciuria
• Rheumatoid arthritis and other inflammatory conditions
• Alcoholism
• Renal Disease
• Liver disease
• Osteogenesis imperfecta
• Marfan's syndrome
• Homocystinuria
Medications
• Glucocorticoids
• Immunosuppressants (cyclosporine)
• Antiseizure medications (particularly phenobarbital and phenytoin)
• GnRH agonists (when used to suppress ovulation)
• Heparin
• Cancer chemotherapy
• Depot medroxyprogesterone acetate
• Excess thyroid hormone

TABLE 2. Guidelines for BMD Testing in Premenopausal Women

• History of fragility fracture
• Diseases or conditions associated with low bone mass or bone loss
° Premenopausal estrogen deficiency (e.g., anorexia nervosa, hyperprolactinemia, prolonged amenorrhea)
° Chronic obstructive pulmonary disease
° Cystic fibrosis
° Hyperparathyroidism
° Rheumatoid arthritis
° Inflammatory bowel disease
° Celiac disease
• Medications that cause bone loss
° Glucocorticoids
° Depot progesterone
° GnRH agonists
° Aromatase inhibitors
° Antiepileptic drugs (phenobarbital, phenytoin, carbamazepine, valproate)
• If pharmacologic therapy of osteoporosis is being considered
• Being monitored for effectiveness of pharmacologic therapy for osteoporosis

Idiopathic Osteoporosis in Premenopausal Women

Premenopausal women with no identifiable etiology after extensive evaluation for secondary causes are said to have idiopathic osteoporosis (IOP). Idiopathic osteoporosis primarily affects Caucasians, men and women equally. Women often present during pregnancy or lactation. The mean age at diagnosis is in the mid-thirties. Fractures are usually multiple, occurring over a 5 to 10 year period. Abnormalities of osteoblast function and decreased IGF-1 have been found in most studies of men with IOP. In a recent bone biopsy study of women with IOP, both those with fractures and those with Z scores ≤ 2.0 but no fractures had evidence of low volumetric BMD of the hip and spine (by central QCT), distal radius and tibia (by high resolution peripheral QCT or HR-pQCT) and iliac crest bone biopsies (by microCT). In addition, both those with fractures and those with low BMD had comparable microarchitectural disruption and reduced estimated strength (by finite element analysis or FEA). In addition, both groups of affected women had increased marrow fat (independent of bone volume fraction), reduced bone mineralization density distribution (BMDD by quantitative backscattered electron imaging) and abnormal bone matrix (by Fourier transform infrared spectroscopy). Bone turnover was heterogeneous, but those in the lowest tertile of bone turnover had the most marked deficits in volumetric BMD, microarchitecture and strength. Serum IGF-1 was higher in the women in the lowest tertile of bone formation rate, suggesting that they may have IGF-1 resistance at the osteoblast level. There were virtually no differences between premenopausal women with IOP who had fractures and those with only low BMD. However, whether these women with low BMD reflect the larger population of premenopausal women with low BMD is unknown. It is possible that the lack of detectable differences may represent ascertainment bias, as women with a family history of osteoporosis or some other reason to suspect poor bone health may have been more likely to participate. In our pilot study, most women with IOP responded to osteo-anabolic therapy with teriparatide, although a subset with extremely low bone formation did not.

MANAGEMENT

There are no official guidelines for management of premenopausal women with low bone mass or osteoporosis. Lifestyle modifications should be encouraged for all women with low bone mass since peak bone mass may improve well into the fourth decade. The following should be encouraged: adequate calcium intake (1000 – 1200 mg elemental calcium daily) preferably from dietary sources; adequate vitamin D intake (400-800 IU vitamin D3 daily) or sufficient to maintain serum 25-OHD levels above 20-30 ng/ml; regular physical activity, particularly weight-bearing exercise; cessation of smoking; avoidance of excessive dieting; maintenance of normal body weight; avoid excess alcohol, caffeine and phosphorus containing drinks. A recent study of 16 premenopausal women with IOP treated only with increased dietary calcium and physical activity revealed small but significant increases in lumbar spine and femoral neck BMD after 2 or 3 years and no new fractures.

When a secondary cause of osteoporosis is detected in premenopausal women, treatment should be targeted to that disease or abnormality. Examples of specific approaches that have been shown to lead to increases in BMD include:

- Institution of a gluten-free diet in celiac disease
- Parathyroidectomy in patients with primary hyperparathyroidism
- Discontinuation of medroxyprogesterone acetate
- Oral contraceptives for women with oligo- or amenorrhea, on gonadotropin-releasing hormone (GnRH) therapy with perimenopausal bone loss

Pharmacologic therapy should be avoided unless the patient is losing bone or fracturing.

- Selective estrogen receptor modulators (SERMs) such as raloxifene should not be used in menstruating women as they block estrogen action on bone, leading to further

bone loss.
- Bisphosphonates carry a Category C rating for safety in pregnancy as they cross the placenta and accumulate in fetal bones in an experimental rat model. While they are probably safe, their long half-life in bone makes their use in reproductive age women a concern. In premenopausal women without fractures or known secondary causes for fractures, bisphosphonates are generally not indicated.
- Teriparatide has been shown to prevent bone loss in premenopausal women on GnRH agonists for endometriosis, to increase BMD in premenopausal women with GIOP, and with IOP. Teriparatide has the advantage of not being retained in the skeleton but whether its effects dissipate after cessation, as is seen in postmenopausal women or men, is unknown.

Aggressive therapy with anti-osteoporosis agents may be necessary for women with glucocorticoid-induced osteoporosis. However, the 2010 American College of Rheumatology guidelines do not recommend pharmacologic therapy for prevention and treatment of glucocorticoid-induced osteoporosis patients under age 50, unless they have a history of spine or hip fracture and have taken or will be taking at least 7.5 mg of prednisone or equivalent daily for >90 days.

Premenopausal women receiving chemotherapy for breast cancer represent another group at risk for rapid bone loss, primarily related to induction of premature menopause. Prospective studies demonstrate bone loss at 1 year of 4–8% in the spine and 2–4% at the hip in premenopausal women who become menopausal after receiving adjuvant chemotherapy. Intravenous bisphosphonates prevent bone loss in premenopausal women with chemotherapy-induced amenorrhea.

Premenopausal women with osteogenesis imperfecta (OI) can be treated with either oral alendronate or intravenous pamidronate.

In our recent pilot study of teriparatide in 21 premenopausal women with IOP, there were large and highly significant increases (~10%) in lumbar spine BMD, with smaller but also significant increases at the femoral neck and total hip, and no change at the radius. Teriparatide was also associated with marked improvements in trabecular volumetric BMD and microarchitecture and cortical thickness on iliac crest bone biopsies. About 20% of the women, however, did not respond (no change in BMD at any site). The nonresponsive women had markedly lower bone turnover at baseline, based on serum bone turnover markers and lower bone formation rate on iliac crest bone biopsies. They also had significantly smaller and delayed rises in serum P1NP and C-telopeptide during teriparatide therapy.

We are currently beginning a new federally funded study of teriparatide in premenopausal women with IOP to confirm these preliminary observations and assess the mechanisms for the lack of responsiveness in premenopausal women with low turnover IOP. We would welcome referrals to this study.

To refer patients, please contact:
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MAIN CONCLUSIONS

1. While the majority of premenopausal women with osteoporosis have a secondary disorder that negatively impacts bone health, a significant proportion of those presenting to tertiary care institutions have IOP.
2. IOP is likely to be a disorder of heterogeneous etiology, with some women having very low bone formation rates and others having normal or high bone formation rates. The etiology of bone loss may vary according to bone turnover status. Those with low bone formation have slightly HIGHER serum IGF-1 concentrations and may manifest a form of IGF-1 resistance at the osteoblast level. Those with high bone formation rates may have a mild form of idiopathic hypercalciuria. Bone biopsy is necessary to determine whether bone formation is high or low as serum bone turnover markers were not predictive in our studies.
3. We found, albeit in a small sample, that

women with unexplained low BMD had just as bad bone quality as those with low trauma fractures.

4. In general, conservative therapy is best for young women. Management of osteoporosis in premenopausal women with secondary osteoporosis should focus on diagnosis and specific targeted therapy of the secondary cause. Pharmacologic therapy should be reserved for the most severely affected women, who have very low BMD (Z scores <-2.5), declining BMD on conservative therapy or major fractures. Management of IOP could include antiresorptive therapy if appropriate to the patient's age and bone remodeling status or osteo-anabolic therapy.

CASE WITH QUESTIONS

A 31 yo woman is referred with a history of multiple vertebral fractures. At age 29 she was involved in a motor vehicle accident. Four months later, she developed acute and severe back pain and was found to have compression fractures of T8, T10, L1 and L4. One year later, her back pain recurred and new fractures of T11, L2 and L3 were documented, along with multiple rib fractures and 2 inches of height loss.

What additional history would you seek?

1. What physical examination findings would you look for?

2. What lab tests would you order?

3. She is anxious to have a child. What would you advise her about breast feeding?

4. Would you recommend therapy and if so, which therapy and why?

DISCUSSION OF CASE AND ANSWERS

You should focus your questions on any prior history of fractures in her past, any diseases (e.g., celiac disease, cystic fibrosis, anorexia nervosa) or medication exposures (e.g., glucocorticoids, anticonvulsants) during childhood or adolescence that could have negatively affected bone health. A family history of fractures is important. A detailed menstrual/reproductive history and alcohol history is key.

1. Signs of Cushing's Syndrome, osteogenesis imperfecta, kyphosis, mastocytosis.
2. Certainly a DXA scan, CBC, chemistry panel, serum 25-OHD and 1,25(OH)2D, PTH, 24 hour urine calcium and free cortisol, celiac screen and other tests as appropriate.
3. In general, I suggest such women avoid breast feeding, as the rapid decrease in BMD could exacerbate their problems and perhaps precipitate more fractures.
4. Management depends on whether there is any secondary cause; if so, it should be treated directly if possible. Conservative management with adequate calcium, vitamin D and weight-bearing exercise. SERMs should be avoided. If she is menstruating normally, there is probably no point in OCPs. BPs should be avoided at this age and if imminent childbearing is being considered. Teriparatide may be of some help, but there are no data on how long the effect of the drug lasts.

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Primary Hyperparathyroidism: A Surgeon's Perspective

M51
Monday, June 17
1:00–1:45 PM & 3:00–3:45 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

The clinical features, diagnosis, and treatment of primary hyperparathyroidism have changed significantly over the last 20 years as a result of technologic advances in the fields of laboratory medicine, radiology, medicine, and surgery.[1] More patients are being diagnosed with primary hyperparathyroidism in the earlier stages of disease, and many may be considered "asymptomatic". When such patients should undergo surgical treatment remains still up for debate. If some are considered candidates for minimally invasive surgery, more referring physicians and patients are comfortable with surgical treatment. It is important for surgeons to understand when a patient can undergo a minimally invasive parathyroidectomy and what the current and emerging indications for surgery are.

BARRIERS TO OPTIMAL PRACTICE

There is good evidence that clinical outcomes are related to the experience of the surgeon performing the parathyroidectomy, such that high-volume endocrine surgeons have higher cure rates and lower complication rates. The rate of persistent HPT can be as high as 30% in less experienced hands. It is difficult to define what "high-volume" parathyroid surgeon means. It has been shown that outcomes continued to improve if surgery is performed by surgeons who perform increasing numbers of parathyroidectomies (>50 cases per year).[1]

LEARNING OBJECTIVES

Criteria for surgery

- Even though a National Institutes of Health (NIH) consensus conference was conducted in 1990, another workshop was held in 2002 and an international workshop was held in 2008 on the management of asymptomatic primary hyperparathyroidism, there is still no consensus among endocrinologists and endocrine surgeons about whether to administer nonoperative medical therapy and monitor patients or to refer them for early parathyroidectomy.
- Established according to the best evidence to date.
- Any patient with symptoms, such as renal stones, osteoporotic bone fractures, hypercalcemic pancreatitis, peptic ulcer disease, and hypercalcemic coma should undergo parathyroidectomy.
- For asymptomatic patients, criteria have been established most recently by the 2008 Third International Workshop on Asymptomatic Primary Hyperparathyroidism.[2]

Criteria for Surgical Referral from the 2008 Third International Workshop on Asymptomatic Primary Hyperparathyroidism[2]

- Serum calcium concentration >1 mg/dL (>0.25mM/L) above the upper limits of normal
- Bone density at the lumbar spine, hip, or distal end of the radius that is >2 standard deviations below peak bone mass (T-score < -2.5)
- All individuals with primary hyperparathyroidism and <50 years
- Patients for whom medical surveillance is either undesirable or impossible

Emerging data on neurocognitive and psychiatric disability in primary hyperparathyroidism

- Over the last 8 years, more data have

emerged on the impact of primary hyperparathyroidism on patients' neurocognitive and psychiatric status.
- Using well validated neurocognitive and depression tests, several studies have assessed prospectively the status of patients with primary hyperparathyroidism before and after undergoing parathyroidectomy and curing their disease. They found that patients have significant improvement in state anxiety and depression scores, as well as improved spatial working memory after parathyroidectomy, and that these continue to improve up to 6 months postoperatively. Path analysis indicated that the normalization of the serum parathyroid hormone level was most closely associated with the improvements observed in neuropsychiatric symptoms.[3,4]
- Based on these data, more physicians and surgeons consider neuropsychiatric symptoms in their determination for consideration of surgical treatment for patients with primary hyperparathyroidism.

Cost-effectiveness of surgery versus medical treatment for primary hyperparathyroidism
- Cost-effectiveness analysis has shown that parathyroidectomy is more cost-effective than observation for managing asymptomatic primary hyperparathyroidism patients who do not meet NIH criteria for parathyroidectomy. Treatment outcomes, their probabilities, and costs (in 2005 dollars) were identified based on literature and cost database review, and outcomes were weighted using quality-of-life utility factors. The incremental cost-effectiveness ratio for parathyroidectomy was $4778 per quality-adjusted life year (QALY) gained.[5]
- While the NIH guidelines recommended surgery for patients <50 years, additional cost-effectiveness analysis with Markov modeling demonstrated that parathyroidectomy is the optimal strategy for many patients with asymptomatic PHPT who are >50 years of age. Cost-effectiveness is optimal when life expectancy reached 5 years for outpatient parathyroidectomy and 6.5 years for inpatient surgery. Observation was the optimal strategy at all shorter life expectancies. Pharmacologic management was not optimal at any life expectancy.[5]

Preoperative imaging studies, and their cost-effectiveness
- There is now consensus, as evidenced by the recommendation of the 2002 NIH workshop and the 2008 international workshop—that preoperative localization is imperative before primary exploration if unilateral exploration is desired.
- Several noninvasive preoperative localization modalities are available, including technetium Tc 99m sestamibi scintigraphy, ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and thallous chloride Tl 201–technetium Tc 99m pertechnetate subtraction scanning. Most recently, four-dimensional CT and positron emission tomography (PET)-CT fusion studies have also been used with success for parathyroid localization.
- Most commonly used studies include parathyroid ultrasound, Sestamibi with SPECT, and four dimensional CT scanning.
- In a recent meta-analysis of ultrasound, sestamibi-SPECT, and four dimensional CT for the preoperative localization of parathyroid adenomas in primary hyperparathyroidism, 43 studies met inclusion criteria for the analysis. The results demonstrate that while there is significant variation in sensitivity and positive predictive value, overall, ultrasound and sestamibi-SPECT are very similar in their ability to preoperatively localize abnormal parathyroid glands in patients with primary hyperparathyroidism. Accuracy may be improved with 4D-CT.[6]
- In a recent cost-effectiveness analysis of the most commonly employed imaging studies, US was least expensive. However, the combination of Sestamibi and US ± 4DCT was most cost-effective because improved localization resulted in fewer bilateral explorations. QALYs were comparable across modalities. Compared to Sestamibi, US, CT, and Sestamibi and US ± 4DCT resulted in a win-win situation, costing less and accruing more utility. Sensitivity analyses

demonstrated the model was sensitive to surgery cost and diagnostic accuracy of imaging, and these may vary by institution.[7]

Minimally invasive parathyroidectomy (MIP) versus bilateral neck exploration parathyroidectomy[8]

- 85% of primary hyperparathyroidism results from a single adenoma and is cured by excision of the culprit gland; directed surgery after accurate preoperative localization is being used with increased frequency. MIP involves the use of unilateral neck exploration under regional or local anesthesia in the ambulatory setting.
- MIP requires preoperative localization, followed by limited exploration, often using cervical block anesthesia and the intraoperative rapid PTH assay to confirm the adequacy of resection. Patients with known multigland hyperplasia are not generally offered MIP.
- Cure rates of MIP are as good as bilateral neck exploration; MIP results in less postoperative hypocalcemia than bilateral neck exploration.

Remedial parathyroidectomy[9]

- Localization continues to be essential before all remedial parathyroidectomies.
- Two confirmatory imaging studies are necessary to increase the likelihood of finding the diseased parathyroid gland(s) in the remedial setting.
- Imaging studies often used are US, Sestamibi-SPECT, 4DCT scan, CT angiography, and MRI
- Invasive testing may be necessary: selective venous sampling for PTH, and selective arteriography for gland identification.
- On-site (radiology) rapid PTH testing can help in the invasive testing arena.
- Adjunctive techniques, such as radio-guided parathyroidectomy, can help as well intraoperatively.
- Surgeon experience is paramount for success.
- Minimally invasive parathyroidectomy can be successfully performed if the parathyroid adenoma is identified preoperatively well.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Strategies for Diagnosis

- Assure that the patient actually has primary hyperparathyroidism.
- Determine if the patient is a surgical candidate.
- Obtain preoperative imaging studies to assess is patient may be a candidate for minimally invasive parathyroidectomy. Alternatively, refer the patient to a high-volume endocrine surgeon and have them choose the imaging study best suited based on their institutional availability.

Strategies for Therapy

- Decision to operate should be made based on clinical judgment, not imaging studies.
- Patient should be referred to a high-volume (>50 parathyroidectomies/year) surgeon for optimization of outcomes.

MAIN CONCLUSIONS

- Parathyroidectomy by an experienced surgeon appears to be the most cost-effective treatment for all patients with primary hyperparathyroidism who likely have more than 5 yrs life-expectancy.
- Criteria for surgery are expanding, as more data are gathered on the long-term effects of this chronic disease.
- New imaging techniques are improving localization. Multiple imaging techniques are cost-effective if they can identify the parathyroid adenoma and allow for MIP.
- MIP is superior to bilateral neck exploration for patients who are well localized.
- All parathyroidectomies have better outcomes with lower failure rates and fewer complications if performed by high volume surgeons (>50 parathyroidectomies/yr).

CASES WITH QUESTIONS

Case 1

30 yo man, healthy, without any symptoms, found on routine serum labs: Calcium 11.2 mg/dl; iPTH 151 pg/ml, Cr 0.5 mg/dl. There is no family hx of known endocrinopathy, euthyroid. 24 hr U Ca: 545 mg in 1.3 L of urine. Neck ultrasound negative for any parathyroid enlargement.

IMAGE A

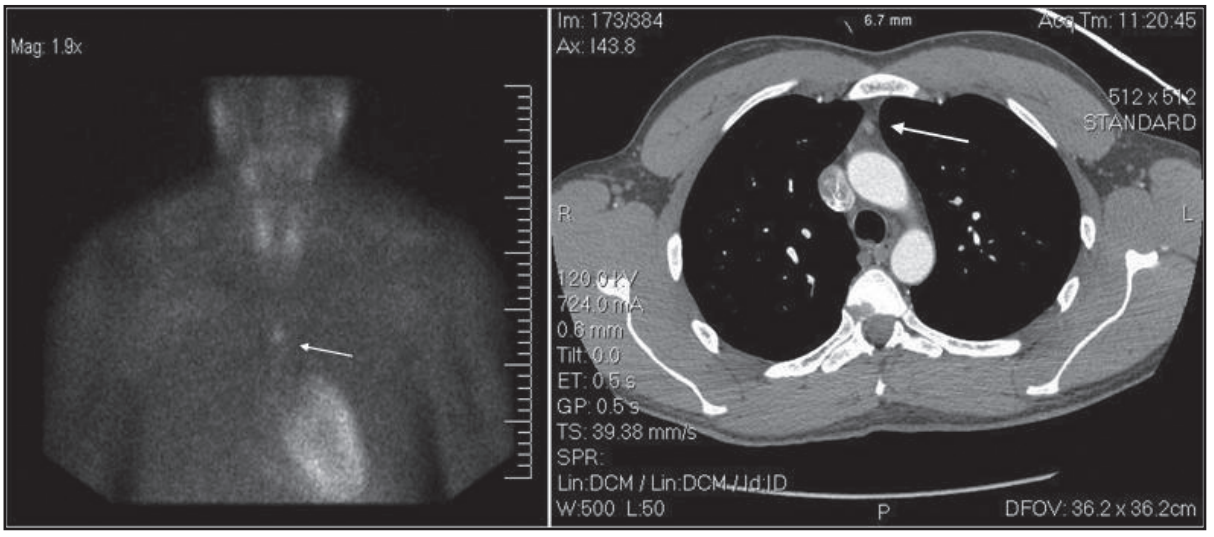
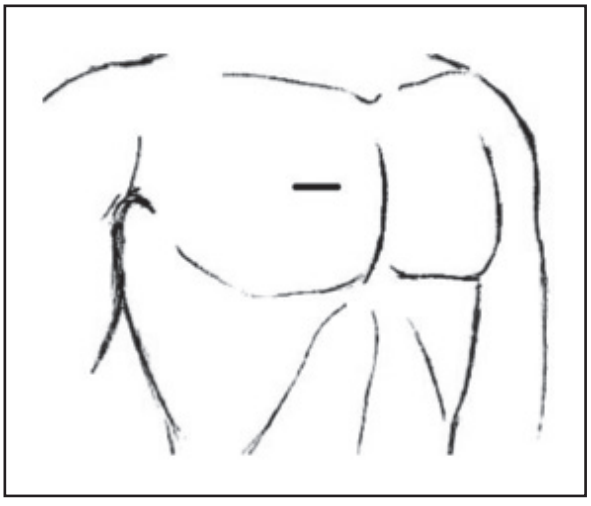


IMAGE B



Questions: Should this patient undergo surgery? If so, should anything further be done before the operating room? What surgical approach should be taken?

Case 2

49 yr old man, routine serum Ca 10.8 mg/dl. Asymptomatic. Bone density: T score -1.5 at wrist, -2.0 at lumbar spine (all worse from 2 years prior). iPTH 50 pg/ml, PO4 2.4 mg/dl, Cr 0.8 mg/dl, 24 hr U Ca 187 mg in 900 cc. Family history: 29 yr old daughter with a serum Ca 10.4 mg/dl. Sestamibi negative. Ultrasound shows bilateral inferior parathyroid glands 9 mm

Questions: What is the differential diagnosis? What further work up should be done? Does this patient need surgery?

Case 3

61 yr old woman with history of nephrolithiasis and osteoporosis (T -2.7). She is managed on alendronate, glucosamine, ASA. No family history of endocrinopathy. Serum calcium 12.1 mg/dl, iPTH 150 pg/ml, Cr 0.7 mg/dl. 24 hr U Ca 475 mg/1.5L. Imaging was obtained (*Image C*)

The patient was taken for MIP and resection of enlarged right upper parathyroid gland (1.8 cm, 450 mg adenoma). ioPTH at baseline 210 pg/ml; 0 min 300 pg/ml; 5 min 150 pg/ml; 10 min 75 pg/ml; 15 min 48 pg/ml and assessed to be cured with a >50% drop from baseline.

1 week post op: Serum Ca 11.2 mg/dl. 1 month postop: Serum Ca 11.0 mg/dl, iPTH 120 pg/ml

Questions: What happened, and why did surgery appear to fail? What should be done next?

DISCUSSION OF CASES AND ANSWERS

Case 1

Additional imaging include sestamibi/SPECT and 4D CT (*Image A*) Surgery, with an anterior mediastinotomy (*Image B*). ioPTH started at a baseline of 167 pg/ml; 10 min post resection: 27 pg/ml; Calcium 6 mo postop: 9.1 mg/dl

IMAGE C

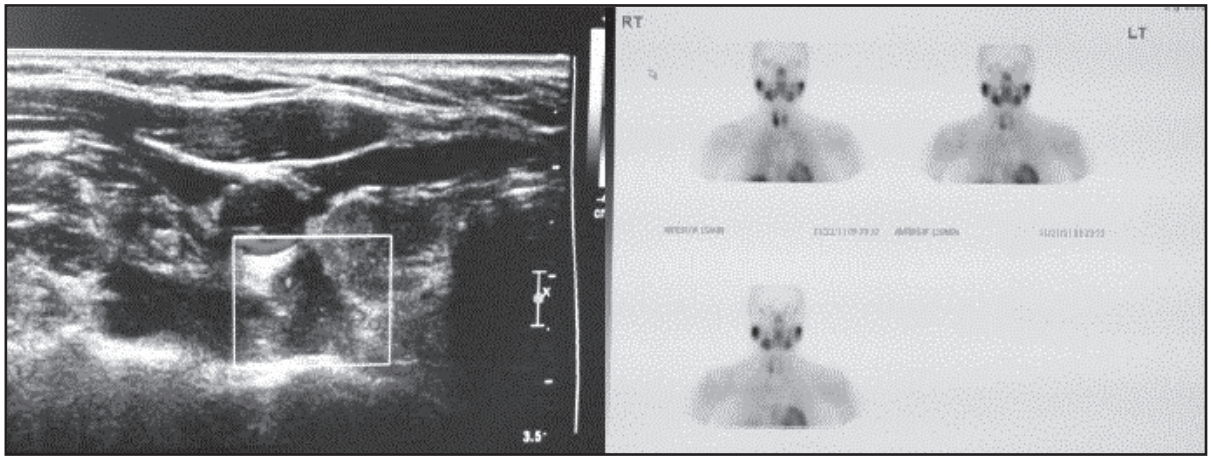
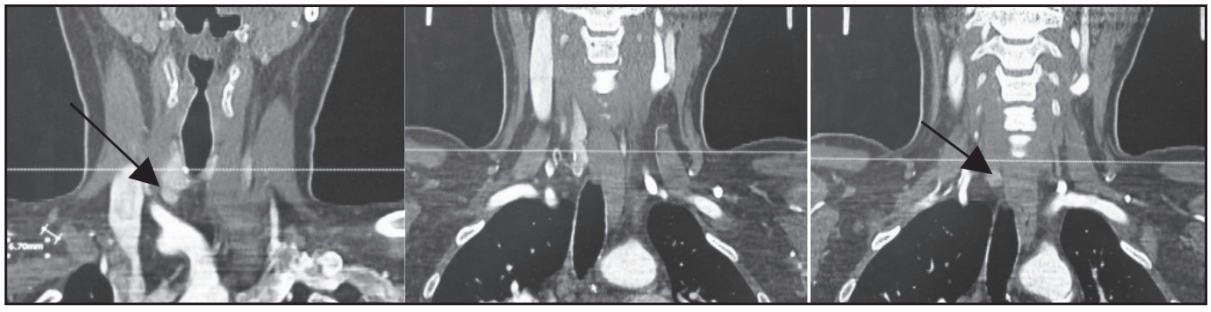


IMAGE D



Case 2

Further work up include Prolactin (normal), gastrin (120 pg/ml fasting), and genetic testing for suspected BFHH. MEN1 gene normal. CASR gene: 2332G>C mutation (exon 7, gly to arg). Diagnosis was BFHH, not primary hyperparathyroidism! Family members also tested positive for the mutation. No surgery was performed.

Discussion: CASR gene mutations are common in BFHH. Autosomal dominant. Two CASR mutations lead to neonatal severe primary hyperparathyroidism, which is life threatening, with very high serum calcium, demineralization of bones, multigland parathyroid hyperplasia. It is inherited as autosomal recessive gene from both parents. Different variants have been reported, and not all have low urinary calcium excretion. BFHH is generally characterized by mild serum calcium elevation, but some may experience pancreatitis, gallstones, renal stone or chondrocalcinosis. R990G mutation can be associated with nephrolithiasis.

Case 3

Reimage the patient and plan for remedial operation. (*Image D*) At reoperation, a 4 gland exploration was performed. 4 large glands were found, including a supernumerary retroesophageal right upper gland (arrow). A subtotal (3 1/2 gland) parathyroidectomy was performed. Postoperative serum Ca 8.9 mg/dl, iPTH 20 pg/ml

Discussion: Supernumerary glands can occur in up to 3% of patients, most commonly in the thymus. This patient may have had asymmetric hyperplasia, with dominant first gland, which is why this showed up as a dominant gland on sestamibi and the immediate ioPTH dropped. The additional glands probably did not start producing PTH until after surgery. Different abnormal glands can have different CaSR set points based on autonomous nests of cells. Failure of ioPTH test is <5%. Ultrasound failed to identify other enlarged glands. 4D CT was useful and identified all enlarged glands.

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Osteoporosis Risk Assessment

M64
Tuesday, June 18
12:15–1:00 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Osteoporosis is a significant public health problem because osteoporotic fractures are common, associated with increased morbidity and mortality, and lead to high health care expenditure(1). For many years the diagnosis of osteoporosis and selection of patients for therapy relied on bone mineral density (BMD) measurement (in the US) or occurrence of fragility fractures. Both of these approaches, however, failed to adequately identify patients who were going to fracture. The BMD diagnosis based on WHO criteria of normal, osteopenia and osteoporosis was insufficient because although those with *osteoporosis (T-score <-2.5) had higher fracture probability*, numerically *more fractures* occurred in subjects with BMD *above this threshold*(2). The case finding approach of evaluating and treating only those who suffered a fracture was unsatisfactory since the ultimate goal is to prevent fractures all together. Improved stratification of fracture risk can be achieved by combining BMD measurement and clinical risk factors. Although several such models have been proposed(3), FRAX(4) has received the most attention and has been incorporated into practice guidelines in many countries including the US(5).

FRAX-based approach is a definite improvement over earlier practice of using BMD for diagnosing osteoporosis. BMD provides a measure of relative risk with 1.5 to 2.5-fold increase in fracture risk per 1 unit decrease in T-score. However, this information is not very useful since the background risk is usually not clear for a given patient. FRAX quantifies absolute risk expressed as a 10-year probability of hip and major osteoporotic fractures (hip, clinical spine, humerus and forearm) taking into account the competing risk of dying(4). FRAX is a robust computer based algorithm, which derives fracture probability based on clinical risk factors (age, BMI, personal history of fragility fracture, parental history of hip fracture, current smoking, excessive alcohol intake, use of oral glucocorticoids, rheumatoid arthritis and other secondary causes or osteoporosis) with or without femoral neck BMD. The risk factors that were included into FRAX were derived from analysis of 60,000 subjects from 9 prospective population-based cohorts from around the world and 11 additional validation cohorts involving 230,000 subjects(6). Because fracture and mortality rates vary between different populations and countries, FRAX is calibrated to provide fracture risk estimates specific to the target population (4).

BARRIERS TO OPTIMAL PRACTICE

On a societal level, the main challenge to reducing fracture risk is to increase awareness of osteoporosis in lay public, medical community, and among regulatory agencies. In clinical practice, however, successful osteoporosis care means identifying the treating those who are likely to fracture while avoiding costly and potentially harmful therapies in those with low fracture risk.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Understand how to combine the fracture risk calculated from FRAX with individual patient's characteristics obtained in the

clinical encounter
- List the information from history and physical exam which can improve fracture risk assessment and help design pharmacologic and life style interventions
- Describe the individualized approach to selecting the type and duration of therapy for osteoporosis.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Osteoporosis risk assessment involves determining the individual patient's fracture risk, evaluating habits and the need for their modification, and assessing the risk/benefit ratio of pharmacologic therapies. Current recommendation is to assess fracture risk using FRAX(5). Although FRAX provides a more precise estimate of fracture risk than BMD alone, it is not perfect and clinical skill and judgment will always be useful when applying a general approach to a specific patient. One of the limitations of FRAX calculation is failure to capture the gradation of risk for some of the clinical risk factors. For example, glucocorticoid use would be coded as 'yes' whether the patient is taking 5 mg or 60 mg of prednisone although the effect on fragility would be quite different. In an attempt to improve the FRAX-derived estimates ISCD and IOF held a position development conference (PDC) addressing the interpretation and use of FRAX in clinical practice(7). While the modifications proposed as a result of PDC (http://www.iscd.org/wp-content/uploads/2012/10/Official-Positions-ISCD-IOF-FRAX.pdf) are certainly helpful, direct patient encounter provides an opportunity to further refine fracture risk estimates based on individual's characteristics. Clinical information that should be sought when evaluating and treating osteoporosis include:

1. *Medical history and overall health status* are important to assess since many pathologic conditions cause bone loss and need to be considered when evaluating fracture history and BMD results, and when choosing appropriate therapy. *Frailty*, which is easily assessed on examination, is associated with osteoporosis and increases the risk of falls and fractures. It is important to enquire about the dose and the duration of use of medications that affect bone such as glucocorticoids, aromatase inhibitors, GnRH agonists which induce hypogonadism, progesterone only contraception etc.
2. *History of fractures* – a person who has had one or more low trauma fractures is by definition fragile even if the BMD results would suggest otherwise. *Type of fractures* are also important since there is greater association of future fractures with vertebral, hip and humerus compared to other fractures. *Number of fractures* is also significant since multiple fractures are a stronger predictor of future fractures than a single fracture. *Vertebral fractures* in particular are a strong predictor of future fractures. They are often not clinically recognized but can be detected using VFA (Vertebral Fracture Assessment), a spine image obtained on the densitometer at the time of BMD measurement(8). In addition, the greater number and/or severity of vertebral fractures the greater fracture risk.
3. *History of falls* – high impact falls without fractures suggest "strong bone". History of frequent falls in the elderly is a risk factor for fractures, which is not included in FRAX.
4. *Activity and exercise history* provides an assessment of fall risk as well as the basis for developing an exercise "prescription", which should be tailored to each patient. A younger, healthy athletic woman with low bone mass may need to be advised to avoid high risk sports. In contrast, an older frail patient may need an exercise regimen to increase weight bearing activity, improve core strength, muscle strength, and balance, and prevent falls.
5. *Dietary history* should assess intake of calories, protein, and calcium. Anorexia nervosa is prevalent in patients with low bone mass and obsession with thinness remains a problem in a number of older women with osteoporosis. Many elderly patients have low intake of calories and protein which contribute to bone and

muscle loss, frailty, fall risk and fracture risk. *Weight history* is important as well since bone loss always accompanies weight loss. When designing the treatment regimen, habitual calcium intake from food assessed through diet history should be taken into account when determining the dose of calcium supplements.

6. *Menstrual and reproductive history* is valuable for several reasons. Delayed puberty in both sexes is associated with lower peak bone mass while hypogonadism resulting from pathologic conditions or medication use can cause bone loss. Early menopause is the period of rapid bone loss(9) and should be taken into account when deciding how often to repeat BMD or whether to consider pharmacologic therapy.
7. *Prior BMD* results provide significant information about peak bone mass, bone loss during physiologic and pathologic states, and response to treatment. It is useful to obtain actual printouts rather than just reports in order to confirm the accuracy of interpretation.
8. Information on prior use of *medication for osteoporosis,* duration of use, tolerability, and therapeutic outcomes (changes in BMD, fractures and their number and circumstances) help plan further therapy or drug holiday.

MAIN CONCLUSIONS

Who should be treated pharmacologically?

According to the current NOF guidelines man and women over 50 should be treated if they have had hip or vertebral fragility fracture (including morphometric), osteoporosis by BMD (T-score<-2.5 at the lumbar spine or femoral neck), or have osteopenia (BMD -1 to -2.5) with FRAX-based probability of major osteoporotic fractures is >20% or hip fractures>3%. The recommendations can be adjusted based on the individual patients' characteristics as described above.

CASES WITH QUESTIONS

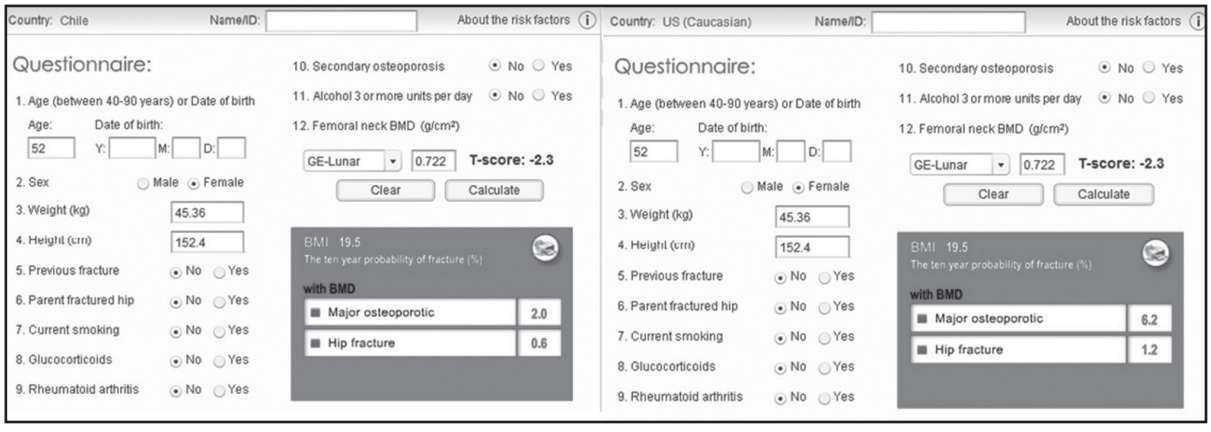
Case 1

A 54 year old Chilean woman is referred for evaluation of low bone density. She has not had fractures or falls. She had menarche at 12, had regular periods and no pregnancies (never married). She denies ever having had an eating disorder or periods of amenorrhea. Last menstrual period was 3 years ago and she still has hot flushes and occasional vaginal dryness. Her mother who is 77 has osteoporosis but no fractures. Paternal aunt had breast cancer. There is no personal or family history of kidney stones. Her dietary calcium intake consists of 3 servings of dairy products per day and she takes 1000IU of vitamin D3 daily. She does not smoke or drink, she works as a laboratory researcher and walks 45 minutes a day.

Physical examination reveals a petite woman with height of 60" and weight of 100lbs. She looks older and more frail than expected for her age.

BMD (DXA) results show T-score of -0.5 at the lumbar spine, -2.3 at the femoral neck, and -2.0 at total hip. FRAX calculation is

FIGURE 1



shown in *Figure 1*. Note the difference in results depending on whether she is classified as Chilean (Latin America) or US white.

The correct approach to managing bone health in this patient is:
1. Life style measures with repeated BMD testing in 5 years.
2. Healthy life style with repeat BMD in 1 year.
3. Pharmacologic therapy (if so, which one? Bisphosphonate, estrogen, raloxifene, denosumab, teriparatide)

The patient will not consider pharmacologic therapy at this point due to fear of side effects. BMD testing performed 3.5 years later shows bone loss of 10.5% in the spine (T-score of -1.5) and a loss of 6.6% at total hip with lowest T-score of -2.6 at femoral neck.

Discussion

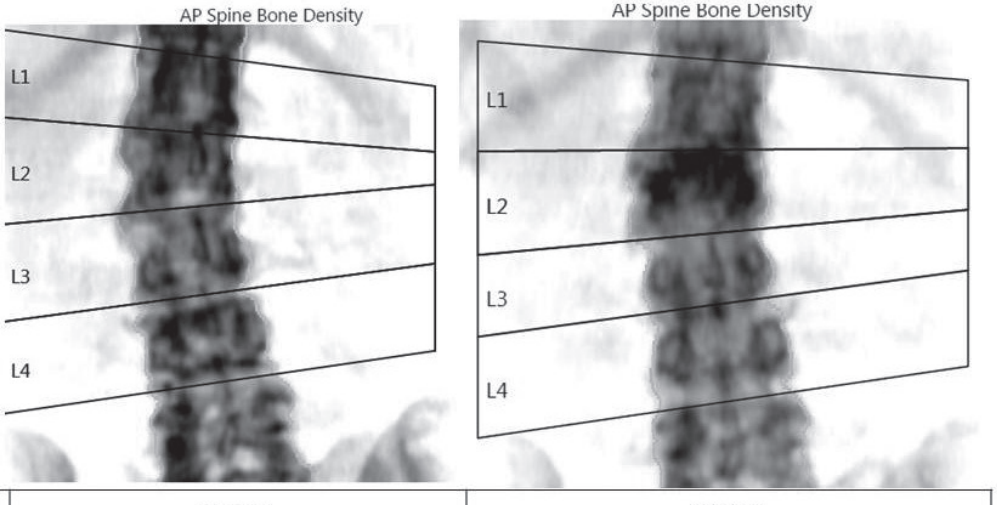
Early postmenopausal women have rapid bone loss the magnitude of which differs among individuals. It is lower in women with high BMI and African American heritage compared to Chinese and Japanese women in the US(9). Early postmenopausal women tend to have low fracture risk calculated from FRAX because the latter is heavily influenced by age. For women who enter menopause with low bone mass, failure to detect the rapid bone loss of early menopause represents a missed opportunity to prevent severe osteoporosis later in life.

Case 2

An internist colleague emails asking about a drug holiday for a 69 year old Chinese woman with "burned out" ankylosing spondylitis (AS). The patient previously had osteoporosis but has been on bisphosphonates for many years and her current BMD T-scores are: +0.1 at the lumbar spine, -2.1 at the femoral neck, -1.8 at the total hip, and -1.4 at the 1/3 radius.

Your answer is:
1. She has had a good response to

FIGURE 2



	2001		2005	
	BMD	T-score	BMD	T-score
L1	1.075	-0.5	1.089	-0.3
L2	0.957	-2.0	1.318	+1.0
L3	0.907	-2.4	1.070	-1.1
L4	1.032	-1.4	0.973	-1.9

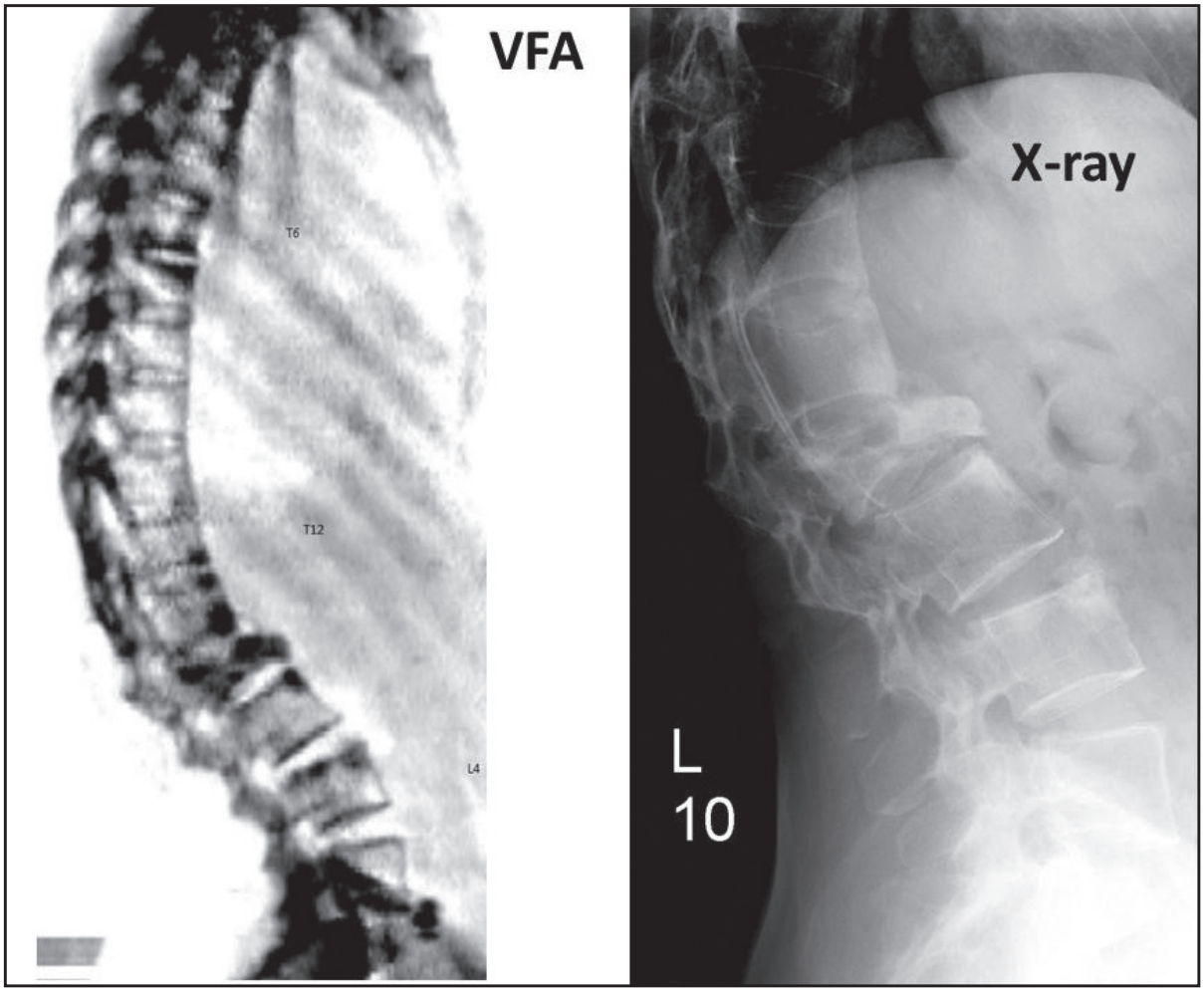
bisphosphonates, current BMD is reasonable and she deserves a drug holiday.
2. You offer to see the patient to better assess her fracture risk.

The patient comes for a consultation. She had menarche at 12, had 5 pregnancies, and had a hysterectomy without oophorectomy at age 40. She took estrogen for 10 years starting at age 46. At age 53 she developed back pain and was diagnosed with ankylosing spondylitis which was treated with NSAIDs. At age 55 DXA (performed because spine radiographs suggested osteopenia) showed osteoporosis (L2-L4 T-score of -2.8, femoral neck T-score of -2.2) and she was started on Alendronate 10 mg/day which was later changed to 70 mg/week. After 12 years of bisphosphonate therapy her rheumatologist suggested a drug holiday due to concern about atypical femur fractures. She does not smoke or drink, she is a retired office worker and she has always been active doing house work, as well as walking and light weight lifting for exercise. Her back pain has not been a problem in the last few years. She takes a supplement containing 500 mg of calcium and 200IU of vitamin D twice a day in addition to a daily multivitamin.

On physical examination she is a short, thin, energetic (not frail) Chinese woman with a height of 57.3" (reported young adult height of 61") and weight of 98.7 lbs. She has mild lower thoracic kyphosis and reduced rib to pelvis distance (<1 fingerbreadth).

Further chart review reveals that at age 62 she had a BMD test showing a new density and increase in BMD at L2 (*Figure 2*) which led to further imaging that revealed a new vertebral fracture at L2 (*Figure 3*). Clinic notes from that time period describe back pain but

FIGURE 3



this was attributed to the known history of AS.

Based on the new information obtained from patient encounter you recommend:

1. Drug holiday as suggested by the rheumatologist
2. Resume a bisphosphonate
3. Resume estrogen
4. Raloxifen
5. Teriparatide
6. Denosumab

Discussion

Drug holiday is a concept unique to treatment with bisphosphonates. Because of their prolonged retention in bone the anti-fracture efficacy is preserved for several years after discontinuation. This conclusion is based on finding that patients who were treated with alendronate for 5 years had no overall difference in fracture rates whether they stopped or continued alendronate for additional 5 years(10). Similar results were observed in patients treated for 3 years with zoledronic acid followed by 3 years of continued drug vs. placebo(11). In both of these studies, however, the incidence of vertebral fractures was higher in patients who stopped the drug suggesting that high risk patients do better on therapy. The impetus to stopping bisphosphonates relates to the rare adverse events of osteonecrosis of the jaw and atypical femur fractures that have been associated with the long term use. There are currently no guidelines for selecting patients for a drug holiday. This decision should be individualized based on initial and follow-up BMD, fracture history, duration of bisphosphonate use, and estimated current fracture risk(12-14). While FRAX was designed for use in untreated patients, recent data suggest that it predicts fractures quite well in patients on therapy(15) allowing the possibility of using the same approach when selecting patients for initial or for continued therapy.

The other point that this case illustrates is the importance of carefully evaluating unexplained increase in bone density. In this patient the explanation was a development of incident fracture at L2 which became apparent due to careful review of BMD scans.

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Secondary Osteoporosis

M12
Saturday, June 15
3:00–3:45 PM & 5:45–6:30 PM

Nelson Watts, MD
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SIGNIFICANCE OF THE CLINICAL PROBLEM

Osteoporosis is considered "primary" if due to aging or decreasing estrogen as occurs with menopause and "secondary" when a drug, disease or deficiency is the underlying cause. (Interesting – postmenopausal osteoporosis is "primary osteoporosis" but in men who have osteoporosis and hypogonadism it is considered "secondary osteoporosis.") "Secondary causes of osteoporosis" is never corrects. "Causes of secondary osteoporosis" is technically correct, but often is applied to patients with silent or difficult-to-detect underlying conditions that MAY be contributing to their osteoporosis, but the extent of the contribution is never known.

For a patient with florid Cushing's syndrome who incidentally has low bone density and/or fractures, it's likely that the sole cause of the skeletal problem is glucocorticoid excess – osteoporosis secondary to Cushing's syndrome. Likewise, the patient with documented normal bone density who experiences bone loss due to treatment with an aromatase inhibitor has osteoporosis secondary to that particular drug. But what about the patient who seems otherwise healthy, is found to have a low T-score (osteoporosis) and laboratory investigation uncovers a low serum 25-hydroxyvitamin D, or a high 24-hour urine calcium, or even "asymptomatic" primary hyperparathyroidism? In my view, all these are potential "contributing"(and treatable) factors or conditions, but I am reluctant to assign that patient to the category of "secondary osteoporosis."

Regardless of the semantics, many patients with osteoporosis have identifiable diseases, conditions or medication use known to cause bone loss. The list is virtually unending, but common and/or serious contributing factors should be sought and addressed before initiating treatment with pharmacologic therapy for osteoporosis and in patients on pharmacologic therapy who seem to be losing ground.

BARRIERS TO OPTIMAL PRACTICE

The only barriers to optimal practice are the willingness of the HCP to seek contributing factors and their knowledge of what to look for and how.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Describe some of the factors that may contribute to bone loss and/or fracture risk
- Identify strategies for identifying those factors
- Explain measures for managing those factors

See *Tables 4* and *5* adapted from: Watts NB, Bilezikian JP, Camacho PM et al. American Association of Clinical Endocrinologists guidelines for clinical practice for the diagnosis and treatment of postmenopausal osteoporosis: executive summary of recommendations. Endocrine Practice 2010; 16:1016-1019.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

The initial approach should be a history and physical exam, with focus on symptoms or

signs that may point underlying causes (for an endocrinologist, Cushing's disease and hyperthyroidism would be examples). A complete list of medications (both prescription and OTC) should be compiled, ideally by actual examination of the patient's supply.

Many potential contributing factors will not be apparent and must be sought by laboratory testing. Our minimum approach is to obtain a CBC, comprehensive metabolic panel, phosphorus and 25-hydroxyvitamin D in everyone (for men, we add a serum testosterone total and free). After assuring adequate vitamin D and a reasonable calcium intake (1000-1200 mg/d) we have patients do a 24-hour urine for calcium, sodium and creatinine. I do not routinely measure PTH.

If history, physical or initial laboratory are suggestive of specific problems, additional investigation should be done (TSH, 24-h urine free cortisol and/or midnight salivary cortisol, SPEP, etc.).

TABLE 4: Some Factors That May Accelerate Bone Loss

Endocrine disorders
• Hyperthyroidism
• Hypopituitarism
• Hypogonadism
• Cushing disease
• Primary hyperparathyroidism
Gastrointestinal disorders
• Celiac disease
• Short bowel syndrome
Hematologic disorders
• Multiple myeloma
• Systemic mastocytosis
Renal disorders
• Chronic renal failure
• Idiopathic hypercalciuria
Neuromuscular disorders
• Muscular dystrophy
• Paraplegia, quadriplegia
• Proximal myopathy
Medications
• Corticosteroids
• Proton pump inhibitors
• Antiepilepsy drugs
• Medroxyprogesterone acetate (Depo-Provera)
• Selective serotonin reuptake inhibitors
• Thiazolidinediones
• Thyroxine in supraphysiologic doses
• Excess vitamin A
• Aromatase inhibitors
• Androgen deprivation therapy
Nutritional deficiencies
• Calcium
• Vitamin D
• Protein

Is a low Z-score predictive?

The answer is "yes and no." While there are studies that suggest that patients with low Z-scores (-1.0 or below, -2.0 or below) are more likely to have "secondary causes" discovered, correctable factors are sufficiently common in patients with higher Z-scores that all patients deserve consideration. Perhaps a very low Z-score should prompt a more extensive investigation.

Common problems and how to deal with them

Low vitamin D

There has recently been a spirited discussion regarding whether vitamin D is needed and if so, how much. My goal is to achieve and maintain a serum 24-OH vitamin D in the range of 30 to 60 ng/mL. NHANES and other surveys indicate that the average 25-OH D in ambulatory subjects is 20 ng/mL. On

TABLE 5: Some Factors That Increase Risk of Falling and Fracture

Neurologic disorders
• Parkinson disease
• Proximal myopathy
• Peripheral neuropathy
• Prior stroke
• Dementia
• Impaired gait or balance (or both)
• Autonomic dysfunction with orthostatic hypotensionImpaired vision
Impaired hearing
Frailty and deconditioning
Sarcopenia
Medications
• Sedatives and hypnotics
• Antihypertensive agents
• Narcotic analgesics
Environmental factors
• Poor lighting
• Stairs
• Slippery floors
• Wet, icy, or uneven pavement
• Uneven roadways
• Electric or telephone cords
• Pets – small or large
• Throw rugs
• Positioning in a wet or dry bathtub

average, 1000 IU of vitamin D daily will raise blood levels by 10 ng/mL (it takes about 3 months to reach a new steady state). For most patients, 2000 IU of vitamin D daily (available without a prescription) will be adequate and safe. With the wide availability of OTC vitamin D preparations, my current approach in most cases is to start with a replacement dose and repeat the 25-OH D measurement 3 months later. Recently, questions have been raised about the reliability of OTC vitamin D supplements, so, in patients who need supplements, it is worth considering rechecking 25-OH D levels annually for a few years to be sure they are remaining in a desirable range.

Hypercalciuria

The upper range of urinary calcium excretion should probably be based on body weight. The average person excretes 2-3 mg of calcium per kg of body weight; upper normal is 4 mg/kg/day (or 1.8 mg/pound/day). High sodium intake is a potential (though in my experience, rare) cause of hypercalciuria. In the absence of a high urine sodium, I would start treatment with HCTZ 12.5 mg daily. If that is not sufficient, increasing the dose of HCTZ to 25 mg/d and then changing to a longer-acting proximally acting diuretic (indapamide or chlorthalidone) should be done.

Glucocorticoid use

Patients on long-term glucocorticoid treatment are at increased risk for fracture and bone loss. Endocrinologists should be familiar with the guidelines of the American College of Rheumatology, which state that pharmacologic treatment for bone protection should be offered to postmenopausal women and men age 50 and older who are on high doses (≥7.5 mg/day of prednisone or equivalent) and to those on lower doses who are at medium (10-year risk of major fracture 10-19%) or high risk (fracture risk ≥20%) using FRAX.

PPI use

Epidemiologic studies and claims databases indicate that long-term high-dose use of PPIs increases the risk of fracture. The mechanism is not known. My approach to patients on PPIs is to give them a list of PPIs and H2 blockers and recommend they work with their PCP or gastroenterologist to see if they might change from their PPI to an H2 blocker or perhaps alternate between the two.

MAIN CONCLUSIONS

There are a large number of diseases, conditions and medications that may contribute to bone loss and/or fracture risk. To identifying those factors requires history, physical exam and laboratory testing. Management depends on which factors are identified.

CASES WITH QUESTIONS

Case 1

74-year-old man, recent wrist fracture. T-scores: -0.7 in the spine, -2.6 in the left femoral neck. He denies any problems with erections or libido. Physical exam: Ht 69" (2" height loss), wt. 165#, unremarkable except for sarcopenia. Lab evaluation: CBC, CMP normal, 25-OH D 23 ng/mL, 24-h urine calcium 163 mg/day, serum testosterone 240 ng/dL (reference range 300-800 ng/mL).

Case 2

68-year-old woman was diagnosed with osteoporosis 2 years ago and started on treatment with alendronate 70 mg weekly which she has been taking correctly and without side effects. Pre-treatment workup included CBC, CMP and 25-OH D, all of which were OK. She is gets 1200 mg calcium daily from dietary sources and walks 40 min/session, 3-4 sessions per week. She is 64" tall and weighs 120#. Repeat DXA shows T-scores of -2.8 in the spine, -2.9 in the left femoral neck and significant decrease in BMD in the spine, femoral neck and total hip.

Repeat blood studies are unremarkable. Urine NTX was 22 nmol BCE/mmol Cr (desirable is 30 or below). 24-h urine creatinine was 0.9 g/day, sodium 120 mEq/day, calcium 283 mg/day. Lab reports reference range for 24-h urine calcium is given as 48 to 352 mg/day.

Case 3

65-year-old woman found to have a femoral neck T-score of -2.6. History included mild

anemia for which iron was being taken but was otherwise unremarkable. CBC showed Hb 11.2 g, Hct 30%, MCV 92. CMP was normal. 25-OH D was 17 ng/mL. 24-h urine calcium as 40 mg/d with creatinine 0.9 g/day.

DISCUSSION OF CASES AND ANSWERS

Case 1

Vitamin D is slightly low; recommend OTC vitamin D 2000 IU/d and repeat 25-OH D in ~ 3 months. Testosterone is low but he has no symptoms of androgen deficiency. Endocrine Society guidelines recommend against treatment with testosterone Would do spine imagining to look for vertebral fractures, offer alendronate if none are found, teriparatide if vertebral fx are present.

Case 2

Knowing that the upper limit for calcium excretion should be weight-based, hers would be 216 mg/day (120 pounds x 1.8 or 54.5 kg x 4). She was started on HCTZ 12.5 mg/d which she took without side effects; 6 weeks later, repeat 24-h urine calcium was 187 mg/day. Treatment with alendronate was continues. 1 year later, DXA showed significant improvement in spine and hip BMD.

Case 3

Vitamin D 2000 IU/d was started. 3 months later, 25-OH D was 22 ng/mL. The vitamin D dose was doubled, the patient advised to take with food, and 3 months later, 25-OH D was 30 ng/mL. At that time, the 24-h urine calcium was repeated and was 38 mg/dL. Her tissue transglutaminase antibody was positive. After GI workup confirmed the diagnosis of celiac disease, a gluten-free diet was instituted. 25-OH D increased to 57 ng/mL with no change in vitamin D intake and 24-h urine calcium increased to 148 mg/day.

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DIABETES

What Type of Diabetes Is It: Type 1, Type 2 or Another Type?

M43
Monday, June 17
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

The increasing prevalence of obesity in children has resulted in the surge of type 2 diabetes in youth, once considered an adult disease. Further, the childhood obesity epidemic has translated to increasing obesity in youth with type 1 diabetes, thus making the clinical distinction between obese youth with autoimmune type 1 diabetes versus type 2 diabetes difficult. On the other hand, a significant proportion of clinician diagnosed youth with type 2 diabetes have circulating islet cell autoantibodies suggesting that these are obese youth with autoimmune type 1 diabetes. Frequently, health care providers are faced with the dilemma of making the correct diagnosis when the clinical picture is not clear with significant overlap between the two. Decisions regarding appropriate therapeutic approaches, based on adequate diagnoses, should target the pathophysiological mechanisms responsible for hyperglycemia and diabetes.

BARRIERS TO OPTIMAL PRACTICE

Obesity is the hallmark of type 2 diabetes in youth in North America. However, the escalating rates of obesity not only in the general pediatric population but also in youth with type 1 diabetes, has made the distinction between type 2 diabetes and autoimmune type 1 diabetes in obese youth difficult. This compounded with unreliable commercial tests for pancreatic autoantibody testing, further complicate the ability to make a proper diagnosis necessary to guide therapy.

LEARNING OBJECTIVES

- To develop a clear understanding of the physiology of the coupling of insulin secretion to insulin sensitivity in health and the pathophysiology of type 2 diabetes in youth.
- To gain insight into the distinguishing features of type 2 diabetes versus autoimmune type 1 diabetes in obese youth by presenting and discussing difficult cases.
- To understand therapeutic approaches aimed at targeting the pathophysiological mechanisms responsible for hyperglycemia and diabetes.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Diabetes mellitus in youth is generally classified into two major categories: type 1 diabetes mellitus characterized by autoimmune destruction of the pancreatic beta cells and absolute insulin deficiency, and type 2 diabetes mellitus (T2DM) characterized by insulin resistance coupled with a non-immune mediated beta cell failure and relative insulin deficiency (1). While type 1 diabetes remains the most common form of childhood diabetes, T2DM in youth has been increasing worldwide over the last decade concomitant with the epidemic increase in childhood obesity (2). Between 2002-2003, the rates of new-onset physician-diagnosed T2DM among children 10-19 years old, in the United States, ranged from 6-76% depending on ethnicity (3), representing a significant increase from the 1-2% rates of non-autoimmune forms of childhood diabetes reported previously (2). On the other hand, awareness and diagnosis of monogenic diabetes (MODY: Maturity

Onset Diabetes of the Young) which results from the inheritance of or de novo mutation(s) in a single gene has been on the rise with recent advances in molecular diagnostics (4). The diagnosis of type 1 vs. T2DM vs. MODY in children relies largely on the clinical presentation with obesity being a major characteristic of children diagnosed with T2DM (1, 3). However, the increasing prevalence of obesity in children including those newly diagnosed with type 1 diabetes has made the clinical distinction between the different types of diabetes more difficult (5-7). The SEARCH for Diabetes in Youth study revealed that ~ 12% of youth with type 1 diabetes are obese and 22% are overweight (6). On the other hand, a significant number, 10-75%, of physician-diagnosed obese youth with T2DM have islet cell autoantibodies (3, 8-10), which is the hallmark of autoimmune type 1 diabetes. In adults with T2DM the presence of islet cell autoimmunity predicts a more aggressive disease course (11,12) and the need for insulin therapy (12,13). In youth T2DM, it was reported that the progression to insulin use was significantly higher in those with islet cell autoantibodies compared to those without (60% vs. 33%) (14). However, neither antibody status nor HLA markers were able to predict the clinical course in adults (12). Initiation of insulin therapy is largely a clinician-driven decision and may not always reflect β-cell function (14).

The pathophysiology of youth T2DM involves impairments in insulin sensitivity and β-cell function, translating to around 86% lower insulin secretion relative to insulin sensitivity, compared with non-diabetic controls of similar body composition and abdominal adiposity (2,15). Progressive deterioration of β-cell function is a well-recognized feature of the disease in adults (16), and is a major challenge in maintaining glycemic control. Limited longitudinal data in pediatrics demonstrate that b-cell function declines on average 20% per year (17), a rate that is four fold faster than what is reported in adults with T2DM. This relentless decline in β-cell function may translate to the higher therapeutic failure rates in youth T2DM (18).

Despite the occasional overlap in the clinical presentation of T2DM vs. autoimmune type 1 diabetes in an obese child, and despite the difficulty in making a diagnostic distinction, there are important distinguishing pathophysiological features between antibody positive (Ab^+) vs. antibody negative (Ab^-) obese youth clinically diagnosed to have T2DM (19-20). Using state-of-the-art methodologies of the hyperinsulinemic-euglycemic and the hyperglycemic clamp, we demonstrated that 1) insulin sensitivity was severely impaired in Ab^- but not Ab^+ patients clinically diagnosed with T2DM, 2) β-cell function was almost completely abolished in Ab^+ and not Ab^- patients, 3) the Ab^- clinician-diagnosed patients with T2DM had features consistent with the metabolic syndrome including higher ALT and systolic blood pressure compared with Ab^+ patients, and 4) rates of ketonuria were higher in Ab^+ vs. Ab^- patients (57.7% vs. 18.8%, p= 0.01). Similar observations of lower -cell function and higher insulin sensitivity in patients with Ab^+ vs. Ab^- clinician-diagnosed T2DM were made during a liquid mixed-meal tolerance test (20). These pathophysiological differences have critical bearing on the management of diabetes, and highlight the importance of making the correct diagnosis between T2DM and obese youth with autoimmune type 1 diabetes.

MAIN CONCLUSIONS

Despite overlap in the clinical presentation of T2DM and autoimmune type 1 diabetes in obese youth, and despite the encountered barriers in making a clear distinction, critical and distinct pathophysiological differences exist between the two. Appropriate choice of therapeutic approaches in each should target the underlying pathophysiological aberrations to correct the hyperglycemia and its consequences.

CASES WITH QUESTIONS

Case 1 (TJ)

An 11 yr. old black female with 2-3 wk. history of polyuria & polydipsia, 7 kg weight loss, nausea & vomiting x 3 days, lethargy, agitation and optundation. Family history is positive for paternal grandfather having T2DM, mother

GDM, now T2DM.

PE
Weight: 82 kg (>>95%), Ht: could not be measured because she was in semi-coma, BMI: ?, BP: 126/62 mmHg, Acanthosis nigricans (AN).

Laboratory data
Emergency department admission plasma glucose: 1100 mg/dl, Urine: Large ketones, HbA1c: 12.5 %, VBG: PH: 7.04, BE: -23; C-peptide: 1.04 ng/ml, ALT: 66 U/L, AST: 84 U/L. Head CT: mild cerebral edema. Following correction of her DKA she was started on MDI insulin regimen.

Three months later: Wt. increased by 8 kg., insulin 1u/Kg/day, HbA1c: 7.4%, C-Peptide: 3.9 ng/ml, Chol: 151 mg/dl, TG:193 mg/dl, HDL: 39 mg/dl, LDL: 81 mg/dl.

Question: What type of diabetes does she have? Ab+ obese type 1 diabetes, or Ab- type 2 diabetes?

Case 2 (RF)
A 12 yr. old Caucasian male, found to have glycosuria during routine pre sports physical, random blood glucose 278 mg/dl, no diabetes symptoms, had gained ~ 2Kg during the prior 2 weeks, is very active, plays football and basketball.

PE
Weight: 86.8 kg, Ht: 174.1 cm, BMI 28.6 kg/m2 (>95th%), BP: 122/78 mmHg, no AN.

Laboratory Data
HbA1c 6.6%, fasting plasma glucose 165 mg/dl, insulin 69.7 mu/ml, trace ketonuria, BUN & electrolytes: normal, Chol: 162 mg/dl, TG:152 mg/dl.

Question: What additional data do you want? What is the diagnosis? How would you treat?

Case 3 (JM)
A 14 yr. old Caucasian male, ADHD on Concerta, 3-4 months polyuria & Polydipsia, 20 Kg weight loss in the preceding 4 months, fever, vomiting, runny nose and cough X 1 week, PCP office: ketonuria and meter glucose >500.

PE
Weight: 113 kg, Ht: 164.3 cm, BMI 42 kg/m2 (>97th%), BP: 127/65mmHg, AN.

Laboratory Data
HbA1c 15.7 %, plasma glucose 313 mg/dl, insulin 69.7 mu/ml, BUN & electrolytes: normal, serum HCO3 18 meq/l, +3 ketonuria & ketonemia,

Question: What type of diabetes does he have? What additional data do you want?

Case 4 (MB)
A 15 yr. old Caucasian male presents to CHP with "established" T1DM on insulin 0.8 u/kg/day, HbA1c 10%. Past History: Diabetes diagnosed at 8 yrs. of age when he presented with polyuria, polydipsia & blood glucose. Has been obese, received Actos in the past, was D/C due to hypoglycemia. Has cystic kidney disease, treated for hypertension (Cozar). Family History: Father had T1DM diagnosed at 16 yrs of age and died of renal failure at 43 yrs. of age; PGF died of T2DM & renal failure at 41 yrs. of age.

PE
Weight 106.7 kg, Ht: 165 cm, BMI 39.2 kg/m2 (>95th%), BP: 130/84 mmHg, abdominal obesity, AN in both axillae.

Laboratory Data
HbA1c: 9.5%, meter glucose: 400-600, Chol: 145 mg/dl, BUN: 34 mg/dl, Cr: 1.7 mg/dl

Question: What is the diagnosis? T2DM or not? What additional data do you want?
Follow Up Course: Insulin to 1.3 u/kg/day, HbA1c ¯ to 7.6%, BMI to 42.6 kg/m2

DISCUSSION OF CASES AND ANSWERS
Will be done in an interactive fashion during the MTP session. Questions will be raised for the audience to answer.

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Diabetes Management: Which Insulins and When?

M3
Saturday, June 15
3:00–3:45 PM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Continuous Glucose Monitoring (CGM) has been available for patients with diabetes, particularly type 1 diabetes, since 2006. However, its use for patients in the United States has had minimal penetration. A recent presentation from the T1D Exchange showed that in over 1,000 patients with type 1 diabetes, one in five adults used CGM, whereas only about 5% of children used the technology. Overall, only 9% of all patients with type 1 diabetes in this large database used CGM.

The clinical trials on this technology have shown that, particularly in adults, A1C levels improve. However, in all age groups, when the technology is worn six or seven days per week, overall glucose control improves and this also includes a reduction of overall hypoglycemic exposure.

The ultimate goal of CGM is to eventually use this technology for a closed loop "artificial pancreas".

BARRIERS TO OPTIMAL PRACTICE

There are many reasons why CGM is not more routinely used. Cost is a major barrier, but included in this category is the time it takes for health care professionals to both train the patients and review the data with patients when they return for follow-up. Simply debating with individual insurance companies is enough to make many providers not pursue this technology.

From the patient side, there have been frustrations with accuracy, nuisance alarms, and pain with insertion. In the T1D Exchange, up to 50% of individuals (especially teenagers) do not continue with this therapy after one year.

LEARNING OBJECTIVES

- As a result of participating in this session, learners should be able to understand basic principles of CGM from both the patient and the provider points of view by reviewing downloaded data.
- As a result of participating in this session, learners should be able to better discuss with payers why this technology will be beneficial for individual patients.
- As a result of participating in this session, learners will be able to better understand how to keep patients using this therapy long term.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

The use of CGM, like any technology, has a "learning curve". The first issue to keep in mind is the fact that these devices are not as accurate as the glucose meters for which they are calibrated. On the other hand, glucose meter technology is far from perfect. And thus patients need to appreciate at the beginning that the meter glucose and the sensor glucose are not always the same.

The second issue has to do with the "lag time". Although the data are sometimes contradictory about how long the actual time for interstitial glucose from the sensor is compared to blood glucose, most of the time we see a ten to fifteen minute lag time. The practical application of this fact suggests that the calibration should ideally be when the glucose levels are stable.

Calibration is obviously critical and

although only two calibrations are absolutely required, it is quite clear that the data are more accurate when three or four daily calibrations are made.

Many patients obviously use the sensor to make insulin decisions but technically, this is against label and insulin decisions should ideally only be made with blood glucose testing. It is difficult to "police" this and in fact, in real life we obviously see patients giving insulin without any glucose data and thus having a CGM point of reference in my view is better than none. As can be expected, we see differences in use of CGM data for insulin doses in different ages based on the T1D Exchange data.

Although the majority of CGM patients in the United States wear insulin pumps, this is certainly not required. As a matter of fact, many patients (especially young women) refuse to wear both a pump and a sensor and the little bit of data we have shows that multiple daily injection patients can do just as well as pump patients.

From a purely practical point of view, the most important aspect of CGM (including from the patient point of view) is the direction of the glucose, especially when arrows are present. The arrows, no matter if up or down, signify significant changes in glucose levels at that time and patients can make appropriate adjustments with their therapy. Giving more or less insulin based on the arrow is perhaps the most fundamental aspect of continuous glucose monitoring. As an example, if the glucose level is 110 mg/dL and a meal is about to be eaten, one would tend to give less insulin if the arrow was pointing downward suggesting the glucose at the time is dropping by 1 mg/dL/minute. Another strategy for this particular situation would be to give the insulin during or even after the meal to give the carbohydrate load "a head start" to avoid hypoglycemia. Although this seems like something a more sophisticated patient would do, we have found most patients wearing CGM can do this.

Another critical and practical aspect of current day CGM devices is the fact that the transmitters have a specific lifetime. In general, the transmitters on the market today only last one year and thus when inaccuracies are noted more than a year after a transmitter is purchased, the most likely reason is a new transmitter needs to be obtained.

In conclusion, CGM has become an important therapeutic modality for the treatment of type 1 diabetes. Its penetration is relatively small but like home blood glucose monitoring and insulin pump therapy previously, we anticipate this therapy will have greater use over time. There are major issues regarding this therapy that need to be understood going in, particularly the issue of absolute accuracy of our current day system. Nevertheless, we anticipate that eventually continuous glucose monitoring will become more utilized both with the current open loop systems of today and closed loops in the future.

MAIN CONCLUSIONS

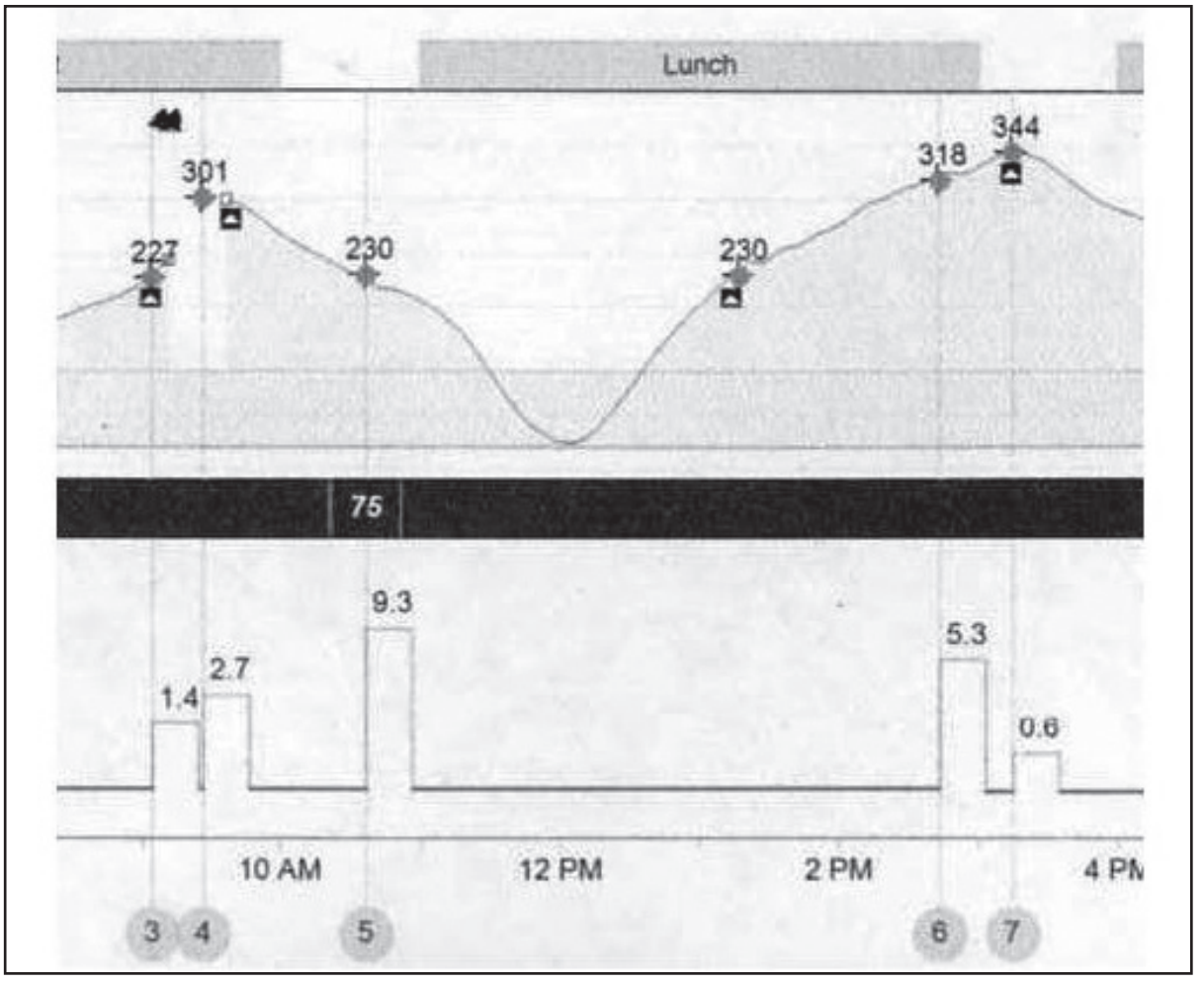
1. CGM has poor penetration for both children and adults in type 1 diabetes, mostly due to cost factors for both patients and providers and lack of enthusiasm from non-academic endocrinologists. This trend is starting to change but the economic viability of providing this case is still not clear.
2. Current technology using interstitial fluid glucose compared to capillary glucose has its own set of issues that need to be appreciated by both provider and patient. Accuracy is the most important of these issues.
3. Patients who could potentially most benefit from this therapy are women planning or currently pregnant, and patients with hypoglycemia unawareness. In adults with over 40 years duration of diabetes, this is over 25% of individuals
4. Long-term success requires regular download review of the data with the patient. This may be the most important factor to predict continuing therapy with CGM.

CASES WITH QUESTIONS

Case 1

This is a 40 year-old woman on a pump who never over-rides her bolus calculator. As

FIGURE 1



can be seen, at 11am she took 9.3 units of insulin as recommended for her 75 grams of carbohydrate. By 3pm her blood glucose was 318 mg/dL. What did she do wrong?

A. Not enough afternoon basal insulin
B. Too high of a sensitivity factor in the AM
C. Need to under-ride bolus calculator with the 11A bolus due to the trend downward
D. Too aggressive of lunch prandial insulin

Case 2

This is a 25 year-old medical student with an A1C of 6.5% getting ready for pregnancy. She uses insulin detemir, 8 units twice daily with premeal insulin apart at 1 unit/15 grams of carbohydrate and an sensitivity factor of 50. What should she do differently?

A. Leave as is
B. Increase breakfast prandial insulin
C. Increase AM detemir only
D. More mid-day exercise

DISCUSSION OF CASES AND ANSWERS

Case 1

Correct answer: C

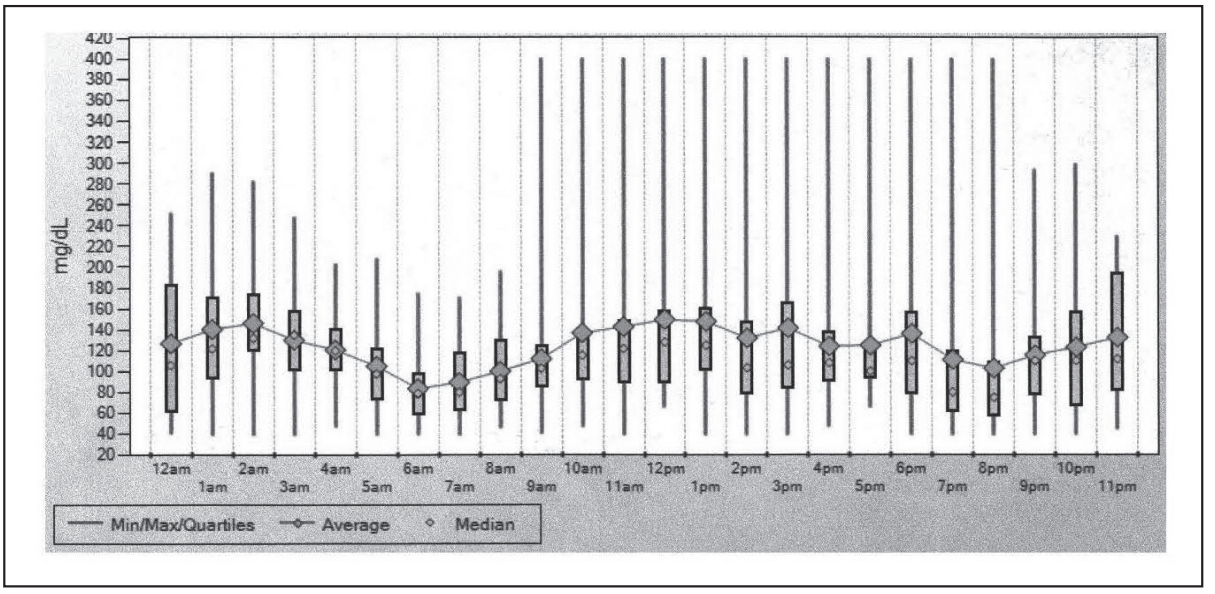
No real conclusions can be made about appropriateness of the carbohydrate ratios, sensitivity factors, or basal doses. The problem is that when the 11A glucose was 230 mg/dL, the trend at the time was downward, and thus the pump's calculation for insulin dose was too high. The important point is the bolus calculators always "see" the glucose as flat, whereas in actuality it may be rising or falling. The patient needs to take this into consideration for each bolus.

Case 2

Correct answer: A

While it is true this patient may be having

FIGURE 2



too much hypoglycemia, some of this is tolerated as she is preparing for pregnancy. The large spike during the day is a one-time spike-when this high acetaminophen always needs to be considered and indeed, that is what she took one day for a headache.

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Hyperglycemia in the Acute Care Setting

M15
Sunday, June 16
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Inpatient hyperglycemia has been demonstrated to adversely affect clinical outcomes in patients with and without diabetes. BG levels > 200 mg/dl are associated with an increase in complications, length of stay (LOS), and mortality in patients admitted with infections, congestive heart failure, myocardial infarction and stroke[1,2].

Approximately 25-40% of hospitalized patients have an underlying diagnosis of diabetes. Another 12 to 20% of patients experience hyperglycemia as a manifestation of the acute illness. In critically ill patient populations, approximately 50% of patients experience hyperglycemia[2].

Despite the well documented negative impact of uncontrolled hyperglycemia on both early and late morbidity and mortality, controversy remains regarding appropriate glycemic targets as well as the methods for achieving these targets[3]. Much of this controversy stems from the observation of a higher incidence of severe hypoglycemia, defined as BG levels < 40 mg/dl that were observed with intensive protocols using IV insulin infusions to achieve what has been defined as "tight" glycemic targets of 80-110 mg/dl[4]. Despite modifications of recommendations for glycemic targets in both critically ill and non-critically ill patient populations, concern for hypoglycemia has resulted in variability in inpatient glycemic management strategies. In one recent review, hyperglycemia (defined as BG > 180 mg/dl) accounted for > 30% of all recorded glucose values in over 500 hospitals reporting their results[5].

Because a program of rational glycemic management that targets BG 100 to 180 mg/dl has the potential to favorably influence both short and long term patient outcomes, the focus of this session will be on defining glycemic targets and reviewing strategies that can safely achieve these glycemic targets with minimal risk for hypoglycemia. It is important that procedures be in place in all hospitals for early detection and treatment of hyperglycemia in patients with and without known diabetes as this allows prompt intervention for achieving and maintaining BG at levels that do not adversely impact patient outcomes (discussed below).

BARRIERS TO OPTIMAL PRACTICE

- Fear of hypoglycemia
- Complexity of ordering multicomponent insulin therapy
- Continued dependence on "sliding scale insulin" regimens
- Insufficient knowledge on the part of many providers on how to appropriately dose and adjust insulin therapy
- Persistent misconceptions regarding use of insulin therapy in patients with "normal" blood glucose values
- Poor coordination of required processes of care that ensure safety of a glycemic management program

LEARNING OBJECTIVES

As a result of participating in this session, learners will be able to:

- Describe the recommended glycemic targets for critically ill and non-critically ill hospitalized patients
- Prescribe and adjust insulin therapy for

patients with diabetes or newly recognized hyperglycemia in the hospital setting
- Define the importance of transition from IV to SQ insulin therapy
- Discuss strategies for the safe transition of insulin treated patients from the inpatient to outpatient clinical setting
- Agree wholeheartedly with the presenter with the following statement:

The use of sliding scale insulin regimens as the sole method of glycemic management is not recommended for inpatients with diabetes or hyperglycemia.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Strategies for Diagnosis

Given the high prevalence of both diagnosed and undiagnosed diabetes in the general population, and the known frequency of illness associated hyperglycemia, all patients require measurement of a random BG at the time of hospital admission[2]. Patients with known diabetes should have this documented in the medical record at time of admission. An A1C should be obtained if a result is not available within the prior two to three months as a way of determining pre-admission glycemic control.

Patients with no prior history of diabetes who have an admission blood glucose (BG) > 140 mg/dl may have undiagnosed diabetes or stress-related hyperglycemia associated with the presenting illness. Measurement of an A1C with initiation of BG monitoring for 24 to 48 hours is recommended in these patients to determine the presence of undiagnosed diabetes and need for scheduled inpatient insulin therapy, which refers to administration of long or intermediate acting insulin in combination with rapid or short acting insulin preparations. A laboratory measure of A1C ≥ 6.5% is consistent with a diagnosis of diabetes.

Patients who are normoglycemic at admission may develop hyperglycemia in response to one of several therapies initiated in the hospital setting, including use of glucocorticoids, immunosuppressants, octreotide, or enteral and parenteral nutrition. Bedside BG monitoring for a period of 24 to 48 hours allows early identification of glycemic excursions that require initiation of scheduled insulin therapy.

Glycemic Goals

Non-critical illness

Premeal and fasting glycemic targets are defined as BG values < 140 mg/dL with maximal random BG < 180 mg/dl for the majority of non-critically ill patients[1,2]. Patients who were comfortable maintaining BG closer to the normal range prior to admission may be candidates to continue this in the hospital provided that this can be safely achieved. On the other hand, patients with multiple co-morbidities, who are at high risk for hypoglycemia, or who have limited life expectancy can have these glycemic goals modified to allow BG of approximately 200 mg/dl to avoid symptomatic hyperglycemia and minimize risk for hypoglycemia.

Critical illness

Glycemic goals of 140-180 mg/dl are recommended for the majority of patients with critical illness. Lower goals of 110-140 mg/dl may be reasonable for surgical patients, particularly those undergoing cardiac procedures.

Therapeutic Strategies

Admission

Patients who are admitted to the hospital can have previously diagnosed type 1 or type 2 diabetes or newly recognized hyperglycemia. Patients with type 1 or insulin treated type 2 diabetes require continuation of at least some component of their insulin regimen when they are hospitalized. Modifications to the home regimen can be made following an assessment of their home insulin doses, their A1C, and current nutritional status.

General Principles

Insulin treated patients who will be eating regular meals

Continue usual doses of basal and nutritional insulin with added correction insulin for BG above desired goal range.

Exceptions

- Patients on basal insulin alone in high doses prior to admission (i.e. > 0.5 – 0.7 units per kg per day): These patients will usually require a redistribution of their insulin doses into basal and bolus insulin components.
- Patients with poor appetite or who have changes in their diet require modification of their premeal insulin doses to avoid both hyperglycemia and hypoglycemia.

Insulin treated patients who will not be eating regular meals

- Continue basal insulin
- Discontinue usual doses of pre-meal scheduled short or rapid-acting insulin analog (RAI-A) preparations until nutrition is resumed.
- Use correction or supplemental insulin at 4-6 hour intervals to treat glycemic excursions above 140 mg/dl[2].

Patients with type 2 diabetes treated with oral diabetes agents (ODA) or non-insulin injectable therapy

Many hospitalized patients have one of the following contraindications to the use of non-insulin agents.

- Metformin is contraindicated in patients with or at risk for renal impairment, decompensated heart failure, and those requiring IV contrast dye or surgery.
- Sulfonylureas can cause severe and prolonged hypoglycemia in patients older than 65 years; when used in combination with basal insulin; or in those with a GFR <30 ml/min/1.73m^2 or poor nutritional intake[6].
- Pioglitazone has a delayed onset of effect and is contraindicated in patients with heart failure or fluid overload.

There is very limited data available regarding the efficacy or safety of other oral or non-insulin injectable agents such as alpha-glucosidase inhibitors, dipeptidyl peptidase IV inhibitors (DPP-IV-I), or glucagon-like peptide analogs (GLP-1) in the hospital setting.

Patients with newly recognized hyperglycemia

- Patients with newly recognized hyperglycemia, defined as persistent BG > 140 mg/dl, may require an observation period of 24 to 48 hours with bedside BG monitoring in combination with correction insulin to determine if there will be a need for scheduled insulin therapy.
- Measurement of an A1C in these patients can help differentiate between previously undiagnosed diabetes and hyperglycemia related to the underlying illness.
- Patients who are unable to maintain bedside BG levels between 100-180 mg/dl without exogenous insulin require conversion to scheduled insulin therapy

Inpatient Insulin Therapy

Rationale for use of insulin therapy in the hospital setting:

- Use of scheduled insulin therapy is effective at achieving and maintaining desired levels of glycemic control
- There is no delay in onset of action
- Insulin doses can be readily titrated and modified according to results of bedside BG monitoring
- Conversion from ODA to a basal-bolus insulin (BBI) regimen has been demonstrated to be both safe and effective in patients with type 2 diabetes treated with ODA prior to admission[7-97].

Implementing Scheduled Insulin Therapy in the Hospital

Non-critical illness

Scheduled subcutaneous insulin therapy consists of three components similar to what is prescribed for patients receiving intensive insulin therapy in the outpatient setting:

- Basal insulin administered as glargine, detemir, or NPH insulin
- Nutritional insulin administered as short-acting (regular) or as a RAI-A (lispro, aspart, apidra). This is ordered to either cover meals, or other nutritional supplements such as enteral or parenteral nutrition.
- Correction or supplemental insulin. This category of insulin therapy has two major uses:
  - To cover glycemic excursions above the

desired range in patients already on scheduled basal or basal bolus insulin.
- ° As initial therapy in patients with newly recognized hyperglycemia or with initiation of therapies known to be associated with hyperglycemia (e.g. steroids, EN or TPN) to determine if there will be a need for scheduled insulin.

Calculating the Insulin Dose

Basal insulin

The starting dose of basal insulin can be determined in one of two ways.

1. One method calculates the initial dose based on body weight at 0.1 to 0.2 units/kg/day. Patients who are lean, who have renal insufficiency, or > 70 years of age may be started on the lower dose, while those who are more obese or with more evidence of insulin resistance will require the higher dose.
2. Patients previously on correction insulin can have the total daily dose of short or RAI-A insulin administered as basal insulin.

Nutritional insulin (also referred to as bolus or pre-meal insulin):

- For patients who are eating

Nutritional insulin can be calculated using one of the following methods:

1. Based on body weight at 0.1 to 0.2 units/kg/day (based on similar clinical characteristics described above for basal insulin) divided into 3 equivalent premeal insulin doses. This type of calculation depends on equal amounts of carbohydrate being provided at each meal. Coordination of care with dietary services can help.
2. Carbohydrate counting: In hospitals with nursing personnel who are well versed in calculating the carbohydrate content of meals (information is often provided by dietary services), administering bolus insulin calculated according to the grams of carbohydrate in a meal allows for greater flexibility in insulin dosing. This can be initiated at 1 unit of regular or RAI-A for each 10-15 grams of planned carbohydrate intake. One suggested algorithm suggests dividing 450/TDD insulin to determine the Insulin to Carbohydrate Ratio (ICR) for regular insulin and 500/TDD for RAI-A.

TABLE 1: Example of a Correction (Supplemental) Insulin Scale

BG	Low Dose	Mod Dose	High Dose	Ptspecific
<70				
70-140	0	0	0	
141-180	1	2	3	
181-220	2	4	6	
221-260	3	6	9	
261-300	4	8	12	
301-340	5	10	15	
>340	6	12	18	

For Patients Receiving Enteral Nutrition (EN)

Several regimens have been demonstrated to be effective for maintaining glycemic control for patients receiving EN10-12.

Continuous EN

- Regular insulin administered every 6 hours*
- NPH and Regular insulin administered every 6 to 12 hours
- Glargine (or detemir) insulin once or twice daily with regular insulin at 6 hour intervals

*Regular insulin is preferred over RAI-A in these patients due to the longer duration of action with need for less frequent insulin dosing than would be required with RAI-A.

Cycled EN

Many patients receive their EN over a period of 8-14 hours (usually overnight) in combination with consumption of usual meals during the day. Insulin regimens can be more complex than with continuous EN, but the principles of focusing insulin dosing according to planned administration of nutrition remains. Approaches that have been used successfully are listed below:

- Administer NPH (or glargine or detemir) with Regular (R) insulin at initiation of EN followed by regular insulin every 6 hours for the duration of the tube feeding. For example, a patient receiving EN from 6P to

10 AM would receive NPH (or glargine or detemir) and R at 6P, with another dose of R insulin at MN and 6AM.
- Patients who are eating during the day can receive RAI-A according to weight based dosing or carbohydrate counting.

Modifying and Adjusting Insulin Therapy

Non-critically ill patients

All insulin treated patients require daily review of their bedside BG data to allow timely modification of insulin therapy. Hospitalization is a dynamic period associated with change in clinical status, insulin sensitivity, severity of illness, caloric intake, physical activity, and administration of some medications, all of which impact glycemic control.

The Endocrine Society Clinical Guideline on Management of Hyperglycemia in the Non-Critical Care Setting recommends that consideration be given to modifying insulin doses for BG < 100 mg/dl, and definitely for BG < 70 mg/dl[2]. This recommendation is supported by a recent report describing a greater frequency of BG values < 100 mg/dl in hospitalized patients who eventually experienced severe hypoglycemic events, described as BG values < 40 mg/dl (Lleva RR et al. ADA abstract).

Several studies suggest that insulin doses be increased by 20% for BG above the desired goal range and that doses be decreased by 10 to 20% for BG < 70-100 mg/dl[7,9]. It is usually recommended that the dose of insulin provoking the high or low BG be the dose that is adjusted (*see Table 2*).

TABLE 2: Approach to adjusting insulin therapy:

If fasting BG is too high or too low	• Adjust basal insulin dose • Or adjust insulin dose prior to evening meal
If pre-lunch BG is too high or too low	Adjust pre-breakfast insulin dose
If pre-dinner BG is too high or too low	Adjust pre-lunch insulin dose
If HS BG is too high or too low	Adjust pre dinner insulin dose
If all BG are out of range	• Adjust basal insulin dose • Consider adjustment in premeal insulin doses

Implementing Scheduled Insulin Therapy in the Hospital

Critical illness

Insulin therapy should be initiated for all critically ill patients with persistent hyperglycemia, starting at a threshold of no greater than 180mg/dl[1]. The BG target for the majority of critically ill patients is a BG of 140-180 mg/dl. Lower targets of 110-140mg/dl may be appropriate for SICU patients, provided that the incidence of hypoglycemia is minimized. There are now several publications demonstrating the safety and efficacy of these revised protocols, reducing concerns for severe hypoglycemia that were observed with earlier protocols targeting a glycemic range of 80-110 mg/dl [13,14].

Intravenous (IV) insulin infusions adjusted according to validated protocols with demonstrated safety and efficacy are preferred. Frequent glycemic monitoring guides glycemic management and minimizes risk for hypoglycemia.

Transitioning Patients From IV to SQ Insulin

As critically ill patients begin to eat regular meals or are transferred to regular nursing units, they require transition from IV to SQ insulin to maintain reasonable levels of glycemic control. The initial dose and distribution of SQ insulin at the time of transition is determined by the current IV insulin requirement with consideration of a patient's nutritional status and use of other medications.

Several different transition protocols have been published[15,16]. The majority of these protocols recommend that 60 to 80% of the insulin administered IV over the preceding 24 hours be administered as basal insulin in either a single or divided dose. Factors that influence this dosing strategy include the administration of EN or TPN, whether or not the patient was eating, or use of vasopressors or other medications that can influence glycemic control.

The most important issue here is that patients who are under a desired level of glycemic control with an IV infusion will require SQ insulin to maintain glycemic control when the IV insulin is stopped. One

recently published protocol implemented daily SQ basal insulin with glargine (dose 0.25 units/kg) within 12 hours of initiation of an IV insulin infusion[17]. These patients experienced less rebound hyperglycemia following transition to SQ insulin than a control group transitioned according to usual care.

Special Situations

Peri-operative glycemic management

There are no studies that define the optimal BG range during the peri-operative period, but it is reasonable to aim for glycemic targets of 140 to 180 mg/dl during surgical procedures. This range minimizes risk for hypoglycemia in patients who are sedated or receiving general anesthesia and are thus not able to communicate the onset of a hypoglycemic reaction. Both pre-operative and postoperative glycemic control have been demonstrated to influence risk of postoperative complications and mortality[9,18]. It is therefore important that diabetes regimens be continued in modified form for patients undergoing surgical or other procedures.

- Treatment recommendations prior to surgery can be categorized according to type of diabetes, nature and extent of the surgical procedure, antecedent pharmacological therapy, and metabolic control prior to surgery.
- Insulin treated patients: Administering 50 to 70% of the usual dose of an intermediate (NPH) or long acting (detemir, glargine) basal insulin maintains a reasonable degree of glycemic control in the majority of patients[19].
- Patients undergoing prolonged procedures (e.g. CABG, transplantation, others) will usually require discontinuation of SQ insulin with start of an IV insulin infusion titrated to maintain BG 140-180 mg/dl.
- Treatment with ODA or non-insulin injectable therapies (incretins, pramlintide): Patients can be advised to take these agents as usual the day prior to surgery, but withhold them on the day of surgery[19].

Frequent glucose monitoring during the peri-operative period is essential in allow early detection of hyperglycemia or hypoglycemia.

Glucocorticoid Therapy

The use of glucocorticoids in high doses is a major cause of hyperglycemia in the inpatient setting. Some patients receive "pulses" of steroids with doses of methylprednisolone up to 1000 mg a day. While the majority of patients with and without diabetes will experience elevations in their BG during steroid therapy, some do not, making it difficult to make general recommendations for all patients who receive these therapies in the hospital[20]. However, there are several general principles that can guide therapy that helps to avoid both severe hyperglycemia and hypoglycemia related to insulin therapy in these patients.[2]

Patients new to steroid therapy

- Bedside BG monitoring for 24 – 48 hours together with a correction insulin scale following initiation of glucocorticoid therapy helps to identify patients who will develop either new onset hyperglycemia or untoward glycemic excursions in those who already have diabetes.
- Patients who require multiple doses of correction insulin will require either initiation or augmentation of scheduled insulin therapy.

Patients with a prior history of glucocorticoid induced hyperglycemia

- These patients will almost certainly become hyperglycemic again with initiation of steroid therapy.
- For patients treated with prednisone or prednisolone once daily in the morning, there are two publications that report good results with use of NPH insulin dosed according to dose of steroid [21,22]. An advantage of this approach (e.g. 0.1 unit/kg NPH insulin for each 10 mg Prednisone equivalent of administered glucocorticoid to maximum dose of 0.4 units/kg for doses ≥ 40 mg) to an existing insulin or other diabetes regimen is that the dose can be automatically held in the event that steroid therapy is abruptly discontinued.
- There are other suggested algorithms for

dosing of NPH that have similarities to what is described above. Clinical judgment is always required in establishing a particular dose for an individual patient.
- Augmentation of an existing insulin regimen with pro-active increases in basal and prandial insulin doses of 20-40% in these patients can help avoid severe hyperglycemia.
- There are some patients who will require IV insulin to achieve and maintain glycemic control following initiation of steroid therapy. For patients in critical care areas, this may not be an issue as they are often already on IV insulin that can be titrated to maintain glycemic control. However, outside critical care areas, it may be useful to use a 12 to 24 hour period of IV insulin to calculate the insulin requirement for SQ insulin.

Transition From Hospital to Home

Patients who are either newly started on diabetes medications or those with diabetes who have alterations in their regimen in the inpatient setting are at risk for hypoglycemia and hyperglycemia following discharge unless clear information is provided with attention needs to necessity for insulin adjustments as therapies started in the hospital are modified in the outpatient setting. This includes tapering of steroid doses, TPN or EN. It is therefore important that patients and their family members or caregivers receive clear discharge instructions including the timing and doses of insulin or other diabetes medications. Prescriptions for supplies (lancets, glucose strips, syringes or pen needles) needed to manage their diabetes are required at the time of hospital discharge (or even earlier). It is essential that the physician or care provider who will be assuming ongoing outpatient care for these patients be informed as to the insulin regimen at time of discharge and expectations for what will need to occur over the ensuing weeks.

MAIN CONCLUSIONS

The recommended glycemic targets for critically ill and non-critically ill hospitalized patients are BG values of 100-180 mg/dl
- Weight based insulin dosing has been demonstrated to be both safe and effective at achieving glycemic control in the hospital setting.
- Insulin doses can be reduced by 10 to 20% overall or targeted to a specific insulin dose for BG less than 100 mg/dl.
- Insulin doses can increased by 10 to 20% overall or targeted to a specific insulin dose for BG > 180 mg/dl.
- Subcutaneous insulin therapy needs to be started prior to discontinuation of IV insulin infusions in order to avoid rebound hyperglycemia
- Information regarding timing and dosing of insulin injections or other diabetes medications, with instructions to adjust for changes in clinical status (e.g. decreasing doses of glucocorticoids) helps to promote a safe transition of insulin treated patients from the inpatient to outpatient clinical setting

CASES WITH QUESTIONS

Case 1

A 49 year old man with type 2 diabetes is admitted to the hospital with pneumonia. His current diabetes medications include glipizide 10 mg twice a day and metformin 1000 mg twice a day. His admission random BG was 223 mg/dl. A bedside BG done 3 hours later is 190 mg/dl. An A1C measured 2 months prior to hospitalization was 7.8%. He weighs 92 kg. His serum creatinine and liver tests are normal.

He will be eating usual meals while he is in the hospital.

What do you recommend for glycemic management? (Circle all that apply)

1. Continue glipizide and metformin in combination with a correction insulin scale administered before meals
2. Discontinue glipizide and metformin and start bedside glucose monitoring with a low dose correction insulin scale before meals
3. Start Lantus to 18 units a day
4. Start lispro or regular insulin 6 units before each meal
5. Start an IV insulin infusion targeting a BG

of 140-180 mg/dl

Case 2

A 38 year old woman with type 1 diabetes (weight 62 kg) and SLE will receive daily methylprednisolone 500 mg for the next 3 days as part of therapy for lupus nephritis. Her current insulin regimen is 20 units of glargine at bedtime and 8 units of lispro before each meal in combination with a low dose lispro correction scale. She reports that she had difficulty controlling her blood glucose levels with BG > 300 mg/dl when she was treated with steroids in the past but she does not remember her steroid dose.

She weighs 62 kg.

What do you recommend? (Circle all that apply)

1. Increase all insulin doses by approximately 20% prior to initiation of the methylprednisolone
2. Increase her current correction scale from the low to moderate dose scale
3. Make no changes in her insulin doses at this time but continue to monitor blood glucose levels more frequently in the 8 hour period following the administered steroid dose
4. Administer NPH insulin 24 units with the first dose of methylprednisolone
5. Start an IV insulin infusion targeting a BG of 140-180 mg/dl

DISCUSSION OF CASES AND ANSWERS

Case 1

Choice "a" is incorrect: His BG was uncontrolled by A1C prior to admission and his BG are uncontrolled in the setting of acute pneumonia. It is therefore important that his BG be brought under control as quickly as possible to improve his ability to overcome this infection. Insulin is the only known therapy that can achieve this quickly. Continuation of glipizide in combination with insulin puts him at risk for hypoglycemia. Metformin therapy has a relative contraindication for continued use in a patient who is at risk for hypoxia.

Choice "b" is correct but insufficient alone. His A1C and hospital BG are high enough to suggest the immediate need for scheduled insulin therapy. Correction insulin in low doses will have little or no effect on his glycemic control and would only prolong the period of hyperglycemia.

Choice "c" is correct, particularly when implemented in combination with choice "b". As described above, there are several studies demonstrating the safety and efficacy of weight based initiation of insulin therapy. Calculating the dose of basal insulin as 0.2 units/kg body weight results in a starting dose of glargine insulin of 18 units. This can be administered immediately, with the decision to continue dosing in the AM or PM at a later time.

Choice "d" may be correct. This patient is described as having type 2 diabetes and it is unlikely that he will develop DKA without premeal insulin therapy. Whether premeal RAI-A such as lispro, aspart, or glulisine or regular insulin is initiated at the same time as the basal insulin (dose calculated as 0.2 units/kg body weight and divided into 3 premeal insulin doses) or at a later time is a matter of clinical judgment. There is some evidence suggesting that use of a "basal plus" insulin (basal insulin plus premeal correction insulin) regimen may be as effective as a BBI regimen in hospitalized patients with type 2 diabetes or new onset hyperglycemia *(Umpierrez G et al. ADA Abstract 2012)*. However, if a decision is made to use the basal plus regimen, close monitoring to determine whether premeal RAI-A or short acting insulin is required is important.

Choice "e" is not incorrect but it is probably not necessary to initiate IV insulin therapy in this non-critically ill patient.

Case 2

Choice "a" is one possible approach to the glycemic management of this patient. In one study, the addition of NPH to a basal bolus insulin regimen was superior to amplification of the current insulin dosing, but it is possible that the increase in doses of glargine and lispro were not comparable to the dose of NPH administered23. One potential pitfall of increasing the usual daily insulin dose is the risk of hypoglycemia in the event that the steroid dose is not administered as planned. When NPH is ordered to be given at the same time as the steroid, this minimizes any

potential risk for hypoglycemia.

Choice "b" is correct but will not provide adequate additional insulin in this patient with a prior history of hyperglycemia following steroid therapy. It also allows hyperglycemia to occur before additional therapy is added, with the associated glucose toxicity that can further aggravate hyperglycemia.

Choice "c" is incorrect: This patient has already provided information that she develops severe hyperglycemia following steroid use. A period of observation with use of correction insulin alone may be reasonable for someone not previously treated with steroids, or for whom their glycemic response to steroid therapy is unknown.

Choice "d" represents an emerging choice for treatment of steroid associated hyperglycemia, particularly when NPH is administered with prednisone or prednisolone as the pharmacokinetic profiles of these agents are complimentary to each other. Since she is receiving such a high dose of methylprednisolone, using a dose of 0.4 units per kg of NPH insulin is reasonable. However, clinical judgment is essential before using any calculation for an insulin dose.

Choice "e" may be useful for the 12 hour period following the infusion of the pulse steroid as a way of calculating the dose of NPH required to maintain a desired range of glycemic control.

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Management of Type 2 Diabetes in Adolescents

M17
Sunday, June 16
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

The rising rates of childhood obesity have led to a public health crisis with a consequence of rising rates of Type 2 Diabetes (T2D) among adolescents in the US. The percentage of youth classified as obese has risen from 4.2 to 19.6% in children ages 6-11 and from 4.6% to 18.1% in adolescents ages 12-19 since the 1960's in the US; with minority populations disproportionately affected. Type 2 Diabetes was considered to be an adult onset disease until two decades ago (1,2, 3). However, now more than 20,000 adolescents in the US are identified with T2D and up to 1 in 3 new cases of diabetes mellitus diagnosed in adolescents is now T2D (4).

Type 2 Diabetes is more common in adolescents with a history of obesity, family history of T2D and African-American, Hispanic, Asian or Native American ancestry. There is a peak in physiologic pubertal insulin resistance which occurs at Tanner stage 3 of puberty which predisposes at risk youth to T2D onset and accelerated treatment failure. It is not surprising that the coinciding timing of peaking insulin resistance, pubertal hormone secretion with rapid body habitus changes and adolescent behavior create a perfect storm for challenges in care for health care providers and affected families.

BARRIERS TO OPTIMAL PRACTICE

- Limited approved medical therapies are available for adolescents with Type 2 Diabetes
- Poor compliance patterns and burden of disease in these families often undermine medical therapy effectiveness

LEARNING OBJECTIVES

- Recognize and initiate an appropriate medical evaluation for a child or adolescent suspected to have Type 2 Diabetes.
- Provide medical therapy and medical monitoring for the child with Type 2 Diabetes
- Be aware of the associated comorbid conditions commonly seen when treating adolescents with Type 2 Diabetes and their impact on therapeutic decisions.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

The SEARCH for Diabetes in Youth study was funded by the CDC and NIDDK to estimate a population based prevalence and incidence of physician diagnosed diabetes in youth <20 years of age since 2001. SEARCH data estimate that 15,000 youth are diagnosed annually with type 1 diabetes (T1D) compared to 3,700 youth diagnosed annually with T2D in the US and that diabetes prevalence and incidence vary across major racial/ethnic groups (5). In all racial/ethnic groups, there is a low incidence of T2D prior to age 10 years. However, the proportion of T2D among older youth ages 10-19 rises to 58% in African American, 45% in Hispanic, 70% in Asian and 86% in American Indian youth compared to only 15% in non-Hispanic white youth. Other factors associated with an increase in risk for youth onset T2D include pubertal timing, visceral obesity, family T2D history and exposure to maternal diabetes/obesity during gestation (5).

Clinical phenotypes often cannot reliably

distinguish between T1D from T2D in children at the time of diabetes presentation. High risk obese adolescents with T2D may be diagnosed during screening if they meet the American Diabetes Association (ADA) adult diabetes criteria, defined as HbA1c ≥6.5% (test performed in an appropriately certified laboratory); or fasting (defined as no caloric intake for at least 8 hours) plasma glucose ≥126 mg/dL (7.0 mmol/L); or 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test performed as described by the World Health Organization by using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; or a random plasma glucose ≥200 mg/dL (11.1 mmol/L) with symptoms of hyperglycemia (6,7). When the adolescent has not had documented symptoms of hyperglycemia, criteria 1–3 should be confirmed by repeat testing. The use of a 6-6.5% range Hbg A1C by itself is a poor diagnostic tool for prediabetes and T2D in obese children and adolescents due to its low sensitivity and specificity when compared to the glucose tolerance test in this population (8).

The ADA, the European Association for the Study of Diabetes and the International Society for Pediatric and the Adolescent Diabetes, and Academy of Pediatric guidelines advocate for the initiation of Metformin therapy concurrently with lifestyle intervention at diagnosis of T2D (6,7). Because it can be challenging to categorize youth with new onset diabetes as T1D or T2D, conservative initial therapy decisions often err towards use of insulin therapy to aggressively lower blood sugars with dietary education provided to families as diabetes antibody marker status is pending. When presenting with dehydration and ketoacidosis or severe illness, carefully monitored rehydration is similar to T1D therapy protocols to achieve volume expansion therapy followed by insulin therapy to gradually decrease the blood glucose values by less than 100 mg/dl per hour until reaching the upper normal range. Insulin therapy is also indicated for known T2D pediatric patients presenting with marked hyperglycemia and/or elevated HgbA1c levels >9% (9).

The approach to determining Insulin therapy should be individualized to the family's ability and willingness to give consistent dosing; options of basal only, basal-bolus or even premixed combination insulin regimens should be considered with calculated insulin dosing that is adequate to combat the adolescent's insulin resistant state. The disadvantages of insulin therapy in the obese T2D adolescent include exacerbated weight gain and hypertension, as well as the risk for hypoglycemia. Initial solo Metformin monotherapy is appropriate for the suspected or known adolescent T2D patient who has mild symptoms with no acidosis and adequate liver and kidney function. Behavioral lifestyle changes should focus on family based dietary advice, exercise goals and weight loss encouragement (9). Complications of hypertension and urinary microalbuminuria (MA) are much more likely to occur in adolescents T2D compared to T1D. Hypertension was present in 65% of youth with T2D enrolled in the SEARCH for Diabetes in Youth Study (SEARCH) (10). Laboratory findings suggestive of hepatic steatosis and severe dyslipidemia often complicate initial therapy decisions. First line therapy with an ACE inhibitor for hypertension or confirmed MA should be initiated if liver function is stable.

The initiation of metformin soon after the diagnosis of T2D may promote beta-cell function and predict a benefit of prolonged durability of metformin effectiveness (11). Guidance to maximize tolerance and compliance of metformin therapy with titration from a starting dose of 500 mg daily to a maximum dose of 1,000 mg/dose given twice daily requires initial reassurance that known gastrointestinal side effects are often transient and minimized by strict adherence to therapy. Adolescents with T2D who require insulin therapy at diagnosis likely benefit from the early addition of metformin to increase the likelihood of successful subsequent weaning of their insulin therapy.

The recent Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) trial compared standard (metformin alone) therapy versus) more aggressive therapy (metformin 1 g twice per day and rosiglitazone

4 mg per day or metformin 1 g twice per day and intensive lifestyle management) as the initial treatment in youth, ages 10 to 17 yr, with short-duration T2D. This study found that metformin alone was inadequate in effecting sustained glycemic control (primary outcome was treatment failure, defined as an HbA1c of 8.0% or greater for at least 6 months or metabolic decompensation) in the majority of this cohort of youth with T2D. Half of participants on metformin monotherapy experienced loss of glycemic control, with an average time to treatment failure of only 11.5 months. Intensive lifestyle promoted more weight loss at 6 months than metformin alone, but this did not translate to improvement in sustained glycemic control. The study results suggest that therapy that is more aggressive than metformin monotherapy may be required in these adolescents to prevent loss of glycemic control. Gender and race-ethnicity treatment outcome differences found in this study suggest the need for individualization of therapy (12,13).

Options for therapy beyond metformin and insulin in the pediatric patient are limited by the lack of approved pharmacologic agents and a paucity of evidenced based safety data or outcomes. There is approval for an incretin based therapy for age 17 years which has the advantage of improved β-cell function without associated weight gain risk (14).

MAIN CONCLUSIONS

The challenges of preventing Type 2 Diabetes in the pediatric population are directly tied to efforts aimed at curbing childhood obesity. Treatment of pediatric and adolescent Type 2 Diabetes typically involves efforts to reverse behavioral lifestyle patterns in families who are often unable to afford or reluctant to comply with medical advice aimed at restoring euglycemia and reducing insulin resistance. Evidence continues to support metformin as a first-line therapy for the T2D however initiation of insulin therapy is required for in pediatric patients who present with ketosis, severe hyperglycemia or with an unclear diagnosis of type 2. Metformin should be initiated once the diagnosis of Type 2 is confirmed by negative autoantibody titers if possible. When metformin therapy fails, recommendations for intensifying therapy are limited by the scarcity of approved pediatric T2D therapy options. Research and evidence based outcome data is much needed to guide best practices for safe and effective therapies in this population. However, clinical trials are hampered by recruitment, retention and protocol compliance challenges attributed to adolescent behavior and family burden of disease. In addition to behavioral and social obstacles, youth with T2D often face interruptions of medical resources and barriers to care in the clinical setting. These obstacles, combined with evidence for escalated risks of treatment failure and early complications of diabetes, portend a worrisome prognosis for adolescents with T2D.

CASES WITH QUESTIONS

Case 1

A 13 year non-Hispanic white female presents with polyuria and polydipsia symptoms. She has lost 5 lbs over the past month. She has been previously healthy; however she was noted to have acanthosis two years ago by her pediatrician. She is a good student with no past history of surgery or medications. She has always been heavy with a presenting weight in the 92% and 50% height. Her ROS is significant only for mild snoring, polyuria, polydipsia and a new yeast vaginitis. She denies headaches or visual changes. Her family history is significant for obesity, hypertension in both parents and a maternal aunt with Graves' disease. Her paternal grandfather has T2D and both maternal grandparents have hypertension. The patient has two healthy siblings who are also obese. Her vital signs are BP 122/72, P105, RR 12 and she appears anxious and tired. She has minimal acanthosis and appears obese with no significant stria. She is mildly dehydrated. She has an otherwise unremarkable exam with Tanner 3 breasts and pubic hair. Initial laboratory studies include an HgbA1c of 10%, glucose of 300 mg/dl, otherwise normal electrolyte and thyroid levels with no ketosis. The family and patient are educated with regard to diet and basic diabetes skills as outpatient initial insulin therapy is begun. Later that week, the laboratory

reports that she has significant elevation of her glutamic acid decarboxylase antibodies.

Questions

1. ***How does obesity-associated insulin resistance impact the disease process of both T1D and T2D?***
2. ***How do you determine the type of diabetes with overlapping T1D and T2D phenotypes?***
3. ***What is the appropriate initial management for this child?***

Case 2

A 17 year old Hispanic male presents to the emergency room by ambulance with his sister who is unable to provide initial family or medical history beyond the fact that her brother was diagnosed with "borderline diabetes" two years ago. The patient is obese with severe acanthosis and T4 stage puberty. He appears dehydrated, acutely ill and he has no focal findings of infection. He has altered mental status and a severe headache. He is afebrile with a BP of 135/85, Kaussmaul breathing with fruity breath. Laboratory studies show a blood sugar of 850 mg/dl, venous pH of 7.0, ketosis, hypernatremia, hypophosphatemia, hypokalemia, three-fold ALT elevation and HgbA1c 12.5%.

Questions

1. ***What is are the initial management and therapy concerns?***
2. ***What percent of adolescents with T2D present in ketoacidosis***
3. ***How will the initial electrolyte and liver function studies impact his therapy?***

DISCUSSION OF CASES AND ANSWERS

Case 1

Positive diabetes autoimmune markers in an adolescent with a clinical phenotype suggestive of T2D indicate that the obese youth more likely has β-cell failure caused by T1D (15). This child will likely require daily total insulin dosing of 1-1.25 units/kg/day insulin given as basal bolus therapy.

The presence of autoimmune markers results can be difficult to predict. The SEARCH study reported a rate of 21.2% of children who were physician-identified as having T2D yet positive for GAD-65 diabetes autoimmunity. Similarly, The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study screened pediatric patients who were clinically diagnosed with T2D by endocrinologists with 9.8% of screened patients positive for one and 3.9% positive for both of the glutamic acid decarboxylase (GAD) and insulinoma-associated protein 2 autoantibodies (16). Although there is little data regarding treatment outcomes in youth with T2D phenotypes and positive diabetes autoimmunity, it is likely that islet autoimmunity predicts greater susceptibility to a greater risk for progression to metabolic decompensation and insulin requirements. The UK Prospective Diabetes Study (UKPDS) described that 94% of their young subjects with physician-diagnosed T2D who were GAD-positive required insulin by the end of the study, compared with 14% of antibody-negative subjects and these subjects failed oral therapy more rapidly.(17)

Case 2

The typical adolescent with T2D is diagnosed during puberty with findings of obesity, acanthosis nigricans and symptoms of polyuria and polydipsia. This patient should be immediately evaluated and likely treated for possible cerebral edema. He needs ICU monitoring for initial cautious rehydration with titration of his electrolyte replacement and insulin drip to gradually drop his glucose. Approximately one third of youth with T2D present with ketosis at diagnosis and up to 25% can present in ketoacidosis (18). The T2D adolescents who present in ketoacidosis often have profound electrolyte disturbances and may require prolonged supplementation of phosphate and potassium due to severe depletion. Rarely, adolescents with new onset T2 present with ominous life threatening findings of a hyperglycemic hyperosmolar non-ketotic syndrome (19).

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Cystic Fibrosis Related Diabetes: A Larger Place for Insulin Therapy?

M62
Tuesday, June 18
12:15–1:00 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Median life expectancy in cystic fibrosis (CF) is in constant improvement and is now over 43 years of age. Due to this increased life expectancy, several co-morbidities have emerged. CF-related diabetes (CFRD) is now the most common co-morbidity in subjects with CF. CFRD is present in about 20% of adolescents and 40–50% of adults with CF, while an additional equivalent percentage of patients present impaired glucose tolerance. Moreover, CF patients who are considered with normal glucose tolerance frequently show significantly increased glucose excursion during intermediate time points of a 2h-OGTT (Oral Glucose Tolerance test) or after a meal as compared to healthy controls. Thus, most CF patients present some degree of dysglycemia.

The CF gene defect (CFTR mutations) is responsible for the excessively thick and viscous secretions that lead to both to the classical pulmonary insufficiency but also to chronic pancreatitis and significant reduction (~50%) of the total islet mass due to fibrosis. Insulin insufficiency, which is in large part caused by reduced b-cell mass, is the hallmark of CFRD. Nonetheless, some degree of residual endogenous insulin secretion will remain present in most CF patients while the contribution of insulin resistance remains controversial. CFRD largely differs from both type 1 and type 2 diabetes and require specific treatment actions (*Tables 1 and 2*). As in any form of diabetes CFRD patients are exposed to microvascular complications risk but their major health problems are the progressive respiratory insufficiency and weight loss.

Healthcare professionals are thus facing a rapidly increasing group for which significant uncertainty remain for optimal diabetes diagnosis and treatment. A major goal in the near future is to establish if CFRD treatment can contribute to improve overall CF outcome.

BARRIERS TO OPTIMAL PRACTICE

- Lack of simple method to detect CF patients who are at higher risk of

TABLE 1: CFRD vs Type 1 or type 2 diabetes

	CFRD	Type 1 diabetes	Type 2 diabetes
Prevalence	35%	0.2%	11%
Peak age at onset	14.5 (11.8 - 16.3)	8.5 (4.9 -11.8)	> 30
Body mass index	Normal to underweight	Normal	Obese
Insulin deficiency	Severe but not complete	Complete	Partial, variable &progressive
Insulin resistance	Uncertain, variable with infection, etc.	Usually modest	Usually significant
Autoimmune etiology	No	Yes	No
Cause of death	Lung disease	Cardiovascular	Cardiovascular

TABLE 2: CFRD vs Type 1 or type 2 diabetes

	CFRD	Type 1 diabetes	Type 2 diabetes
Potential ketones	Rare	Yes	Rare
A1C	Less predictable relation to mean blood glucose	Related to mean blood glucose	Related to mean blood glucose
Usual treatment	Insulin	Insulin	Oral agents, insulin
Microvascular complications	Yes	Yes	Yes
Macrovascular complications	No	Yes	Yes
Metabolic synd. features	No (very rare)	No	Yes

developing CFRD
- Implement recommended screening method within an already extremely complex treatment framework: Annual screening by 2h-OGTT in every CF patients 10 years old and above, without known CFRD.
- Take into account the specific nutritional requirements of CF patients in the treatment of CFRD.
- Implement optimal insulin therapy
- Integrate CFRD treatment within an already extremely complex care

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:
- Have an overview of underlying causes of CFRD
- Explore potential links between abnormal glucose metabolism and CF clinical deterioration: accelerated weight & lungs deterioration
- Understand the potential of early insulin treatment to improve CF outcome

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

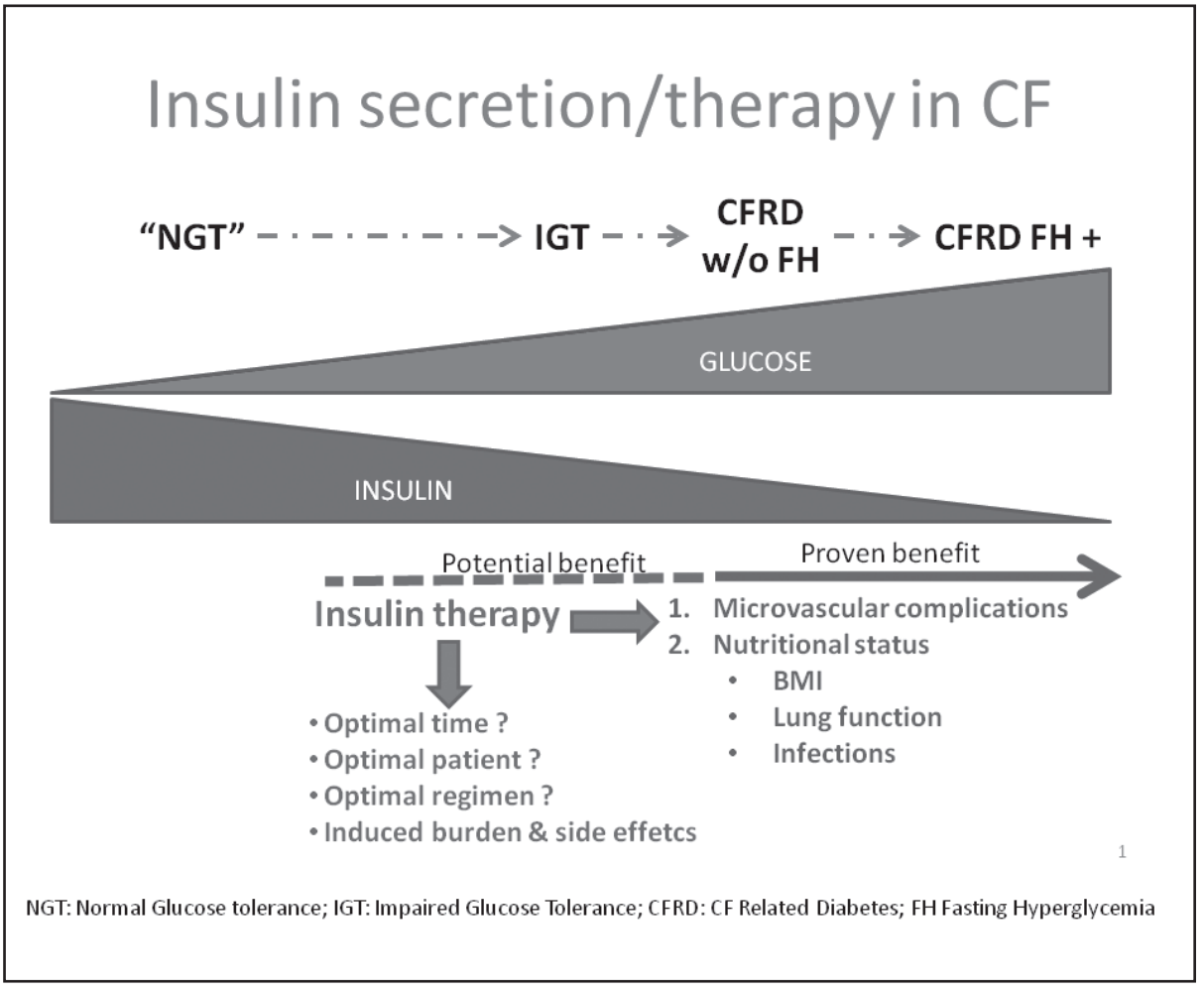
CFRD can be associated with an increased risk of CF clinical deterioration (accelerated weight loss and/or lung function) which starts during the pre-diabetic state. Thus, the extremely frequent dysglycemia observed in CF, exposes patients to a potential dual burden: diabetes specific complications (e.g. retinopathy) as well as CF clinical deterioration. The ideal treatment for dysglycemia should help to prevent, limit or even reverse the associated clinical deterioration in addition to the awaited prevention of diabetes specific complications.

The occurrence of CFRD is preceded by a long phase of glucose intolerance and periods of intermittent diabetes at the time of pulmonary exacerbations. The main glucose abnormality is postprandial hyperglycemia while fasting plasma glucose can remain normal for a long period of time. Diagnosis of CFRD is challenging as symptoms usually related to diabetes can be confused with other CF clinical problems (e.g. growth retardation, fatigue, etc.). Furthermore, a late diagnosis exposes patients to accelerated weight and lung function. Finally, the diagnostic still needs to rely on Oral Glucose Tolerance Test as both fasting plasma glucose and glycosylated haemoglobin are not reliable to diagnose dysglycemia in CF patients. Implementing the recommended annual OGTT screening can be challenging for many health care teams.

CF patients have specific nutritional requirements including the need for a high caloric intake, thus nutritional counseling usually focuses on carbohydrate repartition, ideally including low glycemic index choices.

A major challenge is to define the optimal time and method to implement the treatment of dysglycemia. While hyperglycemia is directly related to diabetes specific complications such as retinopathy, both insulin insufficiency and hyperglycemia might affect CF clinical status (weight loss, reduced lung function and poor growth in children). Hyperglycemia could contribute to decreased pulmonary function by creating a pro-inflammatory and pro-bacterial environment. On the other hand, insulin deficiency directly favors excessive protein and fat breakdown which could

FIGURE 1



NGT: Normal Glucose tolerance; IGT: Impaired Glucose Tolerance; CFRD: CF Related Diabetes; FH Fasting Hyperglycemia

explain why nutritional status and pulmonary function begin to decline 3 to 4 years before the diagnosis of CFRD. In prospective observational studies the rate of pulmonary function decline is proportional to the magnitude of insulin deficiency. Conversely, besides its effect on hyperglycemia, insulin replacement is associated with improved and/or stabilization of nutritional status and/or pulmonary function in patients with CFRD. However, most of these observations originate from uncontrolled studies and only one randomized control trial (CFRDT trial) has clearly shown the superiority of insulin treatment over oral agents (Repaglinide) and placebo to improve body mass index. Thus insulin therapy is the recommended treatment because of its probable ability to both improve glucose control while having anabolic benefits. While initial trials such as the CFRDT trial tested prandial fast acting insulin, more recent data suggest that for anabolic purposes, basal insulin might provide similar benefits with the advantage of being a simpler insulin regimen. However, we await definitive proof that early insulin introduction is beneficial for important CF outcomes such as weight maintenance and best timing for this implementation remain also to be established. Acceptance of this treatment can be challenging for a significant proportion of patients. Explaining to the patients that insulin treatment could help in the maintenance or even the improvement of body weight and/or pulmonary function is usually a key factor to initiate this treatment.

Over recent years, in parallel with improved overall care, nutritional support, dysglycemia screening and earlier treatment a significant reduction of the increased mortality associated with CFRD diagnosis has been observed.

MAIN CONCLUSIONS

With increased life expectancy of CF patients, CFRD has become a major co-morbidity. In an already very complex treatment, the emergence of this new health problem exposes both the patients and healthcare teams to new challenges. Recent evidence suggests that introduction of insulin therapy at earlier stages of the disease might be beneficial on key CF outcomes: lung function and/or weight maintenance. However, the key time for insulin introduction as well as the appropriate insulin regimen (basal and/or prandial) remain to be established. Overall, there is growing evidence showing a relationship between insulin defect/replacement and CF outcomes but it is necessary to implement randomized controlled trial to balance awaited significant benefits with side effects and added burden.

CASES WITH QUESTIONS

To be discussed at time of presentation.

DISCUSSION OF CASES AND ANSWERS

To be discussed at time of presentation.

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Workup and Management of Severe Insulin Resistance Syndromes

M13
Saturday, June 15
3:00–3:45 PM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Severe resistance to the metabolic actions of insulin is an increasing problem, attributable largely to the burgeoning prevalence of severe obesity. Syndromes of Severe Insulin Resistance (SSIR), in contrast, are a group of rare and heterogeneous disorders in which severe IR is seen in the absence of obesity. These disorders may be acquired or congenital, and may be caused by primary defects in adipose tissue function, or in insulin signaling. SSIR are associated with high levels of severe morbidity and premature mortality, attributable to poorly controlled hyperglycaemia, fatty liver disease, atherosclerosis, ovulatory dysfunction and cancer, although not all SSIR are associated with all these conditions. Nevertheless the diagnosis of SSIR is often delayed, and management by physicians with little experience of these disorders is often suboptimal.

BARRIERS TO OPTIMAL PRACTICE

The clinical concept of "insulin resistance" is highest in the consciousness of those working in diabetes services, where insulin is routinely prescribed. However although SSIR are commonly seen in such clinical environments at some point in their natural history, their first presentation is often to different clinical services, including endocrinology, reproductive medicine, obstetrics & gynaecology, lipidology, hepatology, dermatology, plastic surgery, and may antedate development of insulin-requiring diabetes by many years. One major barrier to optimal practice is lack of awareness of the early clinical features of severe IR, which often delays diagnosis of SSIR and thus targeted therapy.

A second major risk and barrier to optimal management of lipodystrophic SSIR lies in insufficiently wide awareness of the uncoupling of severe IR and dyslipidaemia from obesity in patients seen in these conditions. Specifically, the erroneous belief that lack of adipose tissue is caused by undernutrition may lead to prescription of diets with increased calorie and/or fat content, putting patients at risk of severe short and long term clinical complications.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Recognize common clinical presentations of lipodystrophic and non lipodystrophic syndromes of severe insulin resistance (SSIR)
- Understand how laboratory investigation may be used to guide genetic diagnostics
- Understand the principles of management of SSIR, and the limitations of underpinning evidence

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Peri- or Postpubertal SSIR

Clinical suspicion of genetic SSIR should be raised by any of the following:

- Clinical hyperandrogenism, often with oligomenorrhoea or amenorrhoea, in a lean post pubertal female with acanthosis nigricans
- Precocious puberty in a lean child with

acanthosis nigricans
- Marked acanthosis nigricans in any lean patient
- Symptoms suggestive of postprandial hypoglycaemia in a patient with acanthosis nigricans

Clinical suspicion of a lipodystrophic form of SSIR should be raised by any of the following:
- Visible lack of adipose tissue, either globally or affecting only some parts of the body (especially femorogluteal depots)
- Unusually severe fatty liver disease at a young age
- Unusually severe hypertriglyceridaemia with acanthosis nigricans
- Previous episodes of pancreatitis
- An unusually muscular appearance, especially in females

Many of these disorders may also feature a markedly acromegalic appearance, with no evidence of GH excess on biochemical testing.

Prepubertal SSIR

Severe recessive SSIR are generally recognized in early life by their syndromic features. For example:

Donohue Syndrome (formerly "leprechaunism"): Presents with IUGR and failure to thrive in early life, with syndromic features that may include soft tissue overgrowth and linear growth retardation, prominent sex hormone-dependent tissues, organomegaly, cholestasis, nephrocalcinosis, ovarian tumors, and rectal prolapsed. Acanthosis nigricans develops later. Hypoglycaemia and/or hyperglycaemia may be apparent neonatally, but diagnosis of these can be delayed when the importance of the other features is not recognized. Death usually occurs during intercurrent infection or illness in the first 1-2 years of life

Rabson Mendenhall Syndrome: On the same clinical spectrum as Donohue Syndrome but less severe. Presents with failure to thrive, linear growth retardation with hypertrichosis, acanthosis nigricans, coarse facial features, premature dentition, and often nephrocalcinosis. Diabetes may not develop until towards the end of the first decade, and then hyperglycaemia becomes progressively more difficult to control. Death from the complications of hyperglycaemia is common in the second or third decade.

Congenital Generalised Lipodystrophy: Usually noticed by mothers or doctors as a failure to develop adipose tissue, producing a skinny, "wrinkly" appearance, often coupled to accelerated linear growth and abdominal distension due to fatty liver. May sometimes be associated with myopathy depending on the genetic aetiology

"Complex" SSIR

Severe IR is seen at a high prevalence in some other, more complex syndromes in which it may often be overlooked due to the focus on other aspects of the conditions. Such syndromes include a variety of forms of primordial dwarfism, such as osteodysplastic primordial dwarfism of Majewski Type 2 (MOPDII), Alström syndrome, and a group of premature ageing syndromes including Werner syndrome, Bloom syndrome and mandibuloacral dysplasia. Indeed in some of these syndromes, severe IR may be the first presenting feature. Clinicians evaluating any complex syndrome should be alert to acanthosis nigricans and/or severe fatty liver/dyslipidaemia, and should understand that they may imply the presence of severe IR.

Acquired SSIR

The main forms of acquired severe IR in a lean patient, apart from severe intercurrent illness or endocrinopathy, are Type B insulin resistance, caused by the generation of blocking antibodies against the insulin receptor, or acquired generalized lipodystrophy. The hallmarks of both these conditions are relatively sudden onset and rapid progression of severe IR which may feature severe acathosis nigricans, hyperandrogenism, and dramatic weight loss. Lipodystrophy is clinical apparent, and also may feature severe fatty liver, while Type B IR characteristically does NOT feature dyslipidaemia or fatty liver. Wider evidence of autoimmune derangement is common in both conditions.

Many specific diagnoses can be made with confidence on clinical grounds based on understanding of these presentations. For some syndromes, however, further biochemical testing may be extremely valuable in subdividing severe IR and guiding further investigation.

Investigation of SSIR

Suggested Initial Investigation

- Fasting glucose, insulin*, then OGTT with insulin measurements if strong suspicion
- HbA1c
- Fasting lipids
- Testosterone
- Leptin, adiponectin, IGFBP-1, SHBG
- Clinical photography (perhaps MRI/DXA if lipodystrophy suspected)
- Liver and ovarian USS

*Consider type of insulin assay, and ability to pick up native and analogue insulins

These investigations confirm severe IR, and identify the subgroup without dyslipidaemia and fatty liver, and with normal or raised adiponectin (and often SHBG and IGFBP1). This group is very likely to have congenital or acquired loss of insulin receptor function.

- Secondary, more targeted investigation (guided by clinical and biochemical features)
- Genetic testing (most commonly LMNA, PPARG, INSR in peri- or postpubertal patients; INSR, BSCL2, AGPAT2 in prepubertal patients)
- Anti-Ins Abs ("macroIns")
- Anti-InsR Abs
- Immunoglobulins
- C3, C4, C3 nephritic factor

Many patients remain after these investigations without a specific diagnosis, and an important part of management is to consider offer enrolling into a research study.

Principles of Management of SSIR

It is important to note that the rarity of SSIR means that evidence supporting specific management strategies is limited, from case series from several centers at best, to expert opinion at worst. Increasing organization of SSIR services in a few centers is likely to improve this over coming years.

Maximization of insulin sensitivity and reduction of demands on beta cell

- Exercise
- Early use of metformin
- Possibly pioglitazone
- Possibly IGF1 in the most extreme infantile or prepubertal cases of INSR defect.

High dose insulin replacement when beta cells fail

- MDI Insulin, moving to U500 insulin when total daily dose exceeds 250-300 units
- CSII may be beneficial, and may deliver U500 insulin

Offload adipose tissue (critical in lipodystrophic SSIR)

- Low fat diet
- Orlistat*
- GLP1 agonists*
- Bariatric surgery*
- Leptin (if leptin levels very low (threshold not clearly defined, but often taken to be c. 5mcg/l)

*Rational, and likely to be beneficial on theoretical grounds, but supported only by limited case reports and clinical experience to date

Treat complications of Severe IR

- Hyperandrogenism: GnRH suppression with a combined pill with anti-androgenic activity is usually beneficial. In extreme cases GnRH agonist with add back oestrogen may be effective. These therapies are often combined with topical eflornothine, systemic anti-androgens, and cosmetic therapies.
- Postprandial hypoglycaemia: A low GI diet and acarbose may be helpful
- Acanthosis Nigricans: topical keratinolytic therapies or retinoids may offer some benefit
- Cosmetic Distress: A wide range of plastic surgical procedures have been used in lipodystrophy, both to replace fat (e.g. buccal fat pad), or to remove unwanted excess fat (e.g. liposuction)
- Screen for and treat diabetic complications

- Primary prevention of atherosclerosis: treat hypertension and dyslipidaemia

MAIN CONCLUSIONS

- Severe IR should be suspected in anyone with acanthosis nigricans
- Aggressive "PCOS" is the commonest manifestation in peri- or postpubertal females
- Hypoglycaemia may commonly be seen in the early stages
- Careful clinical assessment of adipose distribution is essential.
- Determined insulin sensitization and replacement are key
- Leptin has an important place in management for some cases
- IGF1 therapy can be effective in severe recessive insulin receptoropathies, but the relative balance of risk and benefit is not well established.
- It is rational to treat patients with lipodystrophy and severe metabolic derangement in a similar manner to patients with morbid obesity with metabolic complications, though large scale evidence for efficacy of GLP1 agonists, bariatric surgery and other treatments is not yet available.

CASES WITH QUESTIONS

Case 1

A 15-year-old girl was referred to the endocrinology clinic with hirsutism and primary amenorrhoea. Coarse facial hair had first been noticed at 12 years old, becoming progressively more severe and cosmetically distressing over the past year. A history of diabetes in a paternal grandmother was noted. On examination her body mass index was 21 kg/m2 and height 1.52 m. She had moderately severe acne and severe hirsutism affecting her face, chest and lower abdomen. Puberty was well advanced. Acanthosis nigricans was prominent in both axillae, with numerous skin tags. General examination was otherwise normal.

Investigation revealed a female karyotype, enlarged ovaries with multiple peripheral cysts, an elevated LH:FSH ratio and a high testosterone of 8.2 nmol/l. DHEAS levels were normal, and subsequent ovarian vein sampling confirmed that the serum testosterone to be of ovarian origin. Fasting insulin was extremely elevated at 1088 pmol/l with a glucose of 3.4 mmol/l, and glucose 2 hours after a 75g oral glucose challenge of 12.1 mmol/l. HbA1c was 60 mmol/mol. A lipid profile was normal and there was neither biochemical nor radiological evidence of fatty liver.

1. ***What is the likely diagnosis?***
2. ***How would you investigate next?***
3. ***What treatment would you start?***

Case 2

A 21-year-old woman presented with a 12 hour history of severe central abdominal pain radiating to her back. She reported previous similar but milder episodes overt the preceding two to three years. A family history of non-insulin dependent diabetes was noted. She drank minimal quantities of alcohol and exercised infrequently. Her BMI was 23.5 kg/m2. There was generalized paucity of subcutaneous adipose tissue in the limbs and torso, with evidence of previous breast augmentation surgery. Adipose tissue was increased in the head and neck, giving a somewhat Cushingoid appearance, but there were no other clinical features of Cushing's syndrome, and indeed far from showing muscle wasting peripherally, she was conspicuously muscular, particularly in her calves. There was moderate facial hirsutism and both nuchal and axillary acanthosis nigricans. Examination of the abdomen revealed pronounced epigastric tenderness, some distension, and a palpable liver edge, with very quiet bowel sounds. There were no stigmata of chronic liver disease. On insertion of a urinary catheter, rather pronounced accumulation of labial adipose tissue, but no cliteromegaly, was noted. Serum amylase levels were normal

1. ***What are the likely diagnoses?***
2. ***What is the best strategy to prevent further episodes?***

DISCUSSION OF CASES AND ANSWERS

Case 1

1. She is likely to have a pathogenic

mutation in the insulin receptor gene. Hyperandrogenism is usually particularly severe in the second decade, when pubertal IR interacts with the underlying genetic defect. Testosterone levels may be extremely high (up to 15 nmol/l), and may induce some virilisation. Although these ovarian features of IR are generic to nearly all forms of SSIR, dyslipidaemia and fatty liver are almost never a feature of proximal insulin signaling disorders, while inappropriately normal or high plasma adiponectin levels are also characteristic, and can be used to triage patents with SSIR for INSR gene screening. Whether the benign lipid profile and lack of fatty liver translates into long term protection of these patients with SSIR from atherosclerosis and fibrotic liver disease has yet to be formally determined.

2. Elevated adiponectin of 17.7ug/l was further confirmation of this, and she was subsequently shown to have the p.Pro1178Leu mutation on INSR gene sequencing.
3. Dietary modification, increased exercise, and pharmacological therapy with a maximal dose of metformin, a combined oral contraceptive pill containing cyproterone acetate and topical eflornithine produced a significant improvement in hirsutism and stabilization of glycaemia.

Case 2

1. Acute pancreatitis due to uncontrolled hypertriglceridaemia in Dunnigan Kobberling-type familial partial lipodystrophy is most likely based on the pattern of fat loss, with increased fat in head and neck and labia. Lipaemic serum was reported, and abdominal CT imaging showed a swollen pancreas consistent with pancreatitis. Fasting plasma triglyceride was later found to be 38mmol/l (<2mmol/l), with a fasting blood glucose of 18 mmol/l and plasma insulin of 2,300pmol/l. Note that a normal amylase may give false reassurance in the setting of hypertriglyceridaemic pancreatitis, when it is often spuriously normal. In this case a heterozygous mis-sense mutation, p.Arg482Trp in the LMNA gene was identified.
2. After recovery from the acute pancreatitis, longer term management centers on dietary "off-loading" of adipose tissue through a low fat diet, with adjunctive use of metformin. Fenofibrate was initiated to help control persistent hypertriglyceridaemia, but leptin therapy was not considered initially in view of the base-line serum leptin level of 12 ug/l.

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Insulin Management With Exercise

M49
Monday, June 17
1:00–1:45 PM & 3:00–3:45 PM

Raj Wadwa, MD
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SIGNIFICANCE OF THE CLINICAL PROBLEM

Exercise has multiple benefits for patients with diabetes mellitus, including improvements in glycemic control, weight control, improved cardiovascular health and an improved sense of well being. Regular exercise is recommended for most patients with diabetes mellitus and should be considered part of healthy living with diabetes (1).

For patients on insulin treatment, there are several challenges to incorporating exercise into daily life, including increased glucose variability with the initiation of a new physical activity and the increased risk of hypoglycemia during or after exercise. For the competitive athlete, suboptimal blood glucose control may lead to decreased performance. Insulin adjustments for exercise will depend on multiple factors including the patient's age, baseline insulin sensitivity, exercise type, duration and intensity. Because of the many variables involved, advising patients on insulin adjustments can be challenging but important in order to assist the patient to initiate or maintain an exercise regimen.

In this session, we will discuss key factors to take into consideration for insulin management with exercise. The focus will be on patients with type 1 diabetes using either a regimen of multiple daily injections (MDI), including multiple doses of a rapid acting insulin analog plus 1-2 injections of a basal insulin, or use of an insulin pump/ continuous subcutaneous insulin infusion (CSII) therapy with a rapid acting insulin analog given as a basal infusion and multiple bolus doses throughout the day.

Safety Considerations

The presence of retinopathy, neuropathy, nephropathy or other risk factors for heart attack or stroke may predispose the patient diabetes to increased risk with certain types of strenuous exercise. Such circumstances require consultation with a health care provider before engaging in moderate to intense physical activity. In older adults with diabetes, a medical exam may be indicated before engaging in a new exercise routine. More comprehensive safety recommendations for exercise and diabetes are beyond the scope of this presentation but should be taken into consideration by the clinician (2).

BARRIERS TO OPTIMAL PRACTICE

The **variability in blood sugars** can be more dramatic with exercise leading the patient to get frustrated with the increased challenges that exercise introduces to insulin management and glycemic control. Trial of insulin adjustments and modification of the insulin regimen based on personal experience may be necessary. It is important for the person with type 1 diabetes to keep in mind the multiple benefits of exercise and work with their clinical team to find a way to manage blood sugars and overcome this barrier.

Patients with type 1 and type 2 diabetes should be encouraged to stay active and exercise regularly. Given the risk of hypoglycemia for type 1 diabetes patients, recommendations for management of insulin and prevention of hypoglycemia are essential so patients with diabetes may feel more comfortable with being more active without

worry of hypoglycemia during or after exercise.

In this session, we will discuss anticipated barriers and key factors to consider when adjusting insulin for patients with type 1 diabetes.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

1. List potential barriers to exercise for insulin dependent patients with diabetes mellitus
2. List key factors to take into consideration when adjusting an insulin regimen for exercise.
3. Understand and utilize general recommendations for reduction of basal and bolus insulin for varying levels of physical activity for patients with type 1 diabetes.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT:

Strategies for Management

Physiology of glucose metabolism

In a person without diabetes, exercise leads to an increase in glucose uptake in skeletal muscle. Decreased insulin levels and increased counter-regulatory hormones lead to increased glucose production in the liver and glucose levels remain relatively stable (3).

With **type 1 diabetes**, exogenous insulin delivery replaces endogenous insulin secretion from the pancreas. Counter regulatory hormone release is impaired or blunted and the patient is at increased risk for hypoglycemia with physical activity.

Experience with physical activity in patients with type 1 diabetes demonstrates that blood glucose changes are variable in response to exercise. With aerobic exercise and with longer duration, hypoglycemia is more likely to occur. With anaerobic exercise or shorter bursts of intense activity, hyperglycemia may be seen during exercise due to catecholamine release with certain physical activity. Hyperglycemia is usually transient and may be followed by hypoglycemia several hours after physical activity is complete. Therefore, the type of exercise must be taken into consideration.

Key factors to consider prior to exercise

In addition to the type of exercise, the intensity and duration of exercise should be considered. Longer duration and more intense exercise will require more significant reductions in the insulin doses.

Antecedent hypoglycemia on the day of or day prior to physical activity will put the patient at higher risk for development of hypoglycemia during exercise due to blunting of the catecholamine response.

Monitoring of blood glucose is crucial with exercise. Fingerstick blood sugars should be done prior to exercise, at least every 60 minutes during exercise and immediately after exercise. Monitoring for several hours after exercise may lower the risk for development of post-exercise hypoglycemia. Some competitive athletes with type 1 diabetes will check multiple blood sugars during competition to maintain optimal blood glucose control. Documentation of blood sugars with repeated activities (such as sports practices) may reveal trends that will help the patient make more informed insulin dose adjustments based on personal experience. One may even consider a role for continuous glucose monitoring (CGM). Evidence suggests that use of CGM may reduce the risk of post-exercise hypoglycemia (4), however, CGM is not considered standard of care at this time.

Poor metabolic control may be problematic with exercise. Hyperglycemia can hasten dehydration. Exercise with significant insulin deficiency may worsen ketosis due to increased fatty acid metabolism in place of carbohydrate metabolism. If a patient has a blood sugar over 250 mg/dl prior to exercise, ketone levels should be assessed and managed. **The patient with significant ketosis should not engage in exercise** until ketosis is resolved.

Adjustment of insulin

Adjustment of insulin will depend on the type, duration and intensity of exercise. Aerobic exercises, such as distance running, cycling or swimming, are more likely to lead to hypoglycemia during and after exercise. Anaerobic exercise or bursts of more intense exercise, such as sprints, hockey or weight lifting may lead to hyperglycemia during the

activity followed by hypoglycemia usually 6-12 hours and up to 24 hours after exercise.

General concepts around adjustment of basal and bolus insulin will be described here. Basal insulin in MDI regimens refers to long acting insulin analogs such as insulin glargine and insulin detemir and for those on insulin pumps refers to basal rates of rapid acting insulin analogs, including insulin aspart, lispro and glulisine. Evidence suggests that use of insulin pumps allow for more flexibility and therefore better blood glucose control compared to regimens of insulin injections (5). However, multiple factors must be considered when determining if a patient should utilize insulin pump therapy.

Basal insulin

Changes in basal insulin will depend on the regimen used. Insulin pumps allow for more options for basal adjustment than injections of glargine or detemir given once or twice per day. Regardless of the insulin regimen, the degree of basal adjustments will depend on the intensity and duration of exercise.

If the patient anticipates moderate to vigorous exercise lasting for more than 60 minutes, a 10% decrease in basal dose or at least 0.5 -1 units should be made. For longer duration of exercise, such as long distance running, cycling, or endurance events, larger decreases in basal insulin could be considered to as much as a 50 % decrease.

After exercise, basal insulin should be adjusted to prevent post-exercise hypoglycemia. For those engaging in afternoon or evening sports practices or competition, especially with sustained aerobic exercise, lowering of basal insulin by 20% will significantly reduce the risk of nocturnal hypoglycemia. Future adjustments may then be determined based on experience with initial reductions.

Patients on insulin pumps may need to disconnect the pump for swimming or contact sports. Some may prefer to disconnect the pump or suspend the basal rate during exercise even when disconnecting the pump is optional. Data from the DirecNet study group showed a significant reduction in hypoglycemia during 60 minutes of intense exercise in youth with type 1 diabetes when basal insulin was discontinued during exercise (6). However, patients should be reminded that disconnecting the pump for longer than 3 hours may lead to the development of ketosis due to a lack of insulin in the body. For prolonged exercise, the diabetic athlete may need to reconnect the insulin pump every 1-2 hours to give small boluses to cover basal insulin requirements. After exercise, reduction in basal insulin using temporary basal rates should be considered. Taplin et al found in adolescents with type 1 diabetes that discontinuation of basal insulin during exercise and a 20% reduction in basal rate at bedtime for 6 hours after exercise significantly decreased the risk for post-exercise nocturnal hypoglycemia (7).

Bolus insulin

Reductions of bolus insulin will depend on the intensity and duration of exercise. Pre-meal insulin doses should be reduced for the meal prior to exercise 25-75%, depending on the intensity level of exercise. For high intensity exercise of 60 minutes or longer, an even larger reduction in the bolus could be considered.

Insulin may be more rapidly absorbed if the injection site or pump insertion site is in an extremity that will be exercised. Therefore, consideration for moving injections to less used extremities should be considered. For example, a tennis player should consider moving injections from the dominant arm to another site. A runner should avoid injections in the legs and consider moving injections to the arms.

Hydration and nutrition

Hydration is an important consideration for any athlete and is especially important for the diabetic athlete. The athlete with diabetes is at increased risk for dehydration when hyperglycemia leads to osmotic diuresis. Drinking water is optimal in most cases but fluid replacement with sports drinks or other fluids may be considered in longer events or when carbohydrate intake is needed (8).

While carbohydrate and protein intake before, during and after exercise, particularly for endurance sports are important considerations for the diabetic patient, specific

dietary considerations with exercise are beyond the scope of this session and will not be covered. Descriptions of dietary and fluid replacement recommendations for the athlete with type 1 diabetes have been published (8,9)

Preventive efforts
The active person with type 1 diabetes should have access to a carbohydrate source during exercise for prevention and treatment of hypoglycemia. Access to hydration is also important for physical activity of almost any duration. For youth with type 1 diabetes, it is important for coaches or other supervising adults to be aware of the child with diabetes to allow for access to hydration and treatment of hypoglycemia with carbohydrates when necessary.

MAIN CONCLUSIONS

Management of type 1 diabetes may be more challenging when physical activity is involved. Changes in insulin sensitivity and release of counter regulatory hormones may make blood sugars less predictable and insulin dosing more challenging. The healthcare provider can be of assistance to the patient by giving initial recommendations for insulin adjustments based on exercise type, duration and intensity. Management, including insulin adjustments, dietary intake and hydration should be adjusted based on the patient's experience and tendencies with particular activities. Documentation of blood sugars with frequent fingerstick blood sugars is helpful in this process CGM may also be considered.

CASES WITH QUESTIONS

Case 1

A 16 year old girl with type 1 diabetes for 3 years is active on her high school basketball team. During the season, her team practices for 1-2 hours, three to five days per week and has games 1-2 times per week. She has had more hyperglycemia during the season. She is on an MDI regimen and her last HbA1c was 9.2%.

What further information should be obtained regarding her hyperglycemia?
What insulin adjustments would you recommend?
What other recommendations would you give this patient and her family?

Case 2

A 35 year old man with type 1 diabetes for 23 years has taken up running and has started to train for his first 10 km running event. He has been limited in his efforts due to mild hypoglycemia at 15-20 minutes into his runs and waking at night with mild hypoglycemia. He has been on an insulin pump for 10 years and his last HbA1c was 6.7%.

What other history should have been considered before he started training?
What basal and bolus dose adjustments should be recommended?
He is considering use of continuous glucose monitoring. What do you advise?

DISCUSSION OF CASES AND ANSWERS

Case 1

The 16 year old girl has suboptimal glycemic control based on her most recent HbA1c. She is also having more hyperglycemia, possibly due to inadequate or missed insulin. Clarification about the timing of her hyperglycemia would be helpful. Assessment of blood sugars (ideally using bg logs or meter downloads)and avoiding missed insulin doses are initial steps. She may need additional insulin on less active days if hyperglycemia is more prominent on less active days. If hyperglycemia is occurring before or during basketball games, catecholamine release or high carb pre-game meals may be contributing and small amounts of additional insulin prior to games on game days. Excessive insulin after exercise should be avoided to prevent post-exercise hypoglycemia.

Case 2

The 35 year old man should have had screening for microvascular complications and other CVD risk factors. Assuming this was done and he has no significant complications or CVD risk factors, basal insulin should be reduced during and after exercise. If training runs will be less than 2 hours in duration, he could disconnect or suspend the pump during his running and use a temporary basal rate after exercise. At

night, a basal rate reduction of at least 20% should be initiated and then may be adjusted. Bolus doses should be decreased for the meal immediately after exercise with the percentage decrease dependent on intensity and duration of exercise. A 50% decrease in this meal bolus would be a good starting point. CGM may be helpful in addition to fingerstick blood sugars, especially to review trends in overnight blood sugars. It is important for the patient to understand that use of CGM will not replace fingerstick blood sugar testing.

WEBSITES OF INTEREST

www.insulindependence.org and www.runsweet.com

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Diabetes: Pumps and Sensors

M47
Monday, June 17
1:00–1:45 PM & 3:00–3:45 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Over the last 10-15 years, the management of type 1 diabetes has become significantly more challenging, in large part due to the availability and increasing adoption of complex and wonderful new technologies, such as insulin pumps and continuous glucose monitoring devices. While not new, insulin pumps have been standard-of-care, and current models are equipped with an ever-increasing array of features and embellishments designed to aid the user and clinician. Glucose sensors, once considered a fringe therapeutic novelty, are also becoming standard-of-care and increasingly popular among many people wishing to have the best tools at their disposal. It is critical that diabetes professionals become not only familiar with the benefits and limitations of these devices, but comfortable with using them for routine diabetes management across the lifespan of patients with type 1 diabetes.

BARRIERS TO OPTIMAL PRACTICE

- Clinicians may underutilize insulin pump therapy in their practice because they feel that managing patients with insulin pumps is too difficult, time-consuming, or of unclear clinical benefit.
- Clinicians may not appreciate the benefit of using CGM in their patients with type 1 diabetes because they are not convinced that CGM offers clinical benefit, patients can use them safely and effectively, and that it will not add to the burden of care.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Recognize the advantages and limitations of insulin pump therapy for patients with type 1 diabetes
- Understand the basic concepts of bolus dosing and basal rates
- Recognize the situations in which advanced concepts such as temporary rates and dual-wave/combination boluses, may be useful
- Discuss the advantages and limitations of continuous glucose monitoring in patients with type 1 diabetes
- Make therapeutic recommendations based on samples of CGM tracings

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

(see next page)

MAIN CONCLUSIONS

Insulin pumps and CGMS have become standard components of clinical diabetes management, and it is important for practitioners to become familiar with their routine use. With proper understanding of bolus dose and basal rate adjustments based on blood glucose logs or CGM tracings, most clinicians will find that pumps and sensors actually SAVE time and effort and improve the health and quality of life of their patients. The most important role the clinician is to provide realistic expectations of these technologies for their patients to "set them up for success."

CASES WITH QUESTIONS AND DISCUSSION OF CASES AND ANSWERS

Case 1

The parents of a 6 year old girl with type 1

SUCCINT REVIEW

Insulin pump basics

I. **Basal rate:**
   - **a.** amount of insulin required to maintain stable glucose levels in the absence of food
   - **b.** generally 40-60% of a person's total daily insulin dose
   - **c.** may be initially determined by dividing patient's entire long-acting insulin dose by 24 to give hourly rate (or taking 40-50% of their total daily insulin dose and dividing that by 24 to give hourly rate, rounding down for safety)
   - **d.** most people with T1D require several different basal rates per day, to account for:
     - **i.** dawn phenomenon (higher basal rates required in early morning hours)
     - **ii.** exercise (lower basal rates required after intense exercise)
     - **iii.** hypoglycemia unawareness (lower basal rates at night, for example, to reduce risk of nocturnal hypoglycemia)

II. **Bolus dose:**
   - **a.** Dose of insulin provided to lower glucose in reaction to a high BG test (correction bolus) or to cover the carbohydrate content of a meal or snack (food bolus)

   - **b. Correction bolus:**
     - **i.** Is based on individual's **insulin sensitivity factor (ISF)**, which is the drop in blood glucose (in mg/dL) a person would experience from **1 unit insulin** (for example if a patient's ISF is 1:50, then 1 unit insulin should drop their BG level by 50 mg/dL
     - **ii.** Correction bolus dose may be determined at any time by the **current BG,** the **ISF**, and the **target BG:**

       Correction dose (units) = (current BG – target BG) / ISF

       (example: current BG = 220, target BG = 100, ISF = 40; appropriate correction dose would be (220-100)/40 = 3 units

     - **iii.** **ISF** may be estimated using the "**1800 Rule":**

       1800 / TDD (total daily dose) = ISF

       (example, if patient's TDD was 45 units, the ISF would be 40

   - **c. Food bolus:**
     - **i.** Is based on individual's own **insulin-carbohydrate ratio (ICR),** which is the amount of insulin required for a given amount of carbohydrate intake
     - **ii.** **ICR** may be estimated using the "**450 Rule":**

       450 / TDD = ICR

       (example, for the same patient with TDD of 45 units, the ICR would be 10)

     - **iii.** Timing of boluses important factor:
       1. Pre-meal better than post-meal
       2. In advance of meal even better! Particular when hyperglycemic

More advanced pump concepts:

III. Temporary basal rate

- **a.** Time-limited adjustment to programmed rate, usually expressed as a percentage of that rate or a percent difference of that rate (e.g. 150% / +50%, or 80%/-20%)
- **b.** Extremely useful for managing special situations such as
  - **i.** Exercise
  - **ii.** Illness
  - **iii.** Long duration travel

IV. Combination / Dual-wave bolus

- **a.** Special type of bolus in which not all of the insulin is given at the time of the activation of the bolus: a percentage is given at once, and the remainder is given evenly, over a predetermined number of hours following the activation of the bolus
- **b.** Very useful for specific situations in which gastric emptying is PROLONGED:
  - **i.** High-fat foods (such as pizza)
  - **ii.** Patients with gastropathy
  - **iii.** Patients using pramlintide, exenatide, or liraglutide

V. Insulin on board / Active insulin

- **a.** The amount of insulin previously delivered (from a previous bolus) that is "still in the system" or "actively working"
- **b.** Based on the pharmacokinetic/pharmacodynamic properties of insulin via subcutaneous injection, curvilinear profile over approximately 5 hours
- **c.** Designed to prevent insulin "stacking" from repeated bolus dosing
- **d.** DIFFERENT PUMPS CALCULATE IOB DIFFERENTLY !!!

Continuous glucose monitoring (CGM)

VI. Evidence supporting efficacy

- **a. JDRF-CGM trial**
- **b. STAR-3 Study**
- **c. DirecNet** studies in young children
- **d. Current Clinical Practice Guidelines**

VII. Basic concepts

- **a. CGMS** measure **interstitial fluid** glucose, not **blood glucose**, so must be converted to BG through **CALIBRATION.**
- **b. Calibrations** are based on one point in time, and must be repeated, as sensor accuracy can drift over time
- **c. Lag time:** the physiological difference between timing of glucose fluxes between capillary space and interstitial space – has important effect on sensor accuracy due to timing of calibrations
- **d. Sensors are better at following vectors of glucose change (TREND), not determining actual point accuracy of glucose level (NUMBER)**

VIII. Advanced topics

- **a. Alarms**
  - **i. Threshold alarms** for high or low glucose levels
  - **ii. Rise/fall** or **Rate-of-change** alarms
  - **iii. Impending** or **Predictive** alarms
- **b. Using Trend Arrows to Adjust Bolus dosing**
- **c. Using Reports for Retrospective Analysis and Therapeutic Adjustments**
  - **i. Modal days**
  - **ii. Meal modals**
  - **iii. Individual days**
  - **iv. Overnight**
  - **v. Behavioral assessment**

diabetes diagnosed 9 months ago inquire about the appropriateness of an insulin pump for their daughter. She is currently treated with one morning injection of glargine (8 units) and 1-2 units of rapid-acting analog for each meal or snack. They recently attended a fundraising event and were told by other parents that "the pump changed our lives." The girls A1c is 7.7%, and she had one severe hypoglycemic episodes a few months ago after a pool party.

Questions

1. ***Is this girl a good candidate for insulin pump therapy? Why or why not?***
2. ***What discussions should you have with the parents regarding expectations of pump therapy?***
3. ***What, if any, learning should be in place before commencing pump therapy?***
4. ***What would be appropriate initial settings for the pump? How would these be evaluated?***

Answers

1. Of course she's a good candidate for pump therapy! Young children actually make wonderful pumpers, because they benefit from the small dosing capabilities of modern pumps, and parents or other adult caretakers can administer the insulin for them. There are no real age- or diabetes duration-specific requirements for pump therapy, and having a child become used to the pump long before puberty can be a great advantage. Even infants and toddlers can be successfully initiated on pumps, as long as lock-out features are enabled to prevent accidental button-pushing.
2. The family does need to understand that insulin pumps are not magic, or "one step further away from diabetes", but only a powerful tool for diabetes management. I often tell my families that pumps are not easier than shots, they are actually harder, but provide more control and ultimately more flexibility. The family should understand that the number of BG checks usually increases following initiation of pumping, and that the one real safety concern is ketosis or ketoacidosis following accidental catheter dislodgment.
3. The family should understand the basics of carbohydrate counting, as this skill is central to determining proper bolus doses for meals. Obviously, basic skills such as sick day management should be reviewed with family, in addition to all of the pump-specific instructions.
4. There are several ways to determine this: easiest is to take the long-acting insulin and convert to a basal. 8 units glargine over 24 hours = 0.3 units/hour. To be conservative, one might take 75% of this dose (6 units/24 hours = 0.25 units/hour. We could choose to start with one basal rate for the whole day, or if we knew that she is susceptible to hypoglycemia after daytime exercise, we might reduce her nighttime basal rate to 0.2 units/hr from 9pm to 6am, to reduce the risk of nocturnal hypoglycemia. For the bolus doses, let's say her total daily dose was around 12 units/day. Her ISF would then be 1800/12 = 150 (one unit insulin to bring BG down 150 mg/dL) and her ICR would be 1:38 (one unit insulin for 38 gm CHO, which we could round down to 1:40 for ease). We often choose a slightly more aggressive ICR for breakfast, let's say 1:35, as many children are more insulin resistant first thing in the morning, perhaps related to dawn phenomenon. In any case, these are initial settings only, and should be evaluated by the use of pre- and 3-4 hour post-meal BG checks to evaluate the adequacy of her ICR and ISF, and frequent BG checks overnight for the first week to evaluate her basal rates. Additionally, daytime basal rates can be tested by periodic delaying of a meal. The use of CGM, either real-time or retrospective, is also an excellent tool to evaluate pump settings.

Case 2

A twenty-year old college student new to your practice has recently decided "it's time to take control over my diabetes." (i.e. his new girlfriend demanded that he gets serious about it or she walks…) He has been using a pump, but his most recent A1c is 9.2%. He has taken the seldom-used CGM out of his drawer and is now using it. He is very motivated to download his CGM tracings and send them to you for review. (*Figure 1*)

FIGURE 1

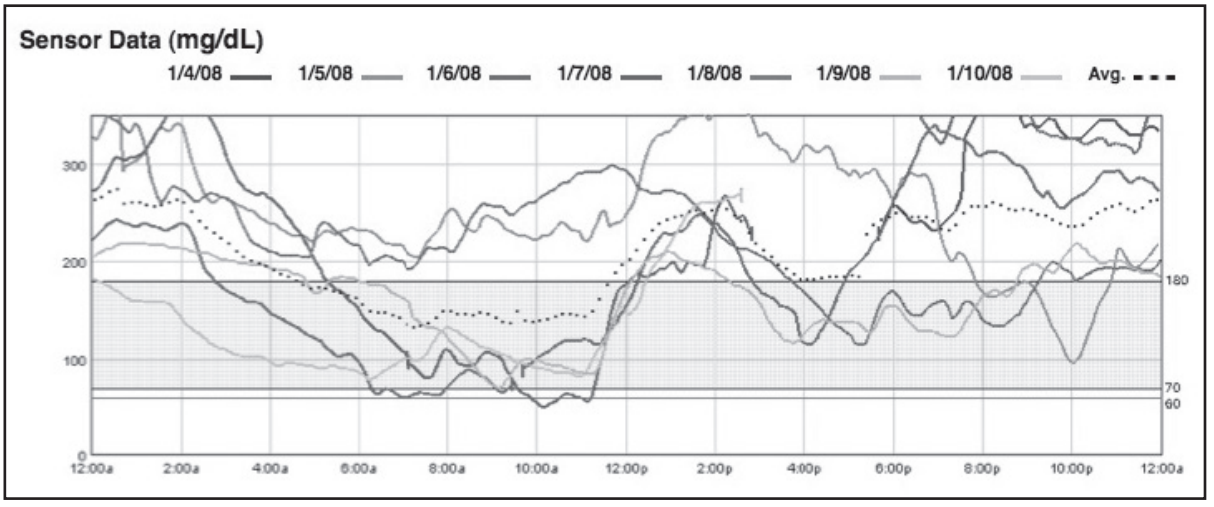
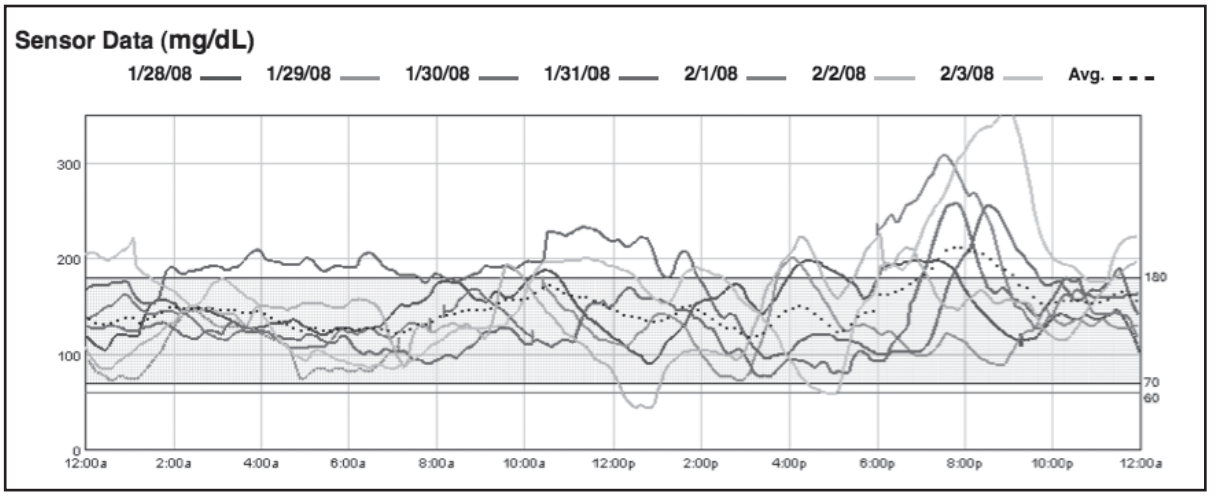


FIGURE 2



Questions

1. ***What pattern(s) islare evident on this sensor modal day graph?***
2. ***What changes would you make to his therapeutic regimen?***

Three weeks later, he sends you the following tracing: (*Figure 2*)

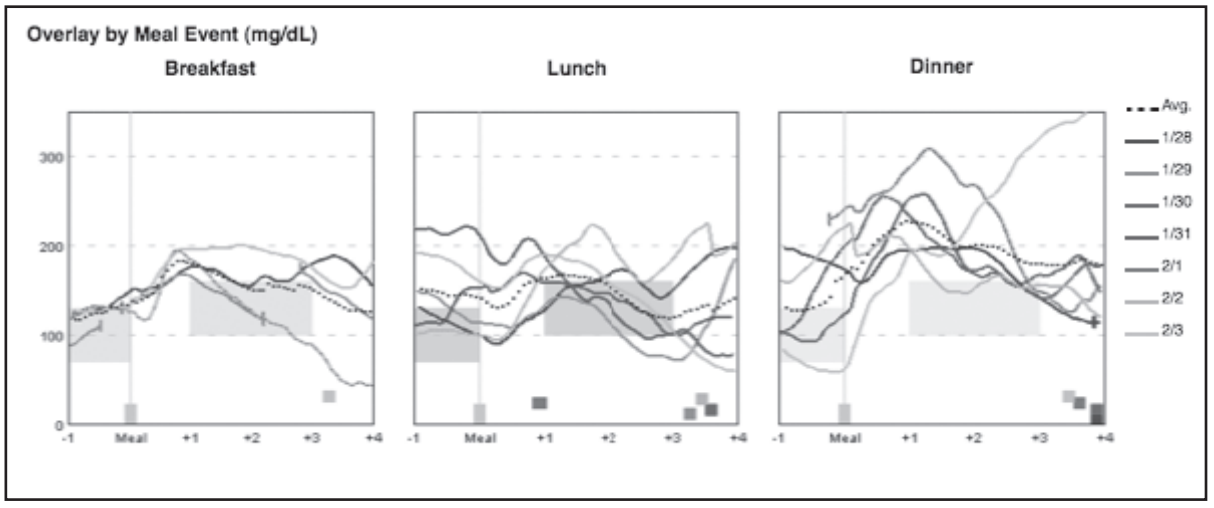
Questions

3. ***What pattern(s) islare evident on this sensor modal day graph?***
4. ***What changes, if any, would you make to his insulin regimen? Does this graph (meal modal) make things easier to see?*** (*Figure 3*)

Answers

1. The first tracing shows many problems, but the most obvious are the elevated glucose levels overnight (left side of the graph) and the elevated levels in the late afternoon/early evening. There are some mid-afternoon swings as well, but these are less consistent.
2. The basal rate should be increased from about 10pm to 5am; he might need additional increases in his dinnertime ICR as well, but additional sensor wears might be needed to tease these apart. Questioning about the food choices in the evening would also be important; I suspect that as a college student, he is snacking late in the evening, and high-fat choices such as pizza might be predisposing him to late increases in his BG levels.
3. This tracing is much more uniform, and the only consistent problem area is late-evening,

FIGURE 3



when BG levels are spiking after 8 pm.

4. An increase in the dinnertime ICR would be useful at this point. Again, questioning as to the meal choices would be helpful as well. He might benefit from the use of combination or dual-wave boluses, if he is snacking on high-fat foods. The use of the meal-modal graph really highlights the swings in dinner compared to the other two meals of the day.

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FEMALE REPRODUCTION

Use of Contraceptive Agents for Non-Contraception

M66
Tuesday, June 18
12:15–1:00 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Hormonal contraceptive agents have been used for a wide variety of reproductive and non-reproductive conditions other than contraception.

BARRIERS TO OPTIMAL PRACTICE

The types of hormones used in hormonal contraception and the routes of administration vary. The plethora of products makes it difficult to optimize care.

LEARNING OBJECTIVES

1. Compare and contrast the types of hormonal contraceptive agents available for use.
2. Delineate the medical conditions, both reproductive and non-reproductive, for which hormonal contraception has putative clinical utility. In many instances, non-contraceptive uses are considered "off-label" and clinical data about the utility of the approach may be sparse.
3. Outline how customary side effects impact the use of hormonal contraception for non-contraceptive uses.
4. Explain how host status and medical conditions impact the pros and cons of contraceptive use for non-contraceptive indications
5. Highlight how host status and medical conditions impact the side effect profile of hormonal contraceptive use.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Hormonal contraception is widely available as a prescription and has proven to be generally safe and effective. Emergency hormonal contraception is also available but beyond the scope of the present discussion.

Hormonal contraceptives are widely utilized for medical and reproductive conditions independent of the need for contraception. Indeed, the term "cycle regulation" was promulgated after the introduction of birth control pills as both a euphemism and a therapeutic option to regularize and make predictable menses.

The wise application of hormonal contraception for noncontraceptive purposes demands an appreciation of the molecular and physiological impact of steroid hormones, including pharmacokinetics and pharmacodynamics, as well as an appreciation of the pathophysiology of particular reproductive and nonreproductive medical conditions.

Pertinent information is outlined in *Tables 1-5*. It is important to emphasize that hormonal contraceptives typically suppress ovarian function by inhibiting GnRH drive and pituitary FSH release. The extent to which ovarian suppression is achieved depends primarily on whether it is administered cyclically or continuously. There has been a trend to lower the dose and use a continuous format with the aim of improving safety and efficacy. Hormonal contraceptives impact the endometrium, especially when progestins are delivered by intrauterine devices.

MAIN CONCLUSIONS

Hormonal contraception can be utilized for noncontraceptive purposes in a variety of reproductive and nonreproductive conditions.

TABLE 1: Commercially Available Reversible Hormonal Contraceptives

Combined Estrogen-Progestin Methods
• Oral
° Estradiol + progestin
° Ethinyl estradiol + progestin
• Continuous
• Cyclic
• Vaginal Ring
• Transdermal
Progestin-Only Methods
• Oral
• Injectable
• Implant
• Intrauterine device
° Mirena®
° Skyla®

TABLE 2: Reproductive conditions for which hormonal contraception has putative utility

• Polycystic ovary syndrome
• Hirsutism
• Acne
• Eumetabolic primary and secondary forms of anovulation
• Nonmalignant ovarian cysts
• Premature ovarian insufficiency
• Perimenopause
• Menorrhagia not due to anatomic cause
• Metrorrhagia not due to anatomic cause
• Fibroids
• Endometrial hyperplasia
• Endometrial polyps
• Endometriosis
• Dysmenorrhea
• Assisted reproduction cycle synchronization

TABLE 3: Non-reproductive conditions for which hormonal contraception has putative utility

• Secondary forms of osteoporosis
• Premenstrual syndrome / premenstrual dysphoric disorder
• Depression
• Anemia
• Coagulopathies with menometrorrhagia

TABLE 4: Contraindications to Combined Estrogen-Progestin Methods

• Hypertension
• Diabetes of long duration or with vascular disease
• Long immobilization, orthopedic surgery, immediately postpartum
• Smoker over age 35 years
• Known or high risk of CVD / CAD / PVD
• Current or personal history of VTE / CVA / MI
• Complex heart disease
• Migraines with aura or at older age
• Thrombophilias
• Hepatitis
• Liver disease
• Significant hypertriglyeridemia
• Breast cancer
• Hormone dependent cancer
• Breastfeeding less than 6

TABLE 5: Combinations of hormonal gents that can be utilized for both contraceptive and noncontraceptive indications

• Combined continuous or cyclic E + P oral contraceptives
• Progestin-only pills ± estrogen (oral or nonoral)
• Progestin-only implants ± estrogen (oral or nonoral)
• Depo-provera ± estrogen (oral or nonoral)
• Progestin IUD ± estrogen (oral or nonoral)
• GnRH-analogs ± add-back hormones
• Contraceptive patch
• Contraceptive rings
• Anti-progestins

CASES WITH QUESTIONS

A 28 year old woman presents seeking advice regarding health maintenance. She carries a diagnosis of PCOS and has been told she should be on metformin. Menses are irregular, G2P2, BMI 30. What do you tell her about the criteria for metformin versus hormonal therapies?

Main points: A Cochrane review by Costello (2007) studied insulin-sensitizing drugs versus the combined oral contraceptive pill, alone or in combination, for hirsutism, acne, risk of diabetes, cardiovascular disease, and endometrial cancer in polycystic ovary syndrome. They reported that OCPs improved menstrual pattern and lowered serum androgen levels more than metformin, while metformin reduced fasting insulin and lowered TG levels more than OCP. Additionally, the side-effect profiles differed between the two drugs.

However, the data were either extremely limited or there were no data on important clinical outcomes such as the development of diabetes, cardiovascular disease, or endometrial cancer. Also, there were no data comparing ISDs other than metformin (that is rosiglitazone, pioglitazone, and D-chiro-inositol) versus OCPs (alone or in combination). In 2012, Kaya et al reported that the elastic parameters of the aorta were improved by adding metformin to OCP treatment and suggested that metformin plus OCP treatment may decrease cardiovascular disease risk in women with PCOS.

A 38 year old woman has been had an endometrioma removed from her left ovary. She experiences significant monthly debilitating dysmenorrhea and is contemplating a hysterectomy and bilateral salpingo-oophorectomy for pain relief. She is also heterozygous for Leiden Factor V and has been told that she cannot use hormonal contraception for suppression of endometriosis and control of pain. Are there any forms of hormonal contraception that might be safely employed in this setting? What additional information would help you to delineate acceptable hormonal options?

Main points: She is a candidate for a levonorgestrel IUD and this could be combined with a low dose (<0.060 mg/day) transdermal estradiol patch.

A 45 year old woman with early stage breast cancer was placed on tamoxifen for 10 years. After 5 years, she developed vaginal bleeding and an ultrasound of the uterus showed a thickened endometrial stripe of and possible endometrial polyp. Hydrosonohysterogram revealed an endometrial polyp and an endometrial biopsy revealed proliferative endometrium. A D&C, hysteroscopy, and polypectomy were done and the pathology was benign. She wants to continue the tamoxifen and wants to know what she can do other than have a hysterectomy to protect against endometrial cancer and other endometrial sequelae of long-term tamoxifen use.

Main points: This is another good use for a levonorgestrel IUD.

A 27 year old woman presents with moliminal migraines and dysmenorrhea. She is taking oral contraceptives containing 21 days of 30 mcg of ethinyl estradiol combined with 1.50 mg of norethindrone acetate followed by a 7 day pill-free interval. The migraines typically occur about 48 hours after the last hormone containing pill when her "menses" start. She wants to know about alternatives.

Main points: She needs a continuous very low dose oral contraceptive such as Lybrel® that contains 20 mcg of EE.

A 47 year old woman presents with intermittent night sweats, mood changes, and heavy menses occurring at unpredictable intervals. She had a bilateral tubal ligation 10 years ago after the uneventful birth of her 4th child. She was symptom free until about 2 years ago, but now she feels out of control. An ultrasound reveals normal uterine anatomy and reduced antral follicle count. A FSH on day 3 of the cycle is 15 IU/L and a day 21 progesterone is 5 ng/mL. Her TSH and free T4 are normal. Her BMI is 26. She has no recognized health problems. She wants to discuss treatment options.

Main points: She is perimenopausal and the menometrorrhagia likely reflects

anovulatory cycling. She is a candidate for continuous lowest dose oral contraceptives or a levonorgestrel IUD + transdermal estradiol.

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Management of PCOS

M16
Sunday, June 16
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Polycystic ovary syndrome (PCOS) is most common endocrine disorder in women and it is now recognized that not only is PCOS the most frequent cause of anovulatory infertility and of hirsutism but it is also associated with characteristic metabolic abnormalities which may carry an increased risk, in the long term, for the development of type 2 diabetes and cardiovascular disease. However, the etiology remains uncertain. The heterogeneity of the clinical presentation has inevitably raised the question as to whether polycystic ovary syndrome is one disorder or whether its origins are as variable as its manner of presentation. There remain critical questions and controversies regarding not only the etiology of the syndrome but also in diagnostic criteria, investigation and management of this complex but fascinating disorder.

In December 2012, an important conference was held at the NIH, Bethesda, MD. *The National Institutes of Health Office of Disease Prevention Evidence-based Methodology Workshop on Polycystic Ovary Syndrome* was convened to review the evidence supporting current concepts in definition, diagnosis, investigation and management. The paper reporting the outcome of this meeting is readily available on line (http://prevention.nih.gov/workshops/2012/pcos/docs/PCOS_Final_Statement.pdf) and the main conclusions referred to below.

Amongst the main recommendations was the controversial suggestion that the name – polycystic ovary syndrome – was too focused on the reproductive features of the syndrome, and should be changed. However a readily acceptable alternative name was not forthcoming.

BARRIERS TO OPTIMAL PRACTICE

As suggested in the introductory paragraph, the uncertainties and arguments surrounding etiology and diagnostic criteria, together with limited data on long-term outcomes of therapeutic intervention, are all factors which have conspired to create controversy about steps in diagnosis and management. Potential barriers to optimal management therefore include:

- Continuing controversy about diagnostic criteria
- Lack of consensus regarding key diagnostic tests
- Uncertainty about long-term consequences of PCOS

LEARNING OBJECTIVES

As a result of participation in this session, learners should be able to:

- Discuss the pros and cons of the various diagnostic criteria for PCOS
- Highlight the key investigations of both reproductive and metabolic features of the syndrome
- Identify women who are at particular risk of long-term sequelae of metabolic dysfunction
- Discuss optimum management of reproductive, cutaneous and metabolic abnormalities in women with PCOS

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Definition and Diagnosis of Polycystic Ovary Syndrome

There has always been debate about the definition of PCOS and it seems likely to remain so until the specific etiology(ies) of the syndrome can be elucidated. The classic definition includes the clinical manifestations of anovulation and hyperandrogenism in women with bilateral polycystic ovaries; obesity is a common but not universal accompaniment. Typically, but not exclusively, these features are associated with hypersecretion of luteinizing hormone (LH) and androgens but with normal, or slightly low, serum concentrations of follicle-stimulating hormone (FSH). In recent years, the ability to identify polycystic ovaries by pelvic ultrasonography has provided new insight into the spectrum of clinical and biochemical presentation of women with a polycystic morphology of the ovaries. It is now evident that this spectrum includes both anovulatory women without hirsutism (but who are usually hyperandrogenemic) and, conversely, those who are hirsute and have regular, ovulatory cycles (but may also have elevated serum LH concentrations). Thus, irrespective of clinical presentation, there is a typical pattern of biochemical abnormalities that seems to unite these subgroups of women with ultrasound evidence of polycystic ovaries.

The recognition that the spectrum of presentation of women with PCOS is broader than was first thought has led to a revision of the diagnostic criteria for PCOS. The ESHRE/ASRM consensus meeting on PCOS, held in Rotterdam in May 2003 resulted in the recommendation that the definition of PCOS be revised to encompass women with hyperandrogenism and polycystic ovaries but who had regular cycles (see *Table 1*). This definition, like the classic definition, excludes patients who have polycystic ovaries on ultrasound but in whom the primary diagnosis is of pituitary or adrenal diseases e.g. hyperprolactinemia, acromegaly, and classical or non-classical congenital adrenal hyperplasia. To add to this definition, the Androgen Excess and PCOS Society (AE-PCOS) suggested a set of diagnostic criteria which was essentially a compromise between the "NIH" and "Rotterdam" criteria in that it include women with hyperandrogenism and regular cycles but excluded women with oligomenorrhea without clear evidence of androgen excess. Despite some inconsistencies in results between groups (that may be attributed to different methods of diagnosis) comparative studies have demonstrated that there is a high degree of concordance of ultrasound with histological features of polycystic ovaries and with clinical and endocrine evidence of the syndrome.

Regarding the conclusions of The NIH Office of Disease Prevention Evidence-based Methodology Workshop on Polycystic Ovary Syndrome about diagnostic criteria, the recommendation was that the broader criteria were more appropriate than the original "NIH" definition.

Prevalence and Presentation of Polycystic Ovary Syndrome

PCOS is a highly prevalent disorder. The "classic" syndrome (i.e. the combination of oligo-amenorrhoea and androgen excess) may be found in more than 5% of women of reproductive age. Using ultrasonographic, clinical and endocrine criteria it has been

TABLE 1. Diagnostic criteria for PCOS (see refs [1-3])

NIH 1990	Rotterdam 2003	AES-PCOS 2006
Chronic anovulation	Oligo- and/or anovulation	Oligo-anovulation and/or polycystic ovarian morphology
Clinical and/or biochemical signs of hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism
Both criteria	2 of 3 criteria	Both criteria

estimated that PCOS accounts for about 30% of women presenting with secondary amenorrhea, more than 80% of women with oligomenorrhea and, perhaps most surprisingly, between 60-90% of women with hirsutism but who have regular menses. PCOS accounts for 75-85% of cases of anovulatory infertility. The prevalence of obesity in women with PCOS varies from 35-40% to over 70%. Its presence influences the clinical presentation of women with polycystic ovaries; hirsutism and menstrual disturbances being significantly more common in obese compared with lean subjects.

The characteristic endocrinopathy of raised mean levels of serum androgens and LH has been reported in all published series of women with PCOS) but the variation in LH levels between individuals (which depends not only on the criteria for diagnosis but also the method of measurement) means that the diagnostic value of a single hormone measurement is limited. Similarly, although serum concentrations of testosterone and androstenedione are elevated in women with PCOS there is a good deal of variation from patient to patient. This is illustrated by the observation that anovulatory but non-hirsute women with polycystic ovaries may have hyperandrogenemia whilst hirsute women with polycystic ovaries may have normal serum androgen levels. This phenomenon may be explained by the fact that both production and clearance of androgens are increased in women with hirsutism. Low serum concentrations of sex hormone-binding globulin (SHBG) - the principal transport protein for testosterone in the blood - may contribute to increased clearance of testosterone. Blood levels of SHBG are inversely correlated with body mass index, which may help to explain why obese subjects with polycystic ovary syndrome are more likely to be hirsute than their lean counterparts, despite similar serum levels of testosterone. The effects of obesity on SHBG are likely to be mediated by insulin. The relevance of hyperinsulinemia and insulin resistance to PCOS is discussed below.

Other hormonal abnormalities including hyperprolactinemia and impaired secretion of growth hormone have been described in women with PCOS. Moderate hyperprolactinemia occurs in 5-10% of women with typical clinical and biochemical features of PCOS. The significance of hyperprolactinaemia in PCOS remains unclear. Impaired growth hormone secretion in women with polycystic ovaries may simply be a function of accompanying obesity rather than a specific feature of the syndrome.

Metabolic Abnormalities and Their Clinical Consequences in Women With Polycystic Ovaries

The reproductive consequences of PCOS have been recognized for several decades but over the last twenty-five years there has been an increasing number of studies illustrating that the syndrome is also associated with a characteristic metabolic disorder. This, in turn, has led to concern about the impact of PCOS on long-term health, particularly with regard to the advent of diabetes and coronary heart disease. The central features of the metabolic disturbance are peripheral insulin resistance and hyperinsulinaemia. The mechanism of these disturbances is not certain but there is evidence for intrinsic abnormalities of both insulin action and pancreatic beta cell function. There is an important interaction of polycystic ovaries with body weight so that whilst lean women with PCO often have normal insulin levels and sensitivity, the majority of those whose body mass index (BMI) is greater than 30 have reduced insulin sensitivity compared with weight-matched controls. It is not surprising therefore that obese young women with PCOS have a high prevalence of impaired glucose tolerance (and indeed some may have frank diabetes) and there seems little doubt that women with PCOS have a significantly increased risk of developing type 2 diabetes in later life. As yet, long-term follow-up studies have been few and far between but in one epidemiological analysis of a large cohort of women with a history of PCOS (mean age 57 years), the relative risk of type 2 diabetes was found to be three times that of the reference population. Abnormalities of lipids and lipoproteins have also been widely reported in women with PCOS.

These metabolic features, together with centripetal fat distribution constitute a cluster of risk factors for cardiovascular disease and this has been a major concern in considering the long-term management of patients with PCOS. However, interpretation of the significance of the metabolic abnormalities in terms of cardiovascular risk is by no means easy. Firstly, there are inconsistencies between studies in the features of the dyslipidemia and secondly, it is not yet clear how the combined risk factors translate into a real risk of developing cardiovascular disease.

The remaining uncertainties surrounding the reports of the dyslipidemia of PCOS emphasize the importance of counseling caution about pronouncing on the implications for cardiovascular health of a diagnosis of PCOS in young women. Whilst there seems little doubt that PCOS, independently of obesity, constitutes a significant risk factor for type 2 diabetes, there is, at present, no direct evidence for increased morbidity or mortality from coronary heart disease. Endothelial dysfunction and ultrasound evidence of carotid intima-medial abnormalities have been reported in young and middle-aged women with PCOS but these must still be regarded as surrogate indices of cardiovascular disease. Epidemiological data available to date provide no conclusive evidence of an increase in morbidity or mortality from coronary heart disease in a population of middle-aged women with a history of PCOS. However, it is quite conceivable that the incidence of coronary heart disease will diverge from normal as this cohort of middle-aged women grows older. Further long-term follow-up studies are required before a definitive link can be established. It has already been demonstrated that lifestyle changes (especially in diet) can markedly improve the metabolic profile of obese women with PCOS and, at the very least, can be expected to reduce the chance of developing type 2 diabetes. The new generation of insulin-sensitizing agents, including metformin, may also have a part to play in limiting the impact of the metabolic complications of PCOS.

Diagnostic Investigations in PCOS

A summary of the key tests that we order in our own unit is given in *Table 2*. Investigations are targeted principally at the presenting complaint. In women with oligo- or amenorrhea, it is important to exclude other causes (particularly in those with amenorrhea), so measurement of gonadotropins, prolactin and assessment of estrogen status are important. Ultrasound imaging of the ovaries and endometrium is very helpful, even if not essential.

In women with symptoms and signs of androgen excess, we routinely measure serum testosterone; some clinics and labs prefer androstenedione as an alternative (which is fine but you do not need both). In subjects with a short history, or severe hirsutism and/or a serum testosterone which is unusually high (a useful guide is a level more than twice the upper limit of the lab's normal range), further investigations are appropriate. These may include assessment of adrenal androgen production (DHEAS, short synacthen test, screening for Cushing syndrome) and, particularly if androgen levels are in the male range, imaging of ovaries and adrenals and (in specialized centers, selective venous sampling of ovarian and adrenal veins.

The important metabolic tests are, in women who are obese (or have a waist circumference >88cm) a 75gm oral glucose tolerance for measurement of glucose. Routine measurement of fasting cholesterol and lipids is still debatable but certainly indicated in those with a history of familial hypercholesterolemia. It is not our policy to measure, routinely, SHBG,17-hydroxy-progesterone (to exclude non-classical CAH) or fasting insulin. These might seem

TABLE 2. Investigation of PCOS

Presenting features	Investigations
Oligo- or amenorrhoea	FSH, (LH) Prolactin Oestradiol, (pelvic ultrasound)
Hirsutism	Testosterone
Obesity	Fasting glucose (OGTT)

Free T, 17-OHP, TFTs, insulin - not routinely needed

controversial, but there will be an opportunity to discuss these issues during the MTP session.

Management of Polycystic Ovary Syndrome

Treatment of the symptoms of anovulation is essentially symptomatic and includes treatment of infertility (induction of ovulation), menstrual regulation in women not desiring pregnancy and treatment of associated symptoms of hyperandrogenism (see below). Clomiphene citrate remains the treatment of first choice for induction of ovulation. Second line management (for clomiphene non-responders) includes low-dose FSH and laparoscopic ovarian diathermy. Large RCTs indicate that the early promise of metformin as a single or adjuvant therapy for restoring ovulation has not been fulfilled.

In management of hirsutism, the important principle is to combine physical methods of hair removal with endocrine treatment. Endocrine treatment usually involves suppression of ovarian androgens by a combined oral contraceptive with or without inhibition of androgen action using an androgen receptor inhibitor, spironolactone or (where available), cyproterone acetate. Topical inhibition of facial hair growth, using eflornithine cream (an ornithine decarboxylase inhibitor) can also be helpful.

In addition, considerable thought should be given to the prevention of the possible long-term consequences of the metabolic disturbance characteristic of PCOS. There is no doubt that diet and lifestyle intervention, in women with PCOS who are obese, improves both reproductive and metabolic function and should be an important part of the management of such patients. The place of insulin sensitizing drugs in management of reproductive and metabolic consequences of PCOS remains controversial and will be a topical item for discussion. In particular, the role of metformin in treatment of anovulation now seems to be very limited. Metformin does, however, still have an important role in management of women with PCOS who have impaired glucose tolerance.

ØMAIN CONCLUSIONS

In summary, polycystic ovary syndrome is the commonest cause of anovulation. The diagnosis is often obvious clinically if there are associated symptoms of hyperandrogenism and can be confirmed by a small number of simple investigations, including a pelvic ultrasound scan. Management is essentially empirically based and may be directed towards induction of ovulation, regulation of menses and control of associated symptoms such as hirsutism and acne. As far as the metabolic implications of polycystic ovary syndrome are concerned, there are, as yet, insufficient data to allow informed management but it would seem sensible to ensure that obese subjects with polycystic ovary syndrome have suitable dietary advice.

CASES WITH QUESTIONS

Case 1

C.L. aged 37, presented with increasing hirsutism, oligomenorrhea and difficulty controlling weight. She had one child, born 10 years previously after spontaneous ovulation (and no delay in conception) and was hoping to conceive again. She had a past history of irregular cycles/ oligomenorrhoea and mild hirsutism from menarche (12y). She had been overweight since adolescence but had gained >10kg in weight in last 5 years. There was no family history of T2DM. Previous investigations: polycystic ovaries on ultrasound; testosterone 3.4 nmol/l (0.5-3.0); LH 14.5 u/l (2.0-12.0); FSH 5.6 u/l (2.0-12.0). Previous management: oral contraceptive (cycle regulation and to reduce serum testosterone and unwanted body hair). Examination: weight 87.2 kg; Ht 1.56m: BMI 35.8; moderate/severe hirsutism affecting face, trunk and thighs.

Q: Diagnosis? What next in terms of further investigation and management?

Case 2

M.Y., aged 31, presented with a 10-month history of oligomenorrhoea and 20infertility. She had suffered mild but increasing hirsutism and acne for 6 months. Initial investigations: LH 11.0 u/l; FSH 4.5 u/l; PCO on ultrasound.

She was prescribed clomiphene and ovulated in first cycle. She returned for assessment after 3 cycles of clomiphene and was complaining of increasingly severe hirsutism; temporal hair recession; hoarse voice. Investigations showed: testosterone 11 nmol/l (normal <3).

Q: Diagnosis? What next for further investigations and management?

DISCUSSION OF CASES AND ANSWERS

Case 1

Repeated endocrine tests were consistent with the original diagnosis of PCOS. Her reduced frequency of menses and increasing hirsutism are typical of the progression of the syndrome in the face of significant weight gain. Further investigations should include an OGTT and management should be targeted at diet and lifestyle changes before considering induction of ovulation.

Case 2

The repeated endocrine tests showed the following results: Testosterone 15 nmol/l; Androstenedione >70 nmol/l (<9); DHEAS 108 mmol/l (<10); 17-OHP 23 nmol/l (<12); Urine free cortisol 1110 nmol/24h (<300). History and results strongly suggest presence of an androgen-secreting adrenal tumor. CT of the adrenals revealed a 10cm tumor above left kidney. She underwent surgical removal: adrenal carcinoma on histology. Post-operatively, much improved: normalization of testosterone, resolution of hirsutism, return of fertility but recurrence after 2 years with liver and lung metastases. Comment: originally diagnosed as PCOS. Case illustrates the importance of the (short) history and initial endocrine tests.

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Management of Prolactinomas During Pregnancy

M6
Saturday, June 15
3:00 PM-3:45 PM & 5:45 PM-6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Prolactinomas are the most common functioning pituitary tumors accounting for almost 40% of all pituitary adenomas [1]. These tumors are more frequently diagnosed in women during childbearing age of 20-40 years [2], probably due to an early effect of elevated prolactin causing menstrual irregularity. Hyperprolactinemia is responsible for a third of all cases of female infertility [3], but with adequate management, the majority of such women are expected to achieve successful pregnancies.

BARRIERS TO OPTIMAL PRACTICE

- Relatively limited prospective long-term data on the safety of medical therapy during pregnancy
- Broad scope of the available guidelines could lead to a diversity of management practices

LEARNING OBJECTIVES

As a result of participating in this session you will be able to:

- Learn common and uncommon presentations of prolactinomas during pregnancy
- Learn an approach to the management of prolactinomas during pregnancy in accordance with the Endocrine Society Guidelines

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

The Endocrine Society recently published clinical guidelines for diagnosis and treatment of hyperprolactinemia [4]. There were 6 specific recommendations regarding the management of prolactinomas during pregnancy. A summary of these recommendations is as follows:

1. We recommend that women with prolactinomas be instructed to discontinue dopamine agonist therapy as soon as they discover that they are pregnant. In selected patients with macroadenomas who became pregnant on dopaminergic therapy and who have not had prior surgical or radiation therapy, it may be prudent to continue dopaminergic therapy throughout the pregnancy, especially if the tumor is invasive or is abutting the optic chiasm.
2. In pregnant patients with prolactinomas, we recommend against performing serum prolactin measurements during pregnancy.
3. We recommend against the use of routine pituitary MRI during pregnancy in patients with microadenomas or intrasellar macroadenomas unless there is clinical evidence of tumor growth such as visual field compromise.
4. We recommend that women with macroprolactinomas who do not experience pituitary tumor shrinkage during dopamine agonist therapy or who cannot tolerate bromocriptine or cabergoline be counseled regarding potential benefits of surgical resection before attempting pregnancy.
5. We recommend formal visual field assessment followed by MRI without gadolinium in pregnant women with prolactinomas who experience severe headaches and/or visual field changes.
6. We recommend bromocriptine therapy in patients who experience symptomatic

growth of a prolactinoma during pregnancy.

MAIN CONCLUSIONS

- Most prolactinomas during pregnancy require little else than clinical monitoring
- Women with large prolactinomas threatening the vision should be adequately counseled prior to considering pregnancy
- Medical treatment during pregnancy should be considered for aggressive prolactinomas

CASES WITH QUESTIONS

Case 1

Ms. DS is 24 years old and was seen for inability to conceive. Her initial screen results showed an elevated prolactin level of 76 μg/L (normal level is 2 to 15 μg/L). A subsequent MRI scan confirmed the presence of a 5-mm pituitary adenoma. She was given Bromocriptine, which normalized her menstruation as well prolactin level. One year ago she asked if she could start Cabergoline instead because of its less frequent dosage. She was shifted to Cabergoline 0.5 mg twice a week and her prolactin levels have remained normal. She called your office yesterday to inform you that she was pregnant.

Case 2

Mrs. TE, a 32-year-old musician, had originally presented with milky breast discharge about 5 years ago. Subsequent investigations revealed an elevated prolactin level of 574 μg/L (normal level is 2-15 ug/L). Pituitary MRI confirmed a 2.1cm pituitary macroadenoma. Visual field testing revealed a defect in her left superior temporal field. She was started immediately on Cabergoline 1.0 mg twice a week, and within 6 months, her serum prolactin level returned to normal, and the tumor shrank to 1.2 cm. Her visual field test results were normal. She has been under yearly surveillance and her serum prolactin level has remained normal. Mrs. TE is now 4 weeks pregnant.

Case 3

Ms. RP, a 30-year-old nulliparous bus driver is 10 weeks pregnant. She was told 8 years ago that she had a large prolactinoma and was given Bromocriptine. She last saw her specialist more than 3 years ago. She has been filling her prescription through her family physician and takes her medication intermittently. Her menstruation has always been irregular and when she started gaining weight 2 weeks ago she did the pregnancy test, which was positive. This was later confirmed by her family physician. She thinks she last took bromocriptine about 3 months ago. On examination, she had bitemporal hemianopia on clinical visual field testing and the MRI showed a 2.9 cm sellar tumor compressing the optic chiasm. Her serum prolactin level was 2400 μg/L.

Questions

How would you treat these patients?

Medical therapy

1. Continue current dopamine agonist therapy throughout pregnancy (yes/No)
2. Discontinue Cabergoline and shift to Bromocriptine due to better safety data (Yes/No)
3. Discontinue dopamine agonist therapy as soon as soon as pregnancy is confirmed (yes/No)
4. Refer for surgical excision of the tumor (yes/No)
5. Recommend therapeutic abortion (yes/No)

Biochemical testing

1. Continue regular monitoring of serum prolactin during pregnancy (Yes/No)
2. Discontinue monitoring serum prolactin during pregnancy (Yes/No)
3. Measure serum prolactin only if patient complains of new-onset headaches and/or vision changes (Yes/No).

Radiological imaging

1. Perform regular pituitary imaging during pregnancy to exclude tumor enlargement (Yes/No)
2. Perform pituitary imaging if serum prolactin is thought to be out of proportion with your clinical judgment (Yes/No)
3. Perform pituitary imaging ONLY if patient complains of new-onset headaches and/or vision changes (Yes/No)

Visual field testing

1. Perform regular formal (Goldmann or Humphrey) visual field testing throughout pregnancy (Yes/No)
2. Perform formal visual field testing only if patient complains of new-onset headaches and/or vision changes (Yes/No)
3. Never perform formal visual field testing (Yes/No)
4. Only perform informal (clinical) visual field testing (Yes/No)

DISCUSSION OF CASES AND ANSWERS

Case 1

The risk of clinically significant increase in size of microprolactinomas during pregnancy (causing headaches, optic nerve compression, or stalk compression) ranges from 1.6% to 5.5% [5-7]. A study of 80 pregnancies in 56 women with microprolactinomas during pregnancy reported mild tumor enlargement in 5 cases on postpartum imaging while 1 patient developed headaches that disappeared when bromocriptine was restarted [8]. The 2011 CPG recommend against routine measurement of serum prolactin during pregnancy. This recommendation is based on the evidence that correlation between serum prolactin during pregnancy and tumor behavior is poor. Pregnancy is associated with physiologic hyperprolactinemia, which can be variable [9] with serum prolactin reaching levels of 150-300 mg/L [10] thus making interpretation of levels during pregnancy unreliable. Consequently, routine measurement of serum prolactin during pregnancy should be avoided since it could lead to unnecessary imaging. The 2011 CPG suggest performing formal VF testing and a pituitary MRI in case of new or worsening headache or a change in vision. Indeed the risk of clinically relevant growth of microprolactinomas during pregnancy is low at around 2.6% [11]. A recent retrospective single-center study of 91 patients (76 microadenomas, 10 macroadenomas and 5 non-tumor hyperprolactinemia) looking at the risk of recurrence of hyperprolactinemia after pregnancy and lactation reported significant remission of hyperprolactinemia, in that 50 out of 76 women did not require treatment after pregnancy or lactation [12].

Case 2

This case represents a macroprolactinoma that is well contained and stable; the propensity of growth during pregnancy of such tumors in the absence of medical therapy is not abundantly clear from the available literature. Should tumors that previously demonstrated a tendency for significant enlargement but have responded to medical therapy be regarded as similar to microprolactinomas in terms of their outcomes in pregnancy? It has been suggested that macroprolactinomas may be a different disease because they tend be less vascular than microprolactinomas [13] and show more shrinkage with DA therapy [13]. The risk of enlargement of macroprolactinomas that had not been treated with surgery or radiotherapy is 8.9 – 32% [11,15] whereas in patients who had surgery or radiotherapy before pregnancy, the risk of symptomatic growth is around 2.5% [11]. Clinical evidence about the behavior of such tumors during and after pregnancy is accumulating and a recent retrospective study reported that after an initial treatment with cabergoline (before pregnancy), 70% of macroprolactinomas (size not specified in the paper) remained in complete remission up to 60 months after delivery [12]. The 2011 CPG recommend against routine MRI in the absence of clinical evidence of tumor growth such as VF compromise. Doing regular formal VF assessment in each trimester, or more frequently if tumor showed evidence of suprasellar extension prior to pregnancy is recommended [16].

Case 3

Management of large macroprolactinomas during pregnancy, as described in case 3, is challenging. A prospective survey of 56 pregnant women with macroprolactinomas revealed a 36% risk of adverse outcomes [5] and the risk of visual impairment is as high as 75% [7]. The risk of further tumor enlargement in such cases is as high as 32% [14]; therefore, the 2011 CPG also recommend continuing DA therapy in case of invasive tumor especially if it is abutting the optic chiasm. The DA therapy of choice is bromocriptine which will usually decrease the size of the adenoma and eliminate the

symptoms [17]. Cabergoline is regarded as more efficacious and may be considered in case the adenoma is unresponsive to bromocriptine [18]. The available safety data on the use of bromocriptine and cabergoline during pregnancy, although retrospectively collected, is generally reassuring. The most widely used DA therapy during pregnancy is bromocriptine and in over 6000 reported pregnancies in women taking bromocriptine at the time of conception, there was no increased risk of miscarriage or congenital malformation [11]. Similarly, another study of 2587 pregnancies in 2437 women exposed to bromocriptine during gestation did not find an increased risk of spontaneous abortion, congenital abnormalities, multiple pregnancies or post- natal maldevelopment [19]. The safety data on the two other agents, cabergoline and quinagolide are accumulating. In over 300 pregnancies in women who were exposed to cabergoline and almost 200 who were exposed to quinagolide during pregnancy, no apparent adverse effects on the pregnancy or fetal development were detected [20]. Follow up data of 107 infants exposed to ergot derivatives during pregnancy indicated no neonatal physical or mental abnormality [21]. More recent studies have not reported complications either [12, 18, 22, 23]. Surgery is ideally recommended before pregnancy in tumors that are resistant to medical treatment [24]. The 2011 CPG recommend that women with macroprolactinomas who do not experience pituitary tumor shrinkage with DA therapy or who cannot tolerate DA therapy be counseled regarding the potential benefits of surgical resection before attempting pregnancy [4]. Furthermore, there have been cases of tumor enlargement during pregnancy even after surgery [25]. Emergency pituitary surgery during pregnancy is associated with significant morbidity for mother (blood loss, hypopituitarism etc.) and fetus. There is a 1.5 and 5 fold increase in fetal loss during the first and second trimester respectively [26]. The 2011 CPG suggest urgently performing formal VF testing and a pituitary MRI in case of new or worsening headache or a change in vision. Due to a significant risk of vision loss and tumor enlargement, we typically perform regular VF testing during pregnancy and would consider MRI monitoring of the tumor during pregnancy.

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Fertility Preservation: Who and When to Refer?

CMF2
Tuesday, June 18
11:15 AM – 12:00 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

More than 135,000 people under the age of 45 will be diagnosed with cancer this year. Most will survive their disease, due to advances that have been made in cancer therapeutics. Nonetheless, these life-saving treatments may cause delays childbearing, infertility and compromise the cancer survivor's chance of having a biological family in the future. Among young cancer survivors, infertility is identified as one of their greatest concerns[1]. Those who are aware of the fertility risks and options, often have a brief 24-72 hour timeframe to make momentous decisions. Maximizing the numbers of young cancer survivors who can benefit from fertility preservation options requires that integrated cancer care teams overcome significant hurdles—in the education, navigation, and support of patients and their families. Timely discussions of fertility preservation for young cancer patients requires that a new "bridge" be formed among the specialties involved in cancer care including survivorship, endocrinology and reproductive medicine in the treatment planning phase of the cancer continuum.

Since 2006, the American Society of Clinical Oncology (ASCO), the American Society for Reproductive Medicine (ASRM), and others have recommended both that **fertility education** be implemented as routine standard of care for young patients and, if interested, patients should be **referred** to reproductive specialists as early after diagnosis as possible[2,3]. Reproductive specialists have modified their programs over the past decade to be able to provide fertility preservation techniques to young cancer patients. However, less than half of oncologists report regularly discussing fertility with their cancer patients [4-6].

BARRIERS TO OPTIMAL PRACTICE

- Information Gap:
  - Lack of knowledge about fertility impact of medical treatment and fertility preservation methods.
  - Emerging techniques are rapidly developed and implemented into clinical care, therefore difficult for providers to stay current.
  - Providers may not be aware of local or regional fertility preservation resources available to their patients.
- Communication Gap:
  - Providers may feel uncomfortable discussing long-term consequences of chemotherapy, radiation and surgical management.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Describe how chemotherapy and radiation impacts the hypothalamic-pituitary-gonadal axis.
- Discuss the currently available established and investigational methods for male and female fertility preservation.

STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Estimating Gonadotoxicity and Risk of Infertility

Rates of compromised fertility and permanent gonadal insufficiency vary and depend on a number of factors. The effects of chemotherapy and radiation depend on the following: patient age, sex, baseline fertility status, specific drug used, location/extent of radiation field, cumulative dose, duration of treatment, mode of administration (oral vs. IV), and need for stem cell transplant. Male and female fertility may be transiently or permanently affected by cancer treatment, or may surface later as premature gonadal failure. Male infertility can result from the disease itself (ie testicular tumor), anatomic issues, HPG insufficiency, or damage/direct depletion of spermatogonial stem cells. Long-term consequences include decreased sperm count, motility, morphology or compromised DNA integrity. *Table 1* illustrates the range of risks associated with several cancer therapy regimens.

Fertility Preservation Options [Table 2]

While sperm cryopreservation is an effective method of fertility preservation in males treated for cancer, testicular tissue cryopreservation, transplantation and xenografting are experimental methods that require further testing in humans. Cryopreserved sperm can be used for artificial insemination or for in vitro fertilization. Female fertility preservation options depend on the patient's age, whether she has a partner, window of time and the possibility of malignancy with ovarian involvement. Each fertility preservation method will be discussed in detail during the session.

POINTS OF INTEREST

- Physicians should inform cancer patients about fertility risks when discussing cancer therapy.
- Early referral to reproductive specialist is critical to maximize options available to patients and the likelihood of success.
- In patients facing infertility due to chemotherapy or other gonadotoxic therapies, fertility preservation is recommended with appropriate counseling.
- Established methods of fertility preservation include sperm cryopreservation for males, and embryo and oocyte cryopreservation for post-menarchal females.
- Experimental procedures such as ovarian tissue cryopreservation should be offered only in a research setting with IRB oversight.
- Preimplantation genetic diagnosis to avoid the birth of offspring with a high risk of inherited cancer is available.

CLINICAL CASES WITH QUESTIONS[9]

Case #1:

Marisol is a 28-year-old woman recently diagnosed with Stage 1 ER+/PR+ breast cancer who is also a BRCA 1 carrier. She has been in a serious relationship with a partner for the past 3 years.

Q1: What fertility preservation options should be discussed with Marisol?

Q2: What special considerations should be kept in mind when considering fertility preservation in this patient?

Q3: Does ovarian stimulation and pregnancy increase her risk of breast cancer recurrence?

Case #2:

Michelle is an 18-year-old patient with newly diagnosed Ewing's sarcoma requiring high-dose cyclophosphamide and ifosfamide who was referred for to you for a fertility preservation consultation. Her oncologist recommended immediate cancer therapy due to the highly aggressive tumor.

Q1: What fertility preservation options should be discussed with Michelle?

Q2: What method would you recommend for fertility preservation that poses no delay in her cancer treatment?

Case #3:

Ann is a 36-year-old, married woman with a history of Hodgkin's lymphoma treated with high dose chemotherapy. She was recently diagnosed with relapse and is interested

TABLE 1: Infertility Risk associated with Specific Cancer Regimens[7,8]

Degree of Risk	Cancer Treatment
High	• Total body irradiation (TBI) • Cranial/brain irradiation >40 Gray (Gy) • Spinal irradiation 24-36 Gy • Whole abdominal or pelvic radiation doses >15 Gy in pre-pubertal girls or >10 Gy in post-pubertal girls • Testicular radiation dose ≥3 Gy in boys • Cyclophosphamide >7.5 g/m2 in boys • Cyclophosphamide > 15-20 g/m2 in girls • Alkylating chemotherapy (ie: cyclophosphamide, busulfan, melaphan) conditioning for transplant • Any alkylating agent (ie: cyclophosphamide, ifosfamide, busulfan, carmustine, lomustine) + TBI, pelvic radiation, or testicular radiation • Protocols containing procarbazine • Surgical removal of one or both testes • Oophorectomy (bilateral)
Intermediate	• 6 cycles of combined cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin in women age 30-39 years • 4 cycles of combined doxorubicin/cyclophosphamide in women age >40 • Whole abdominal/pelvic radiation 10-15 Gy in pre-pubertal girls • Whole abdominal/pelvic radiation 5-10 Gy in post-pubertal girls • Spinal radiation doses 18-24 Gy • Testicular radiation dose 1-2 Gy (due to scatter from abdominal/pelvic radiation) • Cumulative cisplatin dose of about 500 mg/m2 (boys only) • Surgical removal of 1 ovary
Low	• Lymphoma treatment including 4-6 cycles of ABVD (doxorubicin, bleomycin, vincristine, dacarbazine) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) • AML therapy (anthracycline/cytarabine) • ALL therapy • 6 cycles of combined cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin in women age <30 • 4 cycles of combined doxorubicin/cyclophosphamide in women age <40 • Testicular radiation dose 0.2 – 0.7 Gy • Nonalkylating chemotherapy
Very low	• Methotrexate or vincristine or fluoruracil • Testicular radiation dose <0.2 Gy • Radioactive iodine • Interferon-α
Unknown	• Oxaliplatin • Irinotecan • Bevacizumab • Cetuximab • Trastuzumab • Erlotinib • Imatinib • Taxanes • Monoclonal antibody therapy • Tyrosine kinase inhibitors • Immunologic agents

TABLE 2: Male and Female Fertility Preservation Options

Option	Definition	Timing	Time Needed	Comments
Options for Males				
Sperm cryopreservation	Freezing sperm obtained through masturbation or surgical extraction	Before treatment	Minimal	Outpatient procedure
Gonadal shielding	Use of shield during radiation to reduce dose to testes	During treatment	In conjunction with radiation	Only possible with selected fields
Testicular tissue cryopreservation (*experimental*)	Freezing testicular tissue or germ cells with transplantation or xenograft	Limited studies in humans	Minimal	Requires surgical procedure
Use of GnRH agonist	Used to suppress HPG axis	Before / during treatment	Minimal	Conflicting results on efficacy
Options for Females				
Embryo cryopreservation	Ovarian stimulation, harvest oocytes, in vitro fertilization and freezing embryos	Before / after treatment	~10-14 days	Requires daily SQ injections and surgical procedure Requires sperm source
Oocyte cryopreservation	Ovarian stimulation, harvest oocytes and freezing unfertilized oocytes	Before / after treatment	~10-14 days	Requires daily SQ injections and surgical procedure
Ovarian tissue cryopreservation (*experimental*)	Freezing ovarian cortex for future transplantation or in vitro follicle maturation	Before / after treatment	Minimal	Requires surgical procedure Tissue not suitable for transplant in high risk of ovarian metastases
Ovarian transposition	Surgical suspension of ovaries outside radiation field	Before treatment	Minimal	
Gonadal shielding	Use of shield during radiation to reduce scatter radiation to pelvic	During treatment	In conjunction with radiation	No protection against chemotherapy effects
Use of GnRH agonist	Used to suppress HPG axis	Before / during treatment	Minimal	Conflicting results on efficacy
Other Options				
Donor sperm	Use of sperm donated by anonymous donor	After treatment	Varies	
Donor embryos	Use of embryos donated by a couple who underwent IVF	After treatment	Varies	Available through IVF clinic or private agency
Donor oocytes	Use of oocytes donated by anonymous or known egg donor	After treatment	Varies	Patient can choose donor based on various features
Gestational carrier	Use of surrogate to carry pregnancy	After treatment	Varies, time required to find surrogate and transfer embryos	Legal status varies by state
Adoption	Process that creates legal parent-child relationship	After treatment	Varies	

in learning about her options for fertility preservation. She will undergo high dose radiation of the left groin for residual pelvic disease.

Q1: What fertility preservation options should be discussed with Ann?
Q2: Based on her history, what factors will you consider when counseling her about options?
Q3: Would you consider offering her more than one option? If so, how would you time the procedures?

DISCUSSION OF CASES WITH ANSWERS
Case #1:

A1: Embryo, oocyte and ovarian tissue cryopreservation. In discussion with her partner, she elected to proceed with a combination of oocyte and embryo cryopreservation.
A2: Supraphysiologic estradiol levels in setting of hormone-sensitive malignancy. She underwent controlled ovarian stimulation using a combined aromatase inhibitor-gonadotropin protocol and banked 11 embryos and 8 oocytes. She was offered preimplantation genetic diagnosis to evaluate embryos for presence of BRCA mutation.
A3: Based on current literature, ovarian stimulation for fertility preservation and pregnancy appear safe without an increased risk of cancer recurrence [10-12].

In this patient, the widely available technique of embryo cryopreservation was used along with oocyte cryopreservation. Preimplantation genetic diagnosis was added to avoid transferring BRCA affected embryos. The use of aromatase inhibitors in combination with exogenous gonadotropins dramatically reduces the otherwise very high, supraphysiologic estradiol levels that would be attained in a typical in vitro fertilization cycle.

Case #2:

A1: She was extensively counseled about her options including embryo, oocyte, and ovarian tissue banking.
A2: She wished to proceed with ovarian tissue cryopreservation and understood that this was an experimental procedure with the potential for future use by transplantation or in vitro follicle maturation, if the scientific possibilities advanced.

The most widely available female fertility preservation option is creating and immediately cryopreserving embryos for future use. This option for fertility treatment has been available for over 3 decades and virtually all IVF laboratories around the country and the world are able to cryopreserve embryos indefinitely. In the absence of a life partner, however, cryopreserving embryos is a less desirable option than harvesting and freezing mature oocytes. The process of mature oocyte cryopreservation has now reached a point of technical proficiency such that it is no longer considered experimental by the American Society for Reproductive Medicine. A rule of thumb is that if 30 harvested, mature oocytes can be cryopreserved, then a term pregnancy can eventually be obtained. In the case outlined above, there is no life partner, and the patient has an aggressive tumor that precludes the 10-14 day time window needed to perform an egg harvesting. Although current methodologies exist to mature primordial and early primary oocytes from ovarian tissue, the proportion of cells that survive are poor and thus the yield of fertilizable oocytes through in vitro maturation cannot be assured. The possibility that an aggressive tumor with metastasis could seed the ovary prior to its removal makes the option of transplanting the ovary back into this patient a concern. To date, such 'seeding' of tumor by ovarian tissue transplantation has not been reported; however it remains a theoretical concern.

Case #3:

A1: Embryo, oocyte, ovarian tissue cryopreservation were discussed.
A2: Ann's age, baseline ovarian reserve status in setting on previous chemotherapy, exposure of oocytes to prior treatment

may affect oocyte quality

A3: Ann elected to undergo controlled ovarian stimulation, oocyte retrieval and embryo cryopreservation. Her ovarian reserve was impaired from prior chemotherapy with a basal FSH level of 14 mIU/ml. She underwent ovarian stimulation with maximum doses of gonadotropins and was only able to bank three embryos. After embryo banking, she sought additional methods of fertility preservation and elected to proceed with ovarian tissue banking and ovarian transposition. Ten days after egg retrieval, she underwent laparoscopic left ovarian transposition and banked a biopsy of ovarian cortical tissue. She recovered well from the procedures and proceeded with her cancer treatment.

This case highlights the damaging effect of cancer therapy on the ovaries and the challenges that exist when attempting ovarian stimulation after cancer treatment. The ovary is particularly sensitive to the adverse effects of cancer treatments because of the finite number of germ cells present in the post-natal ovary [13,14]. Reproductive lifespan is determined by the size of the follicular pool and therefore, cancer treatments that cause follicular depletion are thought to accelerate the onset of menopause[15]. Large, retrospective cohort studies assessing menstrual function post-chemotherapy have clearly demonstrated that cancer survivors are at risk of both acute and long-term ovarian failure[16,17]. The irreversible gonadotoxic effects of some chemotherapeutic agents are well documented, particularly alkylating agents, such as cyclophosphamide, busulfan, and ifosfamide, common components of polychemotherapy for sarcomas, leukemia, lymphomas, and breast cancer[18]. Pelvic radiation therapy is also known to cause follicular destruction followed by reproductive dysfunction[8,16,17,19]. Exposure to ≥6 Gray of pelvic radiation appears to be toxic to oocytes and many women exposed to such doses will experience premature ovarian insufficiency[20]. Ovarian failure resulting from both chemotherapy and radiation appears to be dose-related as well as dependent on age at the time of treatment. As seen in Ann's case, even before menstrual dysfunction occurs, cancer survivors have evidence of impaired ovarian reserve compared to similarly aged controls[21,22]. We have observed that the response to ovarian stimulation is often reduced in cancer survivors, yielding fewer oocytes and embryos. Although it is not always possible to predict a patient's response to ovarian stimulation with accuracy, the patient's age, measures of ovarian reserve, and treatment history (agents used, cumulative dose, and duration of treatment) are important factors to consider when planning fertility preservation strategies in cancer survivors scheduled to undergo additional gonadotoxic therapies.

ONLINE RESOURCES

University of Colorado Oncofertility Program: http://arm.coloradowomenshealth.com/services/oncofertility

Oncofertility Consortium: http://oncofertility.northwestern.edu/

http://myoncofertility.org/

http://savemyfertility.org/

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Postmenopausal Hormone Therapy: What's New?

M38
Monday, June 17
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Postmenopausal hormone therapy continues to play an important role in the management of menopausal symptoms. It is highly effective for the management of hot flashes, vaginal atrophy and, in many cases, the symptoms of depression that women may experience during the menopausal transition.

Updated meta-analyses of hormone therapy were published in 2012 by the Cochrane group and the United States Preventive Services Task Force (USPSTF) that included 23 and 9 trials, respectively. Both included the Women's Health Initiative (WHI), and the mean age of subjects in both analyses was >60 years. In the USPSTF analysis, results were largely based on the WHI. Based upon their current study, the USPSTF continues to recommend against the use of both combined estrogen and progestin and unopposed estrogen (for women post-hysterectomy) for the prevention of chronic conditions. However, they note that this recommendation does not apply to women considering using hormone therapy for relief of menopausal symptoms.

While the WHI clearly demonstrated the adverse effects of hormone therapy in older postmenopausal women (over age 60), this is not the age group that typically experiences menopausal symptoms or seeks advice on hormone therapy. Almost all women who seek medical therapy for menopausal symptoms do so in their late 40s or 50s.

A number of lines of evidence now suggest that early use of hormone therapy is not associated with an increased risk of coronary heart disease (CHD). Data include a subgroup analysis from the WHI, a meta-analysis of clinical trials, and a trial in a subgroup of women in the WHI demonstrating that women in their 50s receiving unopposed estrogen had lower coronary calcium scores than women receiving placebo. In addition, preliminary data from a trial in younger postmenopausal women (Kronos Early Estrogen Prevention Study (KEEPS)) suggest that intima medial carotid thickness and coronary calcium, markers of subclinical atherosclerosis, are similar in women taking combined estrogen-progestin therapy or placebo.

When counseling women, the clinician should provide estimates for the absolute risks and benefits of hormone therapy for younger postmenopausal women receiving up to five years of treatment. Women should be reassured that the absolute risk of complications for healthy, young postmenopausal women (in their 50s or < 10 years postmenopausal) is very low.

BARRIERS TO OPTIMAL PRACTICE

Lack of awareness of follow-up data from the Women's Health Initiative and meta-analyses of clinical trials demonstrating that women ages 50 to 59 (or those <10 years postmenopause) who start hormone therapy do not appear to be at increased risk for coronary heart disease.

Many clinicians are unaware that menopausal symptoms, in particular, hot flashes, typically begin during the menopausal transition. In addition, hot flashes persist beyond the age of 70 in up to 10 percent of women; this makes stopping hormone therapy challenging in this subset of women.

Lack of awareness of the increased risk of new onset depression during the menopausal transition.

LEARNING OBJECTIVES

At the end of this presentation, the participant is expected to:

1. Identify the absolute risks and benefits for five years of hormone therapy use in younger postmenopausal women (in their 50s).
2. Identify the most common symptoms of the menopausal transition.
3. Choose the most appropriate hormone therapy to manage an individual's menopausal symptoms.
4. Utilize non-hormonal alternative strategies and medications to treat menopausal symptoms.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

The menopausal transition, or perimenopause, begins on average three to four years before the final menstrual period, and includes a number of symptoms and physiologic changes that may affect a woman's quality of life. It is characterized by irregular menstrual cycles, hormonal fluctuations, and symptoms that may include hot flashes, mood lability, sleep disturbances and vaginal dryness. Essentially all women experience irregular menses and hormonal fluctuations before clinical menopause, and up 80 percent develop hot flashes. However, only 20 to 30 percent seek medical attention for treatment.

Hot flashes are often associated with arousal from sleep. However, women may experience sleep disturbances even in the absence of hot flashes; it has been estimated that up to 40 percent of women experience sleep disturbances during the menopausal transition. Primary sleep disorders are common in this population.

Perimenopausal women are also at increased risk for new onset depression. The mood symptoms are responsive to estrogen therapy as well as antidepressants.

Estrogen deficiency leads to a decrease in blood flow to the vagina and vulva. This decrease is a major cause of decreased vaginal lubrication and sexual dysfunction in menopausal women. Symptoms of vaginal atrophy (vaginal dryness and dyspareunia) are typically progressive unless vaginal estrogen is given.

MAIN CONCLUSIONS

There is substantial evidence linking menopause to the symptoms listed in *Table 1*. Estimates of percentages of women who report these symptoms are provided in parentheses. These groupings were based upon the assessment of cohorts of women being followed longitudinally across the menopausal transition. Women who seek intervention for menopausal symptoms should always be questioned about possible mood symptoms, especially if they have not responded to estrogen alone.

CASES WITH QUESTIONS

Case 1

A 50 year old woman on hormone therapy for hot flashes and new-onset depression presents for further management. Her hot flashes have improved, but in spite of multiple adjustments in her estrogen dose, her depression symptoms have not improved.

How would you manage this patient?

Case 2

A 51 year old woman whose last period was four months ago seeks advice for management of hot flashes. She is awakened at least six to

TABLE 1. The management of common symptoms is described in the cases.

Symptoms		
GOOD evidence	Fair evidence	Poor evidence
Vasomotor symptoms (60-85%) Vaginal dryness (27-60%) Sleep disturbances (30-50%)	Cognitive dysfunction Urinary incontinence Sexual dysfunction	Body composition Joint aches and pains
Depressed mood (25-35%)		

seven times a night and has frequent episodes during the day as well that are interfering with her ability to function at work. She has no history of venous thromboembolism, stroke or coronary heart disease. She has no family history of breast cancer.
What would you suggest to her?

Case 3
A 63 year old woman who is post-hysterectomy is referred by her PCP to discuss management of hot flashes She started on hormone therapy at age 50 for severe hot flashes (she most recently was taking 17-B estradiol 0.5 mg orally), but this was discontinued nine months ago because of concerns about excess breast cancer risk. She has had frequent and severe hot flashes since that time; they are interfering with sleep and her ability to function at work. In addition, she has vaginal dryness and dyspareunia. She is otherwise in good health, and has never smoked. She is currently taking black cohosh, isoflavone supplements, and red clover with minimal benefit. A recent TSH was normal. BMI 22 kg/m2, BP 120/70.
What are her treatment options?

DISCUSSION OF CASES AND ANSWERS

Case 1
The patient described in the case appears to need both hormone therapy and an antidepressant. The next step would be to add an SSRI. When women present with vasomotor symptoms as well as mood symptoms, one approach is to start by treating the predominant symptom, eg if she has severe hot flashes, start with hormone therapy, and then add an SSRI if necessary. On the other hand, if hot flashes are mild and mood symptoms are severe, one would start with an SSRI, and then add estrogen if needed.

Case 2
She is a good candidate for hormone therapy. Although the best approach is to start with low dose estrogen (eg transdermal 17-B estradiol (E2) 0.025 mg or oral 17-B estradiol 0.5 mg) and then titrate up as needed for relief of symptoms, higher doses are reasonable for women with severe symptoms. One can then taper the dose later and see if her symptoms can be controlled with a lower dose.

She is started on transdermal E2 0.05 mg with oral micronized progesterone 200 mg days 1 to 12 of the calendar month. She has dramatic improvement of her hot flashes, but she experiences mood symptoms the days she takes the progesterone. You try a lower dose (100 mg) of progesterone administered daily but she has trouble tolerating this as well. Subsequent trials of intravaginal progesterone and low doses of medroxyprogesterone acetate also cause mood symptoms. What are her options now?

Progestins are routinely added to estrogen therapy to prevent endometrial hyperplasia in postmenopausal women with an intact uterus. However, many women have trouble tolerating progestins, particularly those with perimenopausal mood symptoms. Progestins can worsen depression, or negate the positive effects of estradiol on depression in up to 30 percent of women. This patient has been unable to tolerate a number of systemic progestin regimens. A reasonable option at this point would be a progestin-IUD that releases levonorgestrel. There are two available doses, a 52 mg device and a 13.5 mg device. They are approved by the FDA for contraception, and not for menopausal hormone therapy, but for women who cannot tolerate systemic progestins, they are a reasonable off-label use of the IUD. The low-dose IUD has been available in Europe and other countries but is now available in the US. It is smaller and easier to insert than the higher dose IUD.

Case 3
It is not surprising that she had recurrent symptoms after stopping treatment; this is common in women with a prior history of vasomotor symptoms. However, one would anticipate that her symptoms would be beginning to improve after nine months. It is possible that this patient could be in the subset of women whose symptoms persist for many years after clinical menopause.

Black cohosh, isoflavones, and red clover have not been shown to be more effective than placebo. Before considering going back to hormone therapy, non-hormonal options

should first be exhausted. If her symptoms were primarily at night, gabapentin would be a good choice (a single bedtime dose starting with 300 mg and titrating up to 900 mg), but if her symptoms occurred throughout the day, and if she had any symptoms suggestive of depression, an SSRI would be the first choice. Of note, the nonhormonal alternatives, while more effective than placebo, are not as effective as estrogen.

For her symptoms of vaginal atrophy, vaginal estrogen can be started and continued indefinitely. Systemic absorption is minimal, and these preparations are not associated with excess cardiovascular or breast cancer risk. Options include 17-B estradiol vaginal tablets, a 17-B estradiol vaginal ring, and conjugated estrogen or 17-B estradiol creams.

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Contraception for Women With PCOS: Benefit Versus Risk

M28
Sunday, June 16
1:00–1:45 PM & 3:00–3:45 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Polycystic ovary syndrome (PCOS) is a common and complex disorder characterized by androgen excess, ovulatory dysfunction and polycystic ovaries. Women with PCOS typically present with clinical evidence of hyperandrogenism (e.g. hirsutism), menstrual irregularity, and infertility. Accordingly, current treatment regimens are directed at reduction of hirsutism and/or acne, menstrual cycle regulation, and achieving pregnancy. Combined oral contraceptive pills (OCPs), often referred to as the birth-control pills, have been traditionally the mainstay of chronic treatment in PCOS patients not seeking pregnancy. They ameliorate hyperandrogenism and regulate menstrual cycles.

Current available evidence suggests that the benefits of OCPs outweigh the risks in most patients with PCOS. Nevertheless, potential adverse cardiometabolic effects of OCPs represent a concern given that women with PCOS use these drugs for several years.

BARRIERS TO OPTIMAL PRACTICE

- Definition of PCOS by different diagnostic criteria brings significant heterogeneity to the clinical phenotypes with potentially varying degrees of cardiometabolic risk starting from the diagnosis.
- Head-to-head blinded trials comparing different OCPs are lacking.
- Longitudinal follow-up data on benefits and risks of OCPs are not available.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Identify the role of OCPs in the management of PCOS
- Describe the mechanisms of action of OCPs
- Discuss contraindications and long-term safety of OCPs in PCOS

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

OCPs: A Synopsis

The OCPs are oral contraceptives containing low doses of synthetic estrogens and progestins. These hormones have direct inhibitory effect on hypothalamic release of gonadotropin-releasing hormone (GnRH). Estrogens inhibit the selection and development of a dominant follicle by suppression of follicle stimulating hormone (FSH). Progestins inhibit ovulation via suppression of luteinizing hormone (LH) surge. The effects of progestins also include making the cervix hostile to sperm penetration by thickening cervical mucus, and preventing implantation through an alteration of endometrial lining (1).

Virtually all currently available OCPs contain ethinyl estradiol as the synthetic estrogenic compound. Norgestrel, levonorgestrel, norgestimate, and norethindrone are used as synthetic progestins in second-generation pills while progestin component in third-generation pills are either desogestrel or gestodene. Starting from late 1960s, the amount of ethinyl estradiol in OCPs was significantly reduced from initial dose of 150 mcg to the current doses of 20-35 mcg in order to increase efficacy, safety, and tolerability. Pills containing less than 50 mcg of ethinyl estradiol are called “low-dose”

OCPs. Most of the low-dose OCPs contain ≤35 mcg ethinyl estradiol and the dose of synthetic progestin ranges between 0.1-3 mg.

Most synthetic progestins used in OCPs are derived from an altered testosterone molecule, 19-nortestosterone. These progestins vary in their chemical structures, potency and pharmacokinetics. They bind the androgen receptor with different affinities and show different degrees of androgenicity. In this group, desogestrel, norgestimate and gestodene are less androgenic compared to levonorgestrel.

Three synthetic progestins with antiandrogenic effects; cyproterone acetate, dienogest, and drospirenone, are used in OCPs. Cyproterone acetate is derived from 17-hydroxyprogesterone while dienogest and drospirenone are derivatives of 19-nortestosterone and 17-α-spirolactone respectively. Cyproterone acetate is the most potent antiandrogenic progestin. Antiandrogenic potency of dienogest and drospirenone are about 40% and 30% of that of cyproterone acetate respectively.

Noncontraceptive Benefits and Side Effects of OCPs

Noncontraceptive benefits of OCPs include decreased dysmenorrhea, menorrhagia and anemia, improvements in acne and hirsutism, decreased risk of osteoporosis and ectopic pregnancy. Long-term OCP use is also associated with decreased risk of ovarian and endometrial cancer.

The most common side effects of OCPs that result in poor compliance or discontinuation include abnormal menstrual bleeding, nausea, breast tenderness, headache, and mood changes. Most of these side effects lessen significantly after the first few months of use. Many women report that they experience some weight gain during OCP use. However, controlled clinical trials have failed to show any association between low-dose OCPs and weight gain. In fact, a recent Cochrane review of the available 49 randomized trials did not find any evidence supporting a causal association between OCPs and weight gain (2).

An association between use of OCP and risk of venous thrombosis has been consistently reported. The venous thromboembolic event (VTE) rate is 0.8/10.000 women-years in general population whereas these rates are 3-4 fold higher in OCP-users. Newer generation OCPs have about 2-fold increased risk of VTE compared with second-generation OCPs containing levonorgestrel (3) (4). The VTE rates in pregnancy and puerperal period are 6-10 and 50/10.000 women-years respectively (4). Overall, although the relative risk of VTE is increased with OCP use, the background risk in young women is low and the absolute risk is even smaller than the actual risk associated with pregnancy.

Current Contraindications to the Use of OCPs

The World Health Organization (WHO) has developed an evidence-based guideline for the use of OCPs. This document, based on systematic reviews of available clinical and epidemiological research, is updated regularly. The most recent version is published in 2009. Absolute and relative contraindications to the use of low-dose combined OCPs according to the WHO guideline are shown in *Table 1*.

Rationale for the Use of OCPs in the Treatment of PCOS

The OCPs have the ability to address many of the goals of reproductive-aged women with PCOS not seeking pregnancy. They ameliorate hyperandrogenic skin manifestations, regulate menstrual cycles thereby protecting from the risk of endometrial carcinoma, and provide effective and safe contraception (5).

In PCOS, the OCPs remain the mainstay of treatment for clinical androgen excess. They suppress the secretion of LH, and lead to a decrease in ovarian androgen production. The estrogenic fraction increases the levels of sex hormone binding globulin (SHBG), which, in turn, results in a decrease in free testosterone levels. The progestin in the pill can compete for 5α-reductase and the androgen receptor (6).

While almost all of the OCPs contain ethinyl estradiol as the estrogenic fraction, progestins in the pills vary in their androgenic potential. Norethindrone, norgestrel and levonorgestrel are known to have androgenic activity. Alternatively, desogestrel, norgestimate and gestodene

TABLE 1. Contraindications to the use of low dose (≤35 mcg of ethinyl estradiol) combined oral contraceptive pills

Absolute contraindications (i.e. unacceptable health risk)
< 6 weeks postpartum if breastfeeding
Smoker over the age of 35 (≥ 15 cigarettes per day)
Hypertension (systolic ≥ 160mm Hg or diastolic ≥ 100mm Hg)
History of deep venous thrombosis/pulmonary embolism
Current deep venous thrombosis/pulmonary embolism
Major surgery with prolonged immobilization
Known thrombogenic mutations (e.g. Factor V Leiden; Prothrombin mutation; Protein S, Protein C, and Antithrombin deficiencies)*
Current and history of ischemic heart disease
Stroke (history of cerebrovascular accident)
Complicated valvular heart disease
Migraine headache with focal neurological symptoms
Current breast cancer
Diabetes with nephropathy/retinopathy/neuropathy
Other vascular disease or diabetes of >20 years' duration
Active viral hepatitis
Severe cirrhosis
Liver tumors
Selected relative contraindications (risks generally outweigh benefits)
Smoker over the age of 35 (< 15 cigarettes per day)
Adequately controlled hypertension
Hypertension (systolic 140–159 mmHg, diastolic 90–99 mmHg)
Migraine headache over the age of 35
Current gallbladder disease
Past OCP-related history of cholestasis
Mild (compensated) cirrhosis
Use of drugs that affect liver enzymes

**Routine screening is not recommended because of the rarity of the conditions and the high cost of the screening*
Source: Adapted from World Health Organization. Medical eligibility criteria for contraceptive use. Fourth edition. 2009. Available at: http://www.who.int/reproductivehealth/publications/family_planning/9789241563888/en/index.html

are less androgenic and have the advantage of less metabolic side effects including the minimal impact on glucose, insulin, and lipids. Even though any OCP could be used in PCOS effectively, one might prefer the use of OCPs containing progestins with less androgenic activity (desogestrel) or anti-androgenic properties (cyproterone acetate and drospirenone) (7).

The OCPs are the treatment of choice for irregular menstrual bleeding in PCOS. Menstrual dysfunction in PCOS is clinically observed as oligo-amenorrhea, although approximately 15-30% of patients might have regular uterine bleeding in the face of documentable oligo-ovulation. PCOS patients often contact with a health care provider during their teenage years for unpredictable uterine bleeding. Use of OCPs in these patients results in regular withdrawal bleeding in addition to improvement in hyperandrogenism.

Taken together, available evidence strongly suggests that OCPs are effective agents for the long-term management of PCOS. However, there are concerns about the safety of these drugs, particularly potential long-term risks related to carsiovascular disease (CVD) and glucose intolerance (7).

OCP Use and CVD Risk in PCOS

Current literature supports the fact that many women with PCOS have increased cardiovascular risk factors suggesting that the risk of CVD is increased in the disorder. Obesity, insulin resistance, dyslipidemia, and dysfibrinolysis are generally found to be more common in patients with PCOS compared

to healthy women. Nevertheless, despite the existence of several CVD risk factors in women with PCOS, there is no direct evidence of increased or premature morbidity or mortality from CVD in the syndrome (8).

Epidemiological data in healthy women suggest that current use of low-dose OCPs might increase CVD risk although that risk does not continue once OCPs are stopped. The CVD risk is associated with increased age, smoking and hypertension. Accordingly, young nonsmoker women do not appear to possess any CVD risk due to OCP use. Intriguing data from healthy population suggest that OCP use during reproductive years might be protective against CVD later in life (9). Unfortunately, there are no data available in the literature assessing potential association of OCP use and CVD outcome in PCOS. Since patients with PCOS do not appear to have increased or premature morbidity or mortality from CVD despite having increased CVD risk factors, it would be interesting to test the hypothesis that long-term use of OCPs during reproductive years might be protective against CVD morbidity and mortality in PCOS later in life.

OCP Use and Diabetes Risk in PCOS

Insulin resistance with compensatory hyperinsulinemia is a prominent feature of PCOS, diagnosed in both lean and obese patients. Depending on the definition of insulin resistance, method for the measurement of this abnormality, and the population studied, up to 70% of women with PCOS will show insulin resistance and compensatory hyperinsulinemia. Nevertheless, not all women with PCOS have documented insulin resistance, and no measure of insulin sensitivity is included in the current diagnostic criteria of PCOS (10).

Women with PCOS are at substantially higher risk for impaired glucose tolerance (IGT) and type 2 diabetes, with combined prevalence rates between 18-40% for glucose intolerance. Indeed, PCOS has now been recognized as an independent risk factor for the development of type 2 diabetes. Current American Diabetes Association (ADA) guidelines suggest diabetes screening in women with PCOS (11). Detection of glucose homeostasis abnormalities in PCOS is best performed by means of oral glucose tolerance test (OGTT) rather than fasting plasma glucose measurements (10).

The strong association between PCOS and insulin resistance, and increased risk of diabetes in this disorder has boosted the number of insulin sensitizer studies in PCOS within the last two decades. On the other hand, there have been only a few studies evaluating the metabolic effects of OCPs in PCOS. Surprisingly, no randomized double blind studies are available in the literature comparing the metabolic effects of an OCP either with another OCP or with an insulin sensitizer or with an OCP/insulin sensitizer combination (7).

There are a few prospective studies on a limited number of subjects using different combinations of OCPs with a duration ranging from 3-12 months. The results regarding the effects of OCPs on insulin sensitivity, measured by various methods ranging from fasting insulin to clamp studies, are inconsistent and contradictory in that decreased, unchanged, and increased insulin sensitivity measurements have been reported. More importantly, in all but two studies glucose tolerance status did not change (1). Of note, both of these studies included morbidly obese PCOS patients with average BMI of 36.8 and 37.2 kg/m2 respectively (12, 13).

A recent meta-analysis of 35 observational studies and cohorts from RCTs investigated the association of OCP use and dysglycemia, insulin resistance and dyslipidemia (14). Included studies showed significant heterogeneity with several limitations. The authors reported that OCP use was significantly associated with an increase in HDL-C and TG levels ($p=0.004$ for both) whereas no clinically significant adverse cardiometabolic outcome was reported (14).

Overall, these limited available data suggest that low-dose OCP use for up to a year do not have an adverse impact on insulin sensitivity in most of the patients with PCOS although decreased or increased insulin sensitivity might be observed in a small group of individuals (1). Low-dose OCP use within a year do not appear to increase the incidence of type 2

diabetes in PCOS. However, deterioration of glucose tolerance status might be observed particularly in morbidly obese women with PCOS (12, 13). It is highly likely that, similar to healthy individuals, the risk of diabetes development depends on individual patient characteristics such as BMI, age, ethnicity and family history of diabetes as well as individual characteristics of the OCP combination. Finally, it remains to be determined prospectively how these variable effects of OCPs on insulin sensitivity and glucose tolerance status within a year translates into the longer term use of these medications in PCOS.

Long-Term Use of OCPs and Cardiometabolic Risk in PCOS

Only a few long-term observational studies evaluating the metabolic effects of OCPs in PCOS are available in the literature. In a prospective open-label study, lipid profiles and glucose homeostasis were evaluated in 72 PCOS women treated with ethinyl estradiol/cyproterone acetate for 3 years in comparison with 39 healthy women (15). At baseline, women with PCOS had higher levels of total cholesterol and triglycerides and lower levels of HDL-cholesterol. The investigators observed an increase in triglycerides and HDL-cholesterol and a decrease in LDL/HDL ratio in PCOS women after the treatment. More importantly, insulin and glucose plasma concentrations did not change (15).

Another observational study was conducted on 37 PCOS patients with an average follow-up of 10 years (range 12-180 months) to assess the long-term effects of OCPs on cardiometabolic risk factors in PCOS patients (16). The mean ages at the beginning and the end of the follow up were 18 and 29 years for the OCP-users and 21 and 31 years for the non-OCP users. Sixteen patients were on OCP treatment (ethinyl estradiol combined with either cyproterone acetate or gestodene or desogestrel) while 21 patients had never used OCP. None of the anthropometric measurements changed in non-OCP users during the follow-up including body weight, BMI, waist and hip circumferences and waist-to-hip ratio (WHR). Alternatively, waist circumference and WHR significantly reduced in OCP-users. Area under the curve (AUC) for glucose during OGTT decreased in OCP-users and unchanged in non-OCP users whereas AUC for insulin unchanged in OCP-users but increased in non-OCP users. Finally, HDL-cholesterol and SHBG levels increased significantly only in the OCP-users while there was no change in non-OCP users (16).

Taken together, findings of these studies suggest that insulin resistance worsens during the natural course of the syndrome while long-term OCP use either does not change or improve the cardiometabolic risk parameters including insulin resistance, lipoprotein profile, and potentially body fat distribution.

MAIN CONCLUSIONS

- The OCPs are a key component of the chronic treatment of PCOS addressing many of the goals of the reproductive-aged PCOS women not seeking pregnancy.
- Future studies evaluating the long-term effects of OCPs in the treatment of PCOS should adequately consider clinical heterogeneity of the syndrome and variation in the efficacy and safety of different combinations.
- OCP use might increase the risk of diabetes particularly in obese patients with severe insulin resistance.
- The WHO guidelines for the contraindications to OCP use should be exercised in women with PCOS and that the precise individualized treatment targets and risk stratification depending on patient characteristics should be determined.

CASES WITH QUESTIONS AND DISCUSSION OF CASES AND ANSWERS

Case 1

A 20-year-old woman presents with a complaint of having “too much facial and body hair” she finds bothersome and embarrassing. She had noted hair growth around puberty which had gradually progressed. She has been shaving and waxing regularly for her excess hair. She has always had irregular menses with intermenstrual intervals ranging from two to four months. She has never been pregnant and has not

been sexually active. She denies any chronic medications, significant weight change or galactorrhea. She states that her mother had excessive body hair and that no family member has type 2 diabetes.

On physical examination, BP 112/73, pulse 74. She is 1.64 m (5'4"), 68 kg (150 lbs). Her BMI is 25.3 kg/m2. She has prominent coarse hair over upper lip, chin, lower abdomen, lower back, and upper legs (mFG- score: 15). Thyroid is normal palpable. She does not have acanthosis nigricans or any features of virilization or Cushing's syndrome or acromegaly.

Questions

1. ***Which tests are indicated for diagnosis?***
2. ***What additional information is required before recommending an OCP to this patient?***
3. ***Which examinations and tests are needed before a first prescription of OCPs?***

Answers

1. PCOS is the most likely diagnosis in this patient with hirsutism and oligomenorrhea. PCOS is a diagnosis of exclusion. TSH, prolactin, and 17-(OH)P levels are required to exclude thyroid dysfunction, hyperprolactinemia, and NCAH respectively. Pelvic ultrasound will show whether the patient has polycystic ovaries. Testosterone and SHBG measurements are helpful to determine biochemical androgen excess.
2. History of past and present medical conditions, any drug use, and family history are required. Specifically, information regarding CVD risk factors (smoking, hypertension, obesity, glucose intolerance, dyslipidemia, thrombophilia, previous VTE) is important. Occasionally, a patient with PCOS may need to avoid OCP use.
3. Blood pressure measurement and BMI are required before a first prescription of OCPs whereas breast examination, pelvic and genital examination, cervical cytology screening are not routinely recommended as they do not contribute substantially to safety of OCPs. In patients with PCOS cardiometabolic risk assessment needs to be performed including 75g standard 2h OGTT and lipid profile.

Case 2

A 25-year-old woman presents with irregular menses and hirsutism. She has been diagnosed with PCOS at age 16 when her weight went up 10 kg (22 lbs) in a year. She was prescribed OCPs at that time and she states that she has been on and off since then. She reports that her menses do not occur up to six months when she discontinues the pill. She is sexually active and does not desire pregnancy. She is non-smoker and has a negative family and medical history including clotting problems.

On physical examination, BP 118/75, pulse 78. She is 1.61 m (5'3"), 85 kg (187 lbs). Her BMI is 32 kg/m2. mFG- score: 7. Thyroid is normal palpable. Otherwise, unremarkable.

Laboratory tests reveal normal TSH, testosterone and SHBG levels, polycystic ovaries on ultrasound. Fasting and 2h glucose values on OGTT are 85 and 143.

Questions

1. ***What are the treatment options?***
2. ***Are there any contraindications for the use of OCPs in this patient?***

Answers

1. This is an obese PCOS patient with impaired glucose tolerance. Lifestyle change intervention should be an essential component of the long term management for this patient. Metformin may be used for IGT. However, the patient would probably need hormonal contraception as she reports amenorrhea when she does not use OCP. Available data suggest that lifestyle change or metformin would not be as effective as OCP for amelioration of androgen excess. OCP use in this patient is also important for the protection from endometrial carcinoma and for effective contraception. Glucose tolerance and lipids should be evaluated regularly during the follow-up.
2. Obesity increases the risk of VTE and this risk increases further with OCP use. Obese women may also have other comorbidities that increase risk of CVD. However, obesity alone is not an absolute contraindication to oral contraception. Obesity associated comorbid conditions such as hypertension and diabetes should be considered when

counseling and prescribing OCPs. Women over 35 years are more likely to have obesity related risk factors.

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LIPIDS

HDL Hypothesis Update: Is HDL Really Protective vs. Cardiovascular Disease?

M5
Saturday, June 15
3:00–3:45 PM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Cardiovascular disease (CVD) is the greatest cause of death and disability in the US and the world. Atherosclerosis is the most common cause of CVD and dyslipidemia appears to be the single greatest treatable cause of atherosclerosis. Although high levels of atherogenic lipoproteins (LDL, IDL, etc.) are the primary focus of treatment guidelines, low levels of HDL generally are found to be the most powerful as a CVD risk factor in the general population.

The HDL hypothesis is that HDL is a major protective factor against atherosclerosis and CVD, and therefore that low HDL levels are bad and that raising HDL levels is good. This hypothesis was first conceived several decades ago, and is based on many lines of evidence. Not only is HDL usually strongly inversely associated with atherosclerosis and CVD risk, but also, in many settings delivery of HDL or increases in HDL levels appear to directly reduce atherosclerosis and CVD.

Surprisingly, however, some recent study data have called into question the validity the HDL hypothesis. Current controversies regarding the HDL hypothesis have left significant gaps in professional practice in that it is difficult for clinicians to know how to (1) assess CVD risk by HDL-related testing, and (2) treat to reduce CVD risk when HDL levels (or function) are low.

BARRIERS TO OPTIMAL PRACTICE

There is much controversy and little consensus at present about:

- How to interpret recent (and earlier) clinical trials of "HDL-raising" treatments and how to apply their results, if at all, in clinical practice.
- How to assess CVD risk by HDL-related testing (of levels and/or function).
- What treatments to employ (in which patients) in order to reduce the excess CVD risk which may be present in patients with low HDL levels (or otherwise deficient CVD protection from HDL).

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Discuss recent clinical trial and genetic study data and their implications for the HDL hypothesis.
- Delineate key strengths and weaknesses of the major methods for measuring HDL levels and function.
- Implement treatment to reduce CVD risk in patients with low/impaired HDL levels/ function, based on best available evidence.

SUCCINCT REVIEW- STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Issues in Diagnosis and Therapy of "Low HDL"

The most important recent challenges to the HDL Hypothesis are clinical trial data. The first of three clinical trials appearing to show that HDL-raising does not reduce CVD risk is the AIM-HIGH study. This study was designed primarily as "a rigorous test of the HDL hypothesis", using extended-release niacin (ERN) as a tool to explore the question of whether HDL-raising reduces CVD risk. Despite statements to the contrary, it was not a direct trial of ERN effects on CVD,

since a major lipid effect of niacin outside of HDL-raising, LDL-C lowering, was largely counterbalanced by study-based efforts to keep LDL-C within the same low range (40 to 80 mg/dL) in both treatment arms. This was accomplished by uptitration of statin dose and increased frequency of use of ezetimibe in the control arm. Further, in order to maintain the study blind in the face of expected frequent flushing in the treatment arm, the control arm was given low-dose immediate-release niacin IRNA in every "placebo" tablet. This resulted in AIM-HIGH being an active comparator study. That is, high-dose ERNA (1500 to 2000 mg/d) with standard dose statin and little ezetimibe was compared with low-dose IRNA (100 to 150 mg/d) with higher dose statin and more frequent ezetimibe. Thus, AIM-HIGH, contrary to many experts (and ironically contrary to statements by the study authors themselves) was not a test of niacin per se. It was, however, a test of the HDL-raising hypothesis.

Further complicating interpretation of the study data were several study peculiarities: (1) the difference between study arms in HDL-C increase from baseline (15%) was much smaller than anticipated (25%) due to an unexpected 10% HDL-C increase in the control arm, (2) the study was cut short at only about 2 ½ years of treatment, (3) nearly all subjects had had extensive pre-study treatment with a statin, and many had had niacin as well, and (4) virtually all subjects were treated to rather low LDL-C levels of less than 80 mg/d. All four of these facts were likely to reduce the potential benefits of on-study treatment, and indeed no CVD benefit was found in the high-dose niacin arm. Somewhat surprisingly, initial subgroup analyses failed to find any baseline predictors of CVD event reduction, including in patients with low HDL-C or high TG levels. Later, however, a 26% reduction in the primary endpoint was reported with high-dose ERN among patients having both bottom tertile HDL-C and top tertile TG levels at baseline. [Guyton, et al, AHA meeting presentation, November 2012] This is in sharp contrast to the complete lack of apparent benefit (HR 1.03) in the overall study population, who were selected for low HDL-C but not high TG levels at baseline. The fact that the CVD benefit was limited to a sub-population with both very low HDL-C and high TG may have seemed surprising at first, but in retrospect it should have been anticipated.

First of all, this result tends to confirm that of the largest early clinical trial of CVD effects of niacin, The Coronary Drug Project, originally published in 1975, showed that niacin use led to a significant reduction in nonfatal myocardial infarction (NFMI) after 6 years of treatment. Extended follow-up of niacin treated subjects at 15 years (9 years after cessation of randomized study treatment) also showed a significant reduction in total mortality in the niacin-treated group. [Canner PL, 1986] Subsequently, a post-hoc analysis of this study divided subjects into those with and without Metabolic Syndrome. Among 492 subjects in whom HDL-C was measured (of 3906 total subjects), Metabolic Syndrome was defined as usual, except using a body mass index over 28 in place of a waist circumference over 40 inches (all subjects were men), since waist had not been measured. Interestingly, NFMI was reduced 78% with niacin in subjects with Metabolic Syndrome, vs. 24% in those without it. [Canner PL, 2006] Although this difference did not quite reach statistical significance (due to small numbers of events), it is striking in that it follows the same general trend towards greater event reduction with niacin in AIM-HIGH subjects with low HDL-C and high TG reported by Guyton, et al, at the AHA meeting in November 2012.

Importantly, these results with niacin parallel results with two other classes of agents, also used primarily for HDL-raising and/or TG lowering. As a primary example, two relatively recent studies of fenofibrate have shown a result similar to that noted for niacin. Although neither FIELD nor ACCORD-Lipid showed a benefit of fenofibrate for CVD event reduction in their overall study populations (generally not selected for baseline lipids), in both studies, significant reduction in the primary endpoint was seen with fenofibrate in the subgroup of subjects having both low HDL-C and high TG at baseline. Importantly, the second of these, ACCORD-Lipid, was performed with background statin therapy in

all subjects, as was AIM-HIGH.

Another key example of a similar finding is JELIS, a recent study of a prescription omega-3 product, icosapent ethyl (a pure EPA product). Over 18,000 study subjects with a total cholesterol over 250 mg/dL were given statin and then randomized to receive study drug at a low-moderate dose of 1.8 g/d, or to the control arm and there was a statistically significant 19% reduction in CVD events, equal between primary and secondary prevention patients. Baseline LDL-C of 182 mg/dL was equally reduced about 25% in both arms, baseline HDL-C of about 58 was increased about 3% in both arms, while baseline TG of about 150 was reduced only about 9% with EPA vs. about 3% decrease in the control. Among the nearly 15,000 who had not had a prior CV event but who were at high risk due to a total cholesterol over 250 mg/dL Of these, 957 were selected for having a high TG (>150 mg/dL) and low HDL-C level (<40 mg/dL) at baseline and in this group CVD events were reduced by a striking 53% vs. control. Although icosapent ethyl differs from fenofibrate and niacin in that it does not raise HDL-C levels, it does lower TG, as do the other agents.

Thus, CVD reduction has been shown in four contemporary studies (and one older one) using three classes of drugs used for TG-lowering and/or HDL-C-raising, when looking at patients who entered the studies with low HDL-C and high TG levels. Three of the four studies were done against background statin use in all subjects.

HPS2-THRIVE is a very recently reported trial of extended-release niacin plus a flush-blocker agent laropiprant (ERNL) vs. placebo on top of background statin treatment. As with AIM-HIGH, the overall study population did not have a significant benefit, and the investigators asserted that "we now know that [niacin's] adverse side effects outweigh the benefits when used with current treatments" (i.e. statins). There are, however, already evident in the initial presentation of trial results (all that is available at present) several key caveats against accepting that sweeping rejection of niacin add-on treatment. First and perhaps foremost, on average, baseline LDL-C was 63 mg/dL and non-HDL-C about 84 mg/dL, such that subjects were not in need of niacin for lowering these levels. Further, baseline TG was 125 mg/dL and HDL-C was 44 mg/dL, so HPS2-THRIVE tested a drug in patients who, on average, had no lipid-related indication to take it! Despite this general lack of rationale for niacin treatment, there was a very slight trend towards overall CVD benefit (4%, p value 0.3). Further, although the CVD event rate curves did not begin to separate until 2 years of study treatment, afterwards the curves appeared to diverge progressively until study end at about 4 years. Importantly, there appeared to be two cases of clinically important subgroup heterogeneity, and there was a third potential exception to a blanket lack of benefit. First, there was a statistically significant trend towards CVD event reduction in subjects with baseline LDL-C above 58 mg/dL. This is a very low LDL-C, rarely obtained in clinical practice, suggesting that the vast majority of patients in the "real world" might have reduced CVD risk with niacin added to a statin. Second, there appeared to be a substantial difference (heterogeneity p value 0.06) between patients from Europe (probably largely Caucasian, with an apparently significant ~9% decrease in CVD events) and from China (trend towards ~2% increase in CVD events). Since a large majority of clinical practices in the US have far more Caucasian than Chinese (and other genetically related East Asians) patients, again, the overall negative results of HPS2-THRIVE may have relatively little clinical relevance. Third, in light of the favorable results with niacin in the Coronary Drug Project and AIM-HIGH in patients with metabolic syndrome and/or low HDL-C with high TG levels, there might have been benefit in those patients. Hopefully, appropriate subgroup analysis will be done soon to see if the pattern in other recent trials of niacin and other "HDL/TG agents" holds up. Finally, there are explanations and caveats in interpretation of the ~3% excess of "serious adverse events." About one-half of SAEs among diabetics were "minor hyperglycaemic problems", understandable with prior evidence of mild, transient glucose elevations with niacin, but not likely requiring hospitalization.

There was a trend towards excess hemorrhagic stroke, but considering that the average on-study LDL-C was an ultra-low 53 mg/dL, this may simply be a result of vasculotoxicity from excessive LDL-C lowering, similar to the excess of hemorrhagic stroke reported in the most aggressive statin trials. Also, animal trials suggest aneurysm formation from laropiprant. Further, the vast majority of excess myopathy was seen only among the Chinese subjects. Thus, for the moment, niacin has been shown to lack net benefit among Chinese (and likely other East Asian) patients. Caucasians, especially with LDL-C above the lowest levels, appear likely to benefit.

Finally, dalcetrapib, an inhibitor of cholesteryl ester transfer protein (CETP-I) failed to lower CVD despite a 30% increase in HDL-C in the recent dal-OUTCOMES trial [Schwartz, NEJM 2012]. Although not proven, the lack of expected benefit may be due to an adverse impact on aldosterone and the renin-angiotensin system (suggested by a small increase in BP) counterbalanced by only a weak protective effect of HDL-C elevation.

Genetic Studies

A Mendelian randomization study recently explored the relationship between HDL levels and CVD risk [Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. Lancet. 2012;380:572-580.]. A single nucleotide polymorphism in the endothelial lipase gene was associated with HDL-C levels 5.5 mg/dL (roughly 12%) higher than in non-carriers, but was not associated with a lower myocardial infarction (MI) rate. As noted by the authors, a possible explanation for this was the fact that the higher HDL-C did not associate with a lower TG level (as would be typical in a general population). Further corroborating this point, polymorphisms in 14 other genes with isolated HDL-C increases (without decreases in TG) also were not associated with decreased MI risk.

Methods of Measurement of HDL Concentration and Function

Some have sought to explain the apparent problems with the HDL hypothesis by stating that HDL-C levels are not a good metric of potential anti-atherogenic effects of HDL. Two candidates for a better HDL parameter are levels of apo A-I, the major HDL apolipoprotein, and "HDL-P", which is an estimate of HDL particle concentration from NMR profiling of plasma. The problems with these two methods is that neither one has convincingly overcome any of the potentially negative data noted above. Admittedly, however, alternative parameters of HDL concentration appear to provide additional information about HDL complementary to that from HDL-C levels. In addition, many claim that the best way to measure the anti-atherogenic potential of HDL is to measure one or another aspect of HDL function. Although likely also complementary to parameters of HDL concentration, there are several practical drawbacks to this approach at present. First, there are many potentially beneficial functions of HDL and it is hard to know which one functional aspect is best to measure. Second, there is no standardization of tests of HDL function. Third, functional assays are cumbersome by nature and not logistically feasible for general clinical use. Finally, even when the key aspect(s) of HDL function can be established, HDL composition would very likely parallel function, and thus, an advanced HDL composition test may likely be the best ultimate solution to assessing HDL function in a clinical setting.

MAIN CONCLUSIONS

1. Extensive prior study data suggest that "HDL-raising" therapy may reduce atherosclerosis and CVD events in patients with low HDL-C and high TG. Recent studies have appeared to contradict the prior data, but upon closer evaluation they are probably consistent with the earlier results.
2. Measurement of HDL-C alone is probably adequate in low- to medium-risk patients. Advanced HDL testing (apo A-I, HDL-P, HDL subspecies) gives extra information

and might be useful in high-risk patients, but the relative strengths of these various parameters are unclear. Measurement of HDL function remains solely a research tool.

3. The use of niacin, fibrates and/or prescription omega-3 as adjuncts to statins (or alternates in intolerant patients and possibly in patients with naturally low LDL levels) should be considered in patients with low HDL-C and/or high TG levels, but their use must be tempered by the lack of compelling study data at present.

CASE AND DISCUSSION

Patient Profile: 58 y/o white male; high-stress job; Rx statin, BP med, aspirin

Known CAD (sub-clinical) high coronary artery calcium score 210 (1998)

April 2008 (clinic visit)

Exam: BMI 27 (central adiposity); SBP 120 (HBP controlled on BP meds)
Labs (on statin monotherapy—compliant)
LDL-C: 67 mg/dL
Triglycerides: 300 mg/dL
HDL-C: 32 mg/dL
Non-HDL-C: 127 mg/dL
A1c WNL
Treadmill stress test: achieved target heart rate w/o angina or ECG ischemia

Clinical Management Questions

- How high is this patient's CVD risk?—very high given the CAC score >200 and the low HDL-C and HTG residual after statin monotherapy
- Should this patient receive additional treatment?—yes; If so, what?—niacin, a fibrate, or omega-3
- What does NECP ATP-III say about such patients?—consider niacin or a fibrate

June 2008: the patient, Tim Russert (a prominent television journalist), suffered an acute MI at the TV studio, but could not be resuscitated.

Take-Away Messages

1. Patients with even just mild-moderate HTG and/or low HDL-C are at very high CVD risk, even if LDL-C is very low on a statin.
2. The common practice of leaving patients such as this on statin monotherapy, in essence assumes that patients are worse-off with a statin adjunct that without it. Although we do not have definitive proof that the addition of another lipid medication to a statin is beneficial, the existing evidence is reasonably persuasive. Of course, we cannot know whether a statin adjunct would have prevented the MI or have saved Mr. Russert's life, but many lines of data suggest that additions to statin therapy can reduce CVD in cases with low HDL-C and high TG.

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Statin Therapy in Hyperlipidemia: Balancing the Risk and Benefits

M32
Sunday, June 16
1:00–1:45 PM & 3:00–3:45 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

The benefits of statins in reducing the risk of cardiovascular disease in patients with pre-existing cardiovascular disease or diabetes is well recognized and guidelines from numerous professional organizations provide clear indications that these drugs are important in the treatment of patients with these disorders. The Cholesterol Treatment Trialists have published several analyses clearly showing benefit of statin therapy on morbidity and mortality with minimal side effects (1, 2). Additionally, the Cholesterol Treatment Trialists have further shown that more intensive lowering of LDL cholesterol with high dose potent statin therapy is beneficial in high risk patients (3). Because of the wide acceptance of the need for aggressive statin therapy in these high risk patients the benefits of statins in these patient populations will not be discussed.

Rather I plan to focus on a more controversial issue. What are the risks and benefits of statin therapy in low risk primary prevention patients? Cardiovascular disease is very common and the leading cause of death in the US. The lifetime risk of an individual developing cardiovascular disease is substantial (4, 5). At an index age of 45 the lifetime risk of developing cardiovascular disease is 56% in women and 60% for men. However, the short term risk (10year) in many of these patients is low. How should we approach these patients who make up the bulk of the population? Is there a place for early treatment with statins to reduce the future risk of cardiovascular disease in these patients?

BARRIERS TO OPTIMAL PRACTICE

While there have been numerous randomized outcome studies of statin therapy in high risk patients with cardiovascular disease and/or diabetes the number of primary prevention trials is relatively small. Additionally, when one examines these primary prevention studies the individuals included often had risk factors that increased the likelihood of these individuals developing cardiovascular events (i.e. often high risk primary prevention patients were studied with many having a 10 year Framingham risk score > 10%). Because of the lack of definitive trials the approach to treating these low risk patients is not clear and clinicians often have to decide without evidence based guidelines how to approach these patients. A long term study randomizing low risk patients 40-50 years of age to statin or placebo therapy and then following these individuals for 10 to 20 years would be ideal and could definitively demonstrate the appropriate therapeutic approach. Unfortunately, such a study is unlikely to ever be carried out.

LEARNING OBJECTIVES

1. To understand the rationale for the early treatment with statins in patients with a low risk of cardiovascular disease
2. To understand the potential side effects of statin therapy

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

As discussed above there are no definitive studies and it is unlikely that there ever will be definitive studies on whether the treatment

of low risk patients with statin therapy will be beneficial or harmful. Therefore, in the absence of definitive randomized controlled trials one has to examine a wide range of information that sheds light on the issue (6, 7). Based on this incomplete data base one will have to make clinical decisions based on the preponderance of evidence.

Data Suggest That Early Statin Treatment Will Have Benefits

Lifetime risk vs. 10 year risk of cardiovascular disease

In younger individuals the 10 year risk of cardiovascular disease can often be very low but the lifetime risk can be substantial (4, 5). For example, a 40 year old male can have a 10 year risk of cardiovascular disease of only 2.2% and a lifetime risk of 42%. Similarly, a 40 year old female could have a 10 year risk of only 0.7% and a lifetime risk of 25%. Should we focus solely on the short term risk? Are our patients only concerned about their risk of developing cardiovascular events in the next decade or are they interested in trying to maintain good health and prevent cardiovascular events throughout their lifetime?

Atherosclerosis begins early in life

Numerous studies have demonstrated that atherosclerosis occurs early in life and progresses over time. The classic studies of US service members killed in the Korean and Vietnam wars demonstrated that atherosclerotic changes in the coronary arteries can appear early in life. Recent studies of US service members killed in support of Operations Enduring Freedom and Iraqi Freedom/New Dawn between October 2001 and August 2011 have also demonstrated the presence of atherosclerosis but at a lower incidence than seen in the earlier studies (8). Community autopsy studies, carotid intima medial thickness (CIMT) measurements, and coronary calcium scores have similarly demonstrated an early onset of atherosclerosis.

Role of LDL cholesterol and non-HDL cholesterol

The severity of atherosclerosis and cardiovascular events correlates with LDL cholesterol and non-HDL cholesterol levels. Numerous epidemiologic studies from around the world have demonstrated this relationship. The higher the LDL cholesterol and/or non-HDL cholesterol level the more likely one is to have a future cardiovascular event. One can similarly show a strong correlation of CIMT and coronary calcium score with LDL cholesterol and non-HDL cholesterol levels.

Genetic alterations

Genetic abnormalities that increase LDL cholesterol levels, such as mutations in the LDL receptor, PCSK9, or apolipoprotein B 100, increase the risk of cardiovascular disease(9). This can be quite dramatic as patients with homozygous familial hypercholesterolemia will often have cardiovascular events before age 20. Conversely, polymorphisms in genes that result in a decrease in LDL cholesterol levels, such as polymorphisms in PCSK-9, decrease the risk of cardiovascular disease (9).

Effect of lowering LDL on atherosclerosis

Several studies have shown that lowering LDL levels with statin treatment reduces the progression of atherosclerosis or induces regression. For example, the Meteor Trial examined the effect of rosuvastatin on the rate of change in CIMT in relatively low risk patients. The change in maximum CIMT for the 12 carotid sites was -0.0014 mm/y for the rosuvastatin group vs. 0.0131 mm/y for the placebo group ($P<.001$), indicating that statin treatment prevented disease progression. Similarly, in the Reversal Trial, intravascular ultrasound demonstrated that more aggressive lowering of LDL cholesterol with high dose potent statin therapy reduced atheroma volume to a greater extent than moderate reductions in LDL cholesterol, again linking statin reductions in LDL with effects on the progression of atherosclerosis.

Effect of statins on cardiovascular events in primary prevention

Several studies have shown that statin treatment reduces cardiovascular events in patients without known cardiovascular

disease (i.e. primary prevention). For example, the Jupiter Trial compared rosuvastatin vs. placebo and reported a 44% reduction in cardiovascular events (10). Strikingly in the patients in the Jupiter Trial who had a 10 year Framingham risk score of < 10% a marked reduction in cardiovascular events was also observed. In a meta-analysis of statin primary prevention trials, not including the Jupiter trial, a 28% decrease in events was described (11). In a meta-analysis by Tonelli et al. that included the Jupiter Trial, the authors found a reduction in non-fatal MI of 36% and stroke of 19% (12). All-cause mortality was also reduced. Additionally, "when low cardiovascular risk was defined as a 10-year risk of cardiovascular-related death or nonfatal myocardial infarction of less than 10%, the pooled relative risk was similar to that of the primary analysis" indicating that primary prevention in relatively low risk patients is effective (12). One of the criticisms of these statin primary prevention trials has been that they do not consistently show a reduction in mortality. However, this is not unexpected given that in these short term studies in low risk patients most of the deaths are not due to cardiovascular disease. For example in the Jupiter Trial only 5% of deaths were due to MI or strokes. One does not expect that statins will reduce deaths due to cancer, trauma, etc.

Statin Side Effects

Diabetes

In a meta-analysis of 13 trials with a total of 91,140 subjects, 4,278 patients developed diabetes over a mean 4-year follow up (13). There was a 9% increase in the incidence of diabetes during follow-up among subjects receiving statin therapy vs. those receiving placebo or standard care. When only placebo-controlled studies were examined the risk of diabetes increased to 10% in statin group. No clear difference was observed between the statins with regards to diabetes risk. In comparisons of intensive vs. moderate statin therapy, Preiss et al. observed that patients treated with intensive statin therapy had a 12% increased risk of developing diabetes compared to subjects treated with moderate dose statin therapy (14). Older subjects, obese subjects, and subjects with high glucose levels were at a higher risk of developing diabetes while on statin therapy (15). Thus, statins may be unmasking and accelerating the development of diabetes that would have occurred naturally in these subjects at some point in time. In balancing the benefits and risks of statin therapy I think it is important to recognize that an increase in plasma glucose levels is a surrogate marker for an increased risk of developing micro and macrovascular disease (i.e. an increase in plasma glucose per se is not an event but rather increases the risk of future events). In contrast, statin therapy is preventing actual clinical events that cause morbidity and mortality.

Cancer

Analysis of 14 trials with over 90,000 subjects by the Cholesterol Clinical Trialists did not demonstrate an increased risk of cancer or any specific cancer with statin therapy (1).

Liver disease

Initially there was concern that statins could induce liver disease and it was recommended that transaminase levels be routinely monitored in patients on statin therapy. With the publication of large randomized statin trials it became clear that increases in transaminase levels did not occur more frequently in statin treated subjects. Because of these results it is no longer recommended that transaminase levels be routinely monitored in patients on statin therapy. Of note several studies have shown that in patients with pre-existing liver abnormalities statin treatment actually decreases transaminase levels and therefore the concerns of statins causing significant liver dysfunction have markedly diminished (16).

Cognitive dysfunction

Several randomized clinical trials have examined the effect of statin therapy on cognitive study and have not indicated any increased risk. The two largest trials are the Prosper Trial and the Heart Protection Study. The Prosper Trial was designed to determine whether statin therapy will reduce

cardiovascular disease in older subjects (70-82) with pre-existing vascular disease or who were at high risk for vascular disease. In this trial cognitive function was assessed repeatedly in all 5,804 participants using four neuropsychological performance tests. After a mean follow-up period of 42 months, no difference in cognitive decline at any of the cognitive domains was found in subjects treated with pravastatin compared to placebo (all $p > 0.05$) (17). In the Heart Protection Study over 20,000 patients were randomized to simvastatin 40mg or placebo and cognitive function was determined using a modified Telephone Interview for Cognitive Status questionnaire during their final follow-up. In this trial no significant differences were observed between the statin vs. placebo group in the percentages of subjects classified as cognitively impaired, either overall or in any particular subgroup (18). Thus, while the FDA has mandated warnings regarding statin induced cognitive dysfunction randomized clinical trials do not indicate a significant association.

Myopathy

In most randomized clinical trials the risk of serious myopathy has been very low. For example in the Heart Protection Study over 20,000 patients were randomized to treatment with simvastatin 40mg a day or placebo for approximately 5 years. In this trial there were only 5 cases of rhabdomyolysis in the simvastatin group (0.05%) vs. 3 cases in the placebo group (0.03%) (18). If one looks at elevated CPK levels, in the simvastatin group 19 patients (0.19%) had a CPK between 4-10x the upper limits of normal and 11 patients (0.11%) had a CPK > 10x the upper limits of normal. In the placebo group the respective numbers were very similar (13 (0.13%) and 6 (0.06%)) (18). Even in older patients the risk of serious myopathy appears to be very low. For example, in the Prosper Trial described above, none of the elderly patients treated with pravastatin developed rhabdomyolysis or CPK levels > 10x the upper limits of normal. In the Prosper Trial myalgia was reported in 36 patients treated with pravastatin but notably myalgia also occurred in 32 patients in the placebo group. In the AFCAPS/TexCAPS trial patients were specifically asked about musculoskeletal symptoms. In the 3301 subjects treated with lovastatin 2053 reported musculoskeletal symptoms. However, in the 3301 subjects in the placebo group 1971 also reported musculoskeletal symptoms. Thus, in randomized controlled trials, statin treatment does not appear to cause a marked increase in myopathy. An exception is the SEARCH trial where high dose simvastatin (80mg a day) did produce a substantial risk of serious myopathy (0.9%). Because of this increased risk of serious myopathy simvastatin 80mg/day is no longer used. While the results of the randomized trials suggests that myopathy is not a major problem in typical clinical settings a significant percentage of patients are unable to tolerate statins due to myopathies (in many studies as high as 5-10% of patients). Recently there was a randomized trial that explored the issue of myopathy with statin therapy in great detail (19). In this trial the effect of atorvastatin 80mg a day vs. placebo for 6 months on creatine kinase, exercise capacity, and muscle strength was studied in 420 healthy, statin-naive subjects. Atorvastatin treatment led to a modest increase in CPK levels (20.8U/L) with no change observed in the placebo group. None of the subjects had an elevation of CPK > 10x the upper limits of normal. There were no changes in muscle strength or exercise capacity with atorvastatin treatment. However, myalgia was reported in 19 subjects (9.4%) in the atorvastatin group compared to 10 subjects (4.6%) in the placebo group ($p=0.05$). In this study "myalgia" was considered to be present if all of the following occurred: (1) subjects reported new or increased muscle pain, cramps, or aching not associated with exercise; (2) symptoms persisted for at least 2 weeks; (3) symptoms resolved within 2 weeks of stopping the study drug; and (4) symptoms reoccurred within 4 weeks of restarting the study medication. These myalgias were not associated with elevated CPK levels. In the atorvastatin group the myalgias tended to occur soon after therapy (average 35 days) whereas in the placebo group myalgias occur later (average 61 days). In the atorvastatin group

the symptoms were predominantly localized to the legs whereas in the placebo group they were more diverse including whole body fatigue, worsening of pain in previous injuries, and groin pain. While some patients will not tolerate statin therapy due to myalgias this side effect does not appear to result in serious morbidity or long term consequences.

MAIN CONCLUSIONS

While there are not definitive randomized outcome studies demonstrating that the early treatment of low risk patients with statin therapy will be beneficial a considerable body of circumstantial evidence suggests that a substantial reduction in cardiovascular disease will occur with statin therapy in this patient population (6, 7). Given the relatively small risk of statin therapy I think that in many low risk patients the potential benefits of early statin therapy outweigh the potential harm. Additionally, now that statins are generic drugs with a very low cost (many statins can be obtained for approximately $4 per month) the cost benefits of early treatment seem to favor statin therapy (20).

Nevertheless "When the totality of evidence is incomplete, it is appropriate to remain uncertain" (CH Hennekens and D DeMets. JAMA 302:2361-2362, 2009).

CASES WITH QUESTIONS

Case 1

A 50 year old male in good health seeks your advice on reducing his risk for cardiovascular disease. The patient exercises and tries to eat a healthy diet. He does not smoke and has no family history of heart disease. He is on no medications. Height is 5'10" (178cm), weight 200lbs (91kg), BMI 28.7, waist circumference 36 inches (91.4cm), and BP 130/80. His total cholesterol is 220mg/dl, LDL 132mg/dl, HDL 40mg/dl, non HDLc 180mg/dl, and TG 140mg/dl. His 10 year Framingham Risk Score is 6%.

Case 2

The patient's wife, who was with the patient, was concerned about her risk of cardiovascular disease. She is 50 years old and in good health except for hypertension treated with lisinopril 10mg qd. She exercises daily and tries to eat a healthy diet but has had weight issues since having children. She does not smoke and has no family history of heart disease. Her height is 5'6" (168cm), weight 180lbs (82kg), BMI 29, waist circumference 35 inches (88.9cm), and BP 135/80. Her total cholesterol is 220mg/dl, LDL 132mg/dl, HDL 40mg/dl, non HDLc 180mg/dl, and TG 140mg/dl. Her 10 year Framingham Risk Score is 2%.

Questions

1. What would you do next for case 1 and 2?

a Observe with repeat testing
b Start generic statin therapy
c Obtain additional tests- hsCRP, carotid ultrasound, CT to measure coronary calcium score, etc.

2. Which of the following are potential side effects of statin therapy (can be multiple answers)?

a Adrenal insufficiency
b Diabetes
c Hyperthyroidism
d Myopathy
e Cancer

DISCUSSION OF CASES AND ANSWERS

Question 1

There is no correct answer. I would favor starting generic statin therapy in both patients. My logic for initiating therapy is that while patient 1 has a 10 year Framingham Risk Score of only 6% his lifetime risk of cardiovascular disease is 41%. Similarly in case 2 the 10 year Framingham Risk Score is only 2% but her lifetime risk is 43%. I would therefore discuss with these patients the advantages and risks of statin therapy and my belief that statin therapy would in the long term reduce their risk of developing cardiovascular disease. (Can estimate lifetime risk using QRISK calculator (http://www.qrisk.org/lifetime)

Question 2

The correct answers are b and d. Statins have been shown to increase the risk of diabetes and to cause myopathy.

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The Workup and Management of Lipodystrophies

M41
Monday, June 17
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

This MTP session will focus briefly on the general work up and then on metabolic management of congenital and acquired lipodystrophies, with cases on metabolic management. A number of congenital and acquired lipodystrophies exist (see excellent reviews such as Semple et al.[1] and Garg[2] for a comprehensive description of these syndromes). Management of metabolic abnormalities, including abnormal fat distribution, insulin resistance, dyslipidemia, and related metabolic and endocrinologic problems is often difficult in lipodystrophies. New management options, including recombinant human leptin (rhLeptin) and growth hormone releasing hormone (GHRH) are available for specific lipodystrophies and will be discussed.

BARRIERS TO OPTIMAL PRACTICE

1. Recognizing and classifying specific lipodystrophies
2. Knowledge and availability of specific medications to use in lipodystrophies

LEARNING OBJECTIVES

1. Understanding the relationship between abnormal fat distribution and metabolic problems in lipodystrophy
2. Understanding the common mechanisms of acquired and congenital lipodystrophies
3. Understand new treatment options for the management of lipodystrophies

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Lipodystrophies Potentially Seen in Clinical Practice

Congenital generalized lipodystrophy (CGL)

- Phenotype - Characterized by lack of adipose tissue, hepatosplenomegaly, pseudoacromegaly, severe insulin resistance [IR], increased TGL, decreased leptin, hyperandrogenism, acanthosis.
- Genetics - Autosomal recessive; CGL1: AGPAT2 mutations; CGL2:BSCL2 mutations. 50% of CGL have neither mutation.

Familial partial lipodystrophy (FPL)

- Phenotype - Progressive extremity SC fat loss, begins in puberty, increased muscle and liver fat, increased TGL, IR, DM, acanthosis, hirsutism and PCOS.
- Genetics - Autosomal dominant; FPLD1: Koberling type, unknown genetic basis, loss of extremity fat with increased central adiposity; FPLD2: Dunnigan type, LMNA mutations; FPLD3:PPAR gamma mutations, dominant negative. 50% of FPLD have no known mutations.

Acquired generalized lipodystrophy (AGL)

- Phenotype - Multiple etiologies, including drugs, paniculitis, infections, autoimmunity, idiopathic. Accompanied by hepatosplenomegaly, IR, DM, increased TGL and acanthosis.

HIV lipodystrophy

- Phenotype - HIV lipodystrophy is among most common types of lipodystrophy seen clinically (see Brown[3] for comprehensive review). This form of acquired lipodystrophy is characterized by

loss of subcutaneous (SC) fat in extremities and abdomen, and relative or absolute increases in abdominal visceral and upper trunk fat in some patients. The etiology may relate to effects of nucleoside reverse transcriptase inhibitors (NRTI) to reduce SC fat, potentially through perturbations in mitochondrial function, and effects on PPAR signaling. Less clear are the mechanisms leading to increased visceral adiposity that may accompany loss of SC fat. There may be an interaction between the virus, medications, inflammatory and immune factors contributing to the lipodystrophic changes. In addition, these disorders are characterized by dyslipidemia, increased TGL, reduced HDL and IR, which may also be due to effects of specific medications, e.g. protease inhibitors may block GLUT-4 signaling[4].

- Genetics - No clear genetic predispositions to HIV lipodsytrophy have been determined.

Metabolic Consequences of Abnormal Fat Distribution in Lipodystrophy

Each of the congenital and acquired lipodystrophies has a specific phenotypic presentation, although there is considerable heterogeneity. A common theme among the lipodystrophies is abnormal fat distribution in association with metabolic disturbances. The distribution of fat is significant because it often involves reduced subcutaneous fat, and increased ectopic fat, including fat in the liver, muscle and visceral area. Visceral fat is known to relate to insulin resistance, metabolic syndrome, and increased inflammation. In contrast, lower extremity SC fat is thought to be cardioprotective. It remains unknown if there is a direct link between lack of SC fat and increased visceral and ectopic fat in most lipodystrophy syndromes, but this may be the case. Theories linking the lack of subcutaneous to ectopic VAT, include the overflow hypothesis, in which the storage capacity of SC fat is exceeded, and a related theory that SC is partially dysfunctional, and genetically resistant to TGL uptake. The subcutaneous fat depot is an important buffer for exogenous fat intake and makes critical hormones, including leptin, adiponectin, resistin, visfatin and inflammatory cytokines. The lack of leptin may be a critical metabolic abnormality in such patients with lipoatrophic lipodystrophy. In turn excess VAT can be the source of increased systemic FFA released into the portal system, contributing to steatosis, insulin resistance, and inflammation[5].

Assessment and Treatment for Metabolic Abnormalities in Congenital and Acquired Lipodystrophies

In each case, the lipodystrophy should be classified as to its etiology and genetic testing performed when appropriate. The metabolic derangements cluster most typically around insulin resistance and potentially DM, dyslipidemia, characterized by hypertriglyceridemia and low HDL. Associated metabolic complications also include hyperandrogenism, particularly a problem for women, related in part to extreme insulin resistance.

Treatment Strategies for Glucose Dysregulation

These strategies should focus, initially, on increasing sensitization to insulin. Eventually, a relative lack of insulin may result in the need for insulin.

rhIGF-I

rhIGF-I has been used in severe insulin resistance because of cross reactivity at the insulin receptor to lower glucose levels, but is not a commonly available therapy[6]. In addition, IGF-I in combination with IGFBP-3 was shown recently to reduce glucose tolerance and improve glucose disposal on clamp among HIV-infected patients with lipodystrophy. This treatment also reduced triglyceride[7].

Metformin

Metformin may lead to weight loss and further SC fat loss, and this may be undesirable in severe lipoatrophy.

PPAR gamma agonists

These agents have some appeal, because they not only stimulate insulin sensitivity, but increase SC adipogenesis, potentially helping to restore normal lipogenesis. Though

they have not been rigorously tested and are not approved for use in lipodystrophy, they may be a good initial option for patients with lipoatrophy and insulin resistance. Certain glitazones can improve HDL in HIV lipodystrophy (pioglitazone)[8], but rosiglitazone has been related to increased cardiovascular disease and a recent question has arisen regarding the potential for bone loss with this class of agents.

rhLeptin
Leptin levels track with SC fat loss, e.g. leptin levels are lower with more SC fat loss and more severe lipoatrophic lipodystrophy. Leptin is a potent hormone which increases REE and reduces appetite. In obese children with congenital leptin deficiency, leptin administration reduces weight, helps to stimulate puberty[9]. In congenital and HIV lipodystrophy, leptin has been tested and shown significant promise. Investigators at the NIH have the most experience with leptin. For a comprehensive review of the NIH experience, see Chong et al.[10]. In summary, treatment of congenital lipodystrophy disorders, characterized most often by low leptin, results in improved triglycerides and insulin resistance, with resultant improvement in HgbA1c. Leptin treatment may allow such patients to reduce or discontinue specific insulin sensitization strategies or insulin itself. Leptin has also been used to improve menstrual function in women with hypothalamic amenorrhea, and is effective in this regard, though widespread use has not been seen because leptin results in further weight loss. This effect may not be desirable among a group of women for whom weight loss may be contributing to bone loss and hypothalamic amenorrhea[11]. In other studies, Chan et al.[12] and Schurgin et al.[13] have shown that administration of rhLeptin restores fasting induced changes in gonadotropin pulsatility and thyroid function in healthy men and women undergoing caloric restriction.

Treatment Strategies to Reduce Visceral Fat and Restore Subcutaneous Fat in Lipodystrophy
Specific treatments to restore normal body composition are lacking in lipodystrophy, though recently a growth hormone releasing analogue was approved for this purpose in HIV Lipodystrophy and is the first such treatment specifically approved by the FDA in this regard.

Exercise
Lifestyle modification can help to reduce fat and restore metabolic abnormalities, but may not be effective in patients with severe lipoatrophic lipodystrophy, for whom restoration of subcutaneous fat and leptin levels may be more effective. Nonetheless, improved lifestyle may be a useful adjunct to pharmacological therapies.

Weight loss pharmacotherapies
Such treatments per se have not been tested in lipodystrophy and would not be appropriate, as excess weight and fat is not a problem faced by such patients, in whom lack of subcutaneous fat is the more relevant problem.

Metformin
Metformin may be useful in some patients, e.g. those with HIV lipodystrophy, in whom IR is accompanied by excess visceral fat. Problems related to potential lactic acidosis, and further reduction in SC fat have prevented widespread use, but metformin has been shown to be effective in patients with HIV lipodystrophy[14].

Acipimox
This agent blocks lipolysis and is approved in Europe but not the US as a lipid lowering agent in the general population. In studies performed among HIV-infected patients, acipimox was shown to significantly improve insulin sensitivity by clamp, and improve triglyceride and lower FFA. The lack of availability of this agent in the US has limited its use[15].

Glitazones
As above, these agents may be useful to stimulate adipogenesis and reduce insulin resistance based on stimulation of PPAR gamma. In HIV lipodystrophy, these agents have been shown in some studies to result in

small, but statistically significant increases in subcutaneous fat[16]. In the case of HIV lipodystrophy, efficacy may be limited by concomitant nucleoside reverse transcriptase treatment.

Growth Hormone

A number of studies have shown, both among HIV and non HIV patients, that excess VAT is associated with reduced GH. Specifically, a pattern has been shown among patients with HIV lipodystrophy, in which GH pulse frequency is maintained but GH peak and pulse area are reduced. GH is known to be a potent lipolytic drug, with preferential effects on the visceral depot. GH has been shown to reduce visceral fat by 8% relative to placebo among patients with HIV lipodsytrophy, while improving triglyceride levels[17]. However, this strategy was associated with impaired glucose tolerance, even with strictly physiological dosing.

Growth Hormone Releasing Hormone (GHRH) - GHRH is more physiologic than GH per se, as it stimulates pulsatile GH secretion. Moreover, feedback inhibition is maintained with GHRH, in contrast to GH. Studies using clamp methodology have shown that insulin resistance does not increase in response to GHRH in healthy obese men[18], and clinically significant changes in glucose have not been seen in large Phase III studies among patients with HIV lipodystrophy. These studies have shown an approximate 15% reduction in VAT relative to placebo[19][20] with significant improvements in triglyceride, and adiponectin. Interestingly, these effects were specific to the VAT depot, and effects on SAT were not seen. This specificity to reduce VAT without affecting SAT is thought to be a significant benefit as SAT is cardioprotective and further loss in HIV lipodystrophy is not desirable. In addition, quality of life and distress regarding abdominal fat accumulation improved in this group of patients in response to GHRH. GHRH was shown to be well tolerated among HIV patients, without significant symptoms of excess GH, including fluid retention, headache or carpal tunnel. There was no signal in terms of excess malignancy. Approximately 3% of subjects experienced a rash distinct from the injection site. These skin reactions were not systemic, and were though to represent hypersensitivity reactions, that were self-limited and did not result in any excess morbidity. In 2010, the FDA approved the GHRH analogue, tesamorelin, for treatment of excess abdominal fat in HIV lipodystrophy.

MAIN CONCLUSIONS

Lipodystrophies are phenotypically heterogeneous, but more often than not involve reduced subcutaneous fat, sometimes in association with excess abdominal visceral fat and ectopic fat in the liver and muscle. These abnormalities often lead to insulin resistance and dyslipidemia. Low leptin levels are often seen in lipoatrophic lipodystrophies, in association with reduced fat, and recent data suggest that recombinant leptin administration results in improved glucose, and dyslipidemia, and may improve gonadal function. HIV lipodystrophy is the most common form of acquired lipodystrophy and is characterized by loss of subcutaneous fat, perhaps related to nucleoside reverse transcriptase inhibitors, often in association with excess visceral fat. A number of potential strategies are available for such patients. Patients with HIV lipodystrophy and abdominal fat accumulation demonstrate altered GH pulse dynamics and GHRH was recently approved by the FDA as a therapeutic strategy to selectively reduce visceral fat, spare subcutaneous fat and improve triglycerides, without affecting glucose in this population.

CASES WITH QUESTIONS

Case 1

A young girl with congenital generalized lipoatrophic lipodystrophy presents with dyslipidemia and hypertriglyceridemia.

Question

What is the optimal work up and what management strategies are available for her?

Case 2

A young man with HIV begins antiretroviral treatment and gains visceral fat and loses subcutaneous fat. His metabolic disturbances include hypertriglyceridemia and insulin resistance.

Question

What is the optimal management strategy for this patient?

DISCUSSION OF CASES AND ANSWERS

In case 1, leptin use may be appropriate. Effects, benefits and disadvantages will be discussed and placed in the context of other therapies, e.g. insulin sensitizers and lipid lowering therapies. In case 2, a number of strategies exist to modify dyslipidemia, and insulin resistance including insulin sensitizers, metformin and glitazones. In contrast, use of GHRH may simultaneously reduce excess VAT and improve lipids. The use of GHRH, including advantages and disadvantages of this strategy, will be discussed.

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New Guidelines for the Diagnosis & Management of Lipid Disorders in Children and Youth

M25
Sunday, June 16
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

The atherosclerotic process begins in childhood although the clinical manifestations are generally not seen until decades later. Several studies in youth who died accidentally have demonstrated that the extent of atherosclerosis was associated with the presence of cardiovascular risk factors (lipid levels, blood pressure, dysglycemia and tobacco use). While rare, children with markedly elevated LDL-cholesterol levels (>800 mg/dL or ~20 mmol/L) due to homozygous familial hypercholesterolemia have coronary events beginning in their 2nd decade of life. One quarter of women and half of men with the heterozygous form of this disorder (typical LDL-C levels > 200 mg/dL or ~5 mmol/L) will have an event prior to their 50th birthday. Clustering of CV risk factors with obesity in adolescence also predicts increased coronary event rates by the 5th decade [1] . Together these studies highlight the importance of identifying and addressing CV risk factors in children and youth.

To address this need, an expert panel was convened to develop an evidence-based integrated guideline for addressing cardiovascular risk in children and youth. This guideline, which covers the identification and management of CV risk factors (lipids, blood pressure, glycemia, growth / obesity, family history of premature coronary artery disease, tobacco exposure, nutrition and physical activity / screen time) in childhood[2]. In this session we will focus on the new guidelines for diagnosis and management of lipid disorders – while recognizing the importance of other CV risk factors in making clinical decisions on treatment.

BARRIERS TO OPTIMAL PRACTICE

The last NHLBI guideline for an approach to the diagnosis and management of lipids in children and youth was published in 1992. The development and testing of additional medications to address lipid disorders in youth since that time, and the increased prevalence of obesity and recognition of the CV risk associated with that have made the review and update of these guidelines imperative.

Furthermore, recognition of the importance of identifying and treating elevated CV risk in pediatric populations has increased in recent years based on the findings of longitudinal studies – and thus education on these new recommendations is needed.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

1. Develop an approach to cardiovascular health and cardiovascular risk reduction in their pediatric patients.
2. Develop an approach to the diagnosis and management of lipid disorders in children and youth.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Strategies for Diagnosis

Screening strategies

Given the importance of recognizing genetic dyslipidemias with elevated LDL-cholesterol early in life, the lack of expected clinical signs to identify these disorders and the availability of treatments that are efficacious

with good safety profiles, screening strategies have been recommended. While initial strategies focused on screening children with known family history of premature coronary artery disease or of hypercholesterolemia, subsequent research suggests that this strategy results in missing 30 to 60% of children with dyslipidemia. Thus, in the new guideline, a mixed approach for screening is recommended that includes targeted screening for children 1 – 9 years of age based on the family history of premature coronary artery disease or of hypercholesterolemia and universal screening at age 9 – 11 years using a non-fasting blood sample *(see Table 1)*. Premature coronary artery disease is defined by the presence of a male relative with CVD prior to 55 years of age or female relative with CVD prior to 65 years of age.

HIGH Risk = Family history of premature coronary artery disease, parent with dyslipidemia and /or child has other risk factors or high-risk condition.

Normal values

Desired values based on a number of cohort studies are available. Lipid values in late childhood track quite well into adulthood. Based on this information 'acceptable,' 'borderline' and 'abnormal' values for the components of the lipid profile have been ascertained *(see Table 2)*.

Most common dyslipidemias

The most common and clinically important dyslipidemias impact the LDL-cholesterol, the triglyceride and the HDL-cholesterol levels. Cholesterol and triglycerides are transported within particles. Most of the cholesterol in the body is made in the liver, packaged into lipoprotein particles with triglyceride and transported through circulation. The particle we most often refer to is the LDL particle and high LDL-cholesterol levels are associated with increased atherosclerosis. The HDL is a smaller, denser particle that is associated with reverse cholesterol transport and low levels are associated with cardiovascular disease risk.

There are multiple conditions which cause a secondary dyslipidemia and it is important to consider these when evaluating a lipid profile. Secondary causes may include exogenous causes (alcohol, drugs (isoretinoin), corticosteroids, beta blockers, antiretroviral agents, some oral contraceptives), hypothyroidism, renal disease, diabetes, liver disease including hepatitis, biliary cirrhosis, obstructive liver disease, some inflammatory conditions including lupus and juvenile rheumatoid arthritis and several

TABLE 1: Recommended screening strategies throughout childhood.

	0 – 12 mo	1 – 4y	5 – 9y	9 – 11y	12 – 17y	18 – 21y
Fasting lipid profile	--	HIGH risk	HIGH risk		NEW HIGH risk	
Non-fasting nonHDL	--	--	--	UNIVERSAL	--	UNIVERSAL

TABLE 2: Acceptable, borderline and abnormal values for plasma lipid and lipoprotein concentrations in children and adolescents in mg/dL (mmol/L).

	Acceptable	Borderline	Abnormal
Total Cholesterol	<170(4.4)	170-199(4.4-5.1)	≥200(5.2)
LDL cholesterol	<110(2.9)	110-129(2.9-3.3)	≥130(3.4)
Non-HDL cholesterol	<120(3.1)	120-144(3.1-3.7)	≥145(3.8)
Triglycerides 0-9 years 10-19 years	 <75(0.85) <90(1.0)	 75-99(0.85-1.0) 90-129(1.0-1.4)	≥100(1.1) ≥130(1.5)
HDL cholesterol	≥45(1.2)	40-44(1.0-1.1)	<40(1.0

storage diseases. Perhaps the most common secondary dyslipidemia is that associated with central adiposity – and this dyslipidemia is characterized by mild elevation in LDL cholesterol, mild to moderate elevations in triglyceride and suppressed HDL cholesterol. It may be associated with other obesity related metabolic disturbances including polycystic ovary syndrome, prediabetes and hypertension.

Of the primary dyslipidemias, most important to identify are those with elevated LDL-cholesterol. Heterozygous familial hypercholesterolemia is a relatively common disorder (1 in 400), is autosomal dominant in inheritance and results in markedly elevated LDL-cholesterol, suppressed HDL cholesterol and normal triglycerides. It is strongly associated with early onset coronary artery disease. Familial combined hyperlipidemia is characterized by elevated LDL-cholesterol and triglycerides and also often with low HDL cholesterol. While the genetic underpinnings are more complex, this disorder may present at any time through to adulthood but is also associated with increased risk of coronary artery disease.

Other primary disorders of lipid metabolism are much rarer.

Strategies for Management

The management plan is dependent on the age of the child or youth, the dyslipidemia identified and the presence or absence of other cardiovascular risk factors. In general, the management plan includes dietary recommendations, a focus on all aspects of heart health and, in selected cases, the use of pharmacotherapy. The guideline has developed a series of algorithms to address when treatment progresses to pharmacotherapy.

Diet

The dietary recommendations for heart health include a diet with a total of 25 – 30% fat and with saturated fat intake of <10% of calories. This has been shown to be safe in healthy children. For children with elevated LDL cholesterol, further restriction of saturated fat to <7% and restriction of dietary cholesterol to < 200 mg / day is recommended. While the addition of plant sterol or stanol esters (up to 20 g/day) can result in further declines in LDL cholesterol, long term safety and efficacy have not been studied. For children with mild to moderately elevated triglyceride level, reduction in simple carbohydrates intake and weight loss can result in decline in triglyceride level.

Pharmacotherapy

Statins are a class of drug which inhibit endogenous cholesterol synthesis. Multiple studies, up to 2 years duration have shown the efficacy of statins in reducing LDL cholesterol and the safety profile has been good. As with adults, statins can be associated with adverse effects including myopathy and increases in hepatic enzymes. These medications have only been used and are only recommended for use in children and adolescents, 10 years of age or older who have familial hypercholesterolemia – i.e. with LDL cholesterol levels greater than 190 mg/dL (4.9 mmol/L) or 160 mg/dL (4.2 mmol/L) with a family history of premature coronary artery disease or 2 additional CV risk factors. It is very important that females on statin therapy receive appropriate counseling regarding pregnancy risk as this medication is not safe during pregnancy.

Statins are also utilized for some children with conditions that contribute to increased CV risk. These include: Chronic kidney disease / end stage renal failure or renal transplant; Kawasaki disease with coronary aneurysms and post orthotopic heart transplant.

Bile acid sequestrants are moderately effective in reducing LDL cholesterol, but their gastrointestinal side effects have tended to limit compliance.

Pharmacotherapy for elevated triglyceride in children is rarely needed and is only considered if triglyceride levels exceed 500 mg/dL (6 mmol/L) – to prevent pancreatitis. These individuals should be seen by a lipid specialist.

MAIN CONCLUSIONS

In evaluating the potential CV risk attributed to a dyslipidemia it is important to consider the underlying etiology, family history, age of the patient and the presence of other CV risk factors. In considering these factors, and staging the management plan - a balanced

approach to reduction in CV risk amongst children and youth can be established.

CASES WITH QUESTIONS

Case 1

LM – 8 year old boy. This boy is seen for routine follow-up in the pediatrician's office and the family history reveals that Dad recently had a myocardial infarction (37 years of age).

How does Dad's history influence your evaluation of this child?

LM is healthy with no known ongoing illnesses. He was born at full term (Birthweight 3.1kg). Growth has been normal. On exam he is at the 50thcentile for height, weight and BMI. His blood pressure is 104/71. The remainder of his clinical exam is normal.

Do you need any further information? What investigations would you do?

His fasting lipid profile is: TC 8.6 mmol/L (327 mg/dL); HDL-C 1.65 mmol/L (64 mg/dL); triglyceride 1.04 mmol/L (92 mg / dL) and LDL-C (calculated) – 6.47 mmol/L (249 mg / dL).

What is your impression of these results? What is your management?

Case 2

SU – 16 year old girl. This young lady is referred to you for evaluation and management of her dyslipidemia. She has had a non-fasting lipid profile done with the following results: TC 6.16 (234 mg/dL), TG 5.81 (511 mg/dL) and HDL-C 0.83 (32.0 mg / dL). She has a history of obesity since she was 6 years of age. Tried Weight Watchers once several years earlier and lost 10 pounds over 16 weeks – but thinks she probably has put this weight back on. Key findings regarding her lifestyle behaviors are: Activity – Walk 30 min/d (to school); Sedentary time– TV 1.5 h; MSN 3 – 5 h / d; Nutrition- No breakfast; 1 fruit or vegetable serving / day; 1.1 L sweet drinks / d ; Non-smoker but has some friends who smoke. Her current medications include an oral contraceptive for irregular menses and a 'mild sleeping pill' prescribed by her psychiatrist. There is NO family history of premature coronary artery disease or diabetes.

On examination she is 163 cm tall and weighs 116 kg. Her waist circumference is 102 cm. Her BP is 124/70. She has acanthosis nigricans and mild hirsutism.

Do you require any further information?

The following results were obtained with further testing including an oral glucose tolerance test:

Fasting lipid profile TC 5.36 (, TG 3.51, HDL-C 0.86, LDL-C 2.89		
Fasting glucose 5.3 mmol/L; Insulin 561 pmol/L		
ALT, AST, thyroid function, Lp(a) – Normal		
OGTT	Glucose	Insulin
0 min	5.1 mmol/L	424 pmol/L
2 hr	8.3 mmol/L	3518 pmol/L

What would your next steps be?

DISCUSSION OF CASES AND ANSWERS

Answers

This young boy's likely diagnosis is familial hypercholesterolemia. The initial management would be focused on dietary change with a supportive family-based behavior modification program. As he is younger than 10 years of age, pharmacotherapy would likely not be considered, but please see figure for algorithm describing clinical decision making for a similar case.

Note

HI level CVRF = Hypertension requiring drug therapy (>99th centile + 5 mmHg); cigarette smoker; high risk condition (Diabetes, renal disease, heart transplant, Kawasaki with coronary aneurysms); BMI>97thcentile

MOD CVRF = Hypertension not requiring drug therapy; obesity; low HDL; moderate risk condition (Kawasaki with regressed coronary aneurysm, chronic inflammatory disease, HIV, nephritic syndrome)

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MALE REPRODUCTION

Managing Erectile Dysfunction

M18
Sunday, June 16
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

The prevalence of sexual dysfunction will vary depending upon the age and population being evaluated. Population-based studies have found that some symptoms of sexual dysfunction may be present in up to 40% of men age 40. The prevalence increases by about 10% per decade after age 40. The prevalence also is increased especially in men with risk factors of vascular disease.

BARRIERS TO OPTIMAL PRACTICE

Many patients are reluctant to discuss symptoms of sexual dysfunction, and many physicians are uncomfortable in discussing symptoms of sexual dysfunction, especially with the opposite sex.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Evaluate patients with ED for cardiometabolic/cardiovascular, endocrine or psychogenic factors
- Use pharmacologic and nonpharmacologic management strategies in the care of patients with ED, hypogonadism

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Strategies for Diagnosis of Erectile Dysfunction

History

It is critical to know the age of the individual, the rapidity of onset and the duration of ED. Psychogenic ED typically occurs in younger men and is more abrupt in onset, frequently associated with relational issues, and may be partner specific. In contrast, organic ED usually is more gradual in onset, associated with co-morbid diseases and drugs that affect the vascular, neurological and endocrine systems.

Physical exam

One should evaluate the patient for evidence of vascular, neurological or endocrine disease. Hypertension, absence of pedal pulses, femoral bruits, peripheral or autonomic neuropathy, gynecomastia, abnormal male hair patterns, reduced testicular size, penile abnormalities and prostate size can be used to identify potential causes of the ED.

Laboratory

Screening for systemic disease with a complete metabolic profile and a complete blood count is necessary. A lipid profile is useful for assessing cardiovascular risk. Measurement of total testosterone in an early morning specimen can be used to screen for testosterone deficiency. If the man is obese or over 60, an SHBG level and a calculated free testosterone level should be obtained. If the testosterone level is low, it should be repeated and serum LH and prolactin levels should be assessed to determine if he has primary or secondary hypogonadism. If gynecomastia is present, an estradiol level can be helpful. Thyroid tests are indicated when abnormal thyroid function is suspected.

Cardiovascular evaluation

Cardiovascular risk should be assessed with the Framingham Risk Score. Patients with intermediate risk scores (10-20) should have

an exercise stress test or other tests to evaluate possible coronary. Patients at high risk (>20) should be referred to a cardiologist.

Optional tests
Penile tumescence during sleep or visually stimulating movies can be helpful for separating psychogenic from organic ED. This can be done with a home monitor or in a sleep laboratory. Duplex ultrasound, before and after injection of a vasodilator, can be used to assess the adequacy of arterial inflow and venous outflow.

Strategies for Managing Erectile Dysfunction
Specific treatments
We should refer patients to the appropriate specialist when there is evidence for psychogenic ED, Peyronie's disease, or pelvic trauma. Patients who develop ED after prostate or pelvic surgery are difficult to treat. In most cases they should be managed by a urologist with expertise in this area. Patients with testosterone deficiency should first be treated with testosterone replacement unless there are contraindications.

Non-specific treatments
Phosphodiesterase type 5 inhibitors (PDE5Is) represent the first line treatment for ED in most men. Sildenafil and vardenafil have an onset of action of about 1 hour and duration of action of 4-5 hours. Absorption is affected by food, so they should be taken on an empty stomach. The duration of action of tadalfil is about 24-36 hours. Avanafil is the newest agent. Its onset of action is 20-40 minutes. These agents can be effective in patients having a variety of etiologies for their ED. The major side effects are headaches and nasal congestion. Very rare patients have reported loss of vision or hearing. They should not be taken with nitrates, and one should start with the lowest dose in patients taking alpha-blockers. Dose adjustment is necessary if there is underlying renal or liver disease or if the patient is taking a CYP450 3A4 inhibitor. Typically, these agents are taken on demand; however, there is some evidence that erectile function is better when tadalafilfil is taken daily. Daily tadalafil also has been shown to decrease lower urinary tract symptoms (LUTS) in men who have both ED and LUTS. Evidence that testosterone treatment can enhance the effects of a PDE5I in men with testosterone deficiency is conflicting.

Penile injection therapy
Penile injection of alprostadil (PGE1) alone or in combination with phentolamine can be used to treat ED that is unresponsive to a PDE5I. While effective in many or most men with ED, it is not acceptable to man. The dose must be titrated by a physician, usually a urologist, who is experienced and set up to do this. Side effects include penile pain in 15-30% of men, fibrotic penile plaques after multiple injections and rarely priapism.

Vacuum erection device
These devices create a vacuum around the penis that increases blood flow into the penis. An elastic constricting band is placed at the base of the penis to retain the additional blood in the penis and to maintain the erection. While the device will work for most men with ED, it is best accepted by those in a stable relationship. It should be used cautiously or not at all in men on anticoagulation or who have sickle cell disease.

Intraurethral alprostadil
While intraurethral administration of alprostadil is acceptable to patients, it is less effective than penile injections and often associated with significant penile pain. This therapy is rarely used.

Penile prosthesis
Surgical implantation of semi-rigid rods or an inflatable penile prosthesis can be considered for those patients who have not responded to other less-invasive therapies. While prostheses are effective, they are expensive and can be associated with infection or mechanical failures.

Case 1.
30 y/o HM with and testosterone deficiency and ED

History
- Age 8: cerebellar astrocytoma, surgery & XRT

- VP Shunt: malfunctioned at puberty, revised
- Age 10: ADD, Ritalin
- Age 13: started puberty; developed axillary and pubic hair; achieved normal height
- Age 28: decreased libido, unable to achieve good erections
- Shaves every 2 days
- Some decrease in energy; muscle strength okay
- Homosexual and not interested in fertility
- Only has university insurance

Physical Examination
- VS: Ht: 5'9"; Wt: 208; BMI: 30.7; BP: 125/79; P 93
- Gen: WD, WN
- Skin and Hair: moderate body hair with some recession of temporal hairline
- Chest: gynecomastia, 5cm diameter bilaterally
- GU: Penis is normal; Testes: 4.3x2.5cm; prostate is small
- NS: DTRs are 3+, symmetrical

Labs

2/26/10: Estradiol 24 (<56), Prolactin 7.6 (3-30), hCG <5 (<5), CMP, WNL.

3/12/10: FSH 4.3 (1.5-14), LH 5.5 (1-9), Testosterone 186 (241-827), SHBG 15 (13-71), Calculated free T 5.1 (6-27), FT4 0.84 (0.73-1.95)

5/25/12: Testosterone 322 (292-1052), SHBG 26 (16-94), Calculated free T 7.3 (4.8-25), Cortisol 14 (>7)

6/18/12: Testosterone 183 (292-1052), SHBG 21 (16-94), Calculated free T 4.4 (4.8-25)

DEXA

Date: 6/5/12, T-score L total hip -1.3, T-score L femoral neck -1.9, T-score L spine -2.3

Answers:

Erections have improved with testosterone treatment, emphasizing that testosterone treatment has an effect on erections as well as on libido. However, this effect is only seen in patients with low testosterone levels.

Case 2.

51 y/o WM Banker with obesity, HTN, hypercholesterolemia, hypogonadism & ED

History
- Obesity: Age 18: 250
- Hypogonadotropic hypogonadism: 2006, decreased libido & ED; MRI, WNL; he did not like T-gel or T-patch
- HTN: metoprolol 50 qd; olmesartan 40/hctz 25; hydralazine 25 bid
- Hypercholesterolemia: atorvastatin 10
- Sleep apnea: possible sleep apnea; not using CPAP
- Vitamin D deficiency: PE

Physical Examination
- VS: Height 5'9.25"; Weight: 321; BMI 47.1; BP 150/90; P 64
- General: generalized obesity
- Neck: thick
- GU: external genitalia are normal; prostate is normal size without nodules or induration

Labs

4/10/08: Testosterone 178 (292-867), SHBG (16-94), Calculated free T 56 (34-194), LH 1.7 (1.5-9.3), FSH 4.5 (1.6-8.0), PSA 0.5 (<4.0), T cholesterol 130 (<200), Triglycerides 88 (<150), HDL cholesterol 42 (>39), LDL cholesterol 70 (<100)

Framingham Risk Calculator
- Age: 51 Gender: male
- Total Cholesterol: 130 mg/dL
- HDL Cholesterol: 39 mg/dL
- Smoker: No
- Systolic Blood Pressure: 150 mm/Hg
- On medication for HBP: Yes
- Risk Score* 4%

Means 4 of 100 people with this level of risk will have a heart attack in the next 10 years

Recent Labs:

10/15/12: eGFR 63 (>60), Glucose 102 (65-100), T cholesterol 125 (<200), Triglycerides 178 (<150), HDL 37 (>39), LDL 52 (<100), Testosterone 307 (292-867), SHBG 15 (16-94), Calculated free T 8.8 (4.8-25), GSH 2.2 (0.5-4.7), FT4 1.12 (0.73-1.95), PSA 1.4 (<4.0), Hematocrit 49.4

Treatment
- Obesity: discussed options

- Hypogonadotropic hypogonadism, Rx 200 mg TC q 2 wks
- ED: tadalafil 20 mg
- HTN: metoprolol 50, olmesartan 40/hctz 25; hydralazine 25 tid
- Vitamin D Deficiency: 2000 u/d
- Hypercholesterolemia: atorvastatin 10

Answers:
His libido was improved by testosterone injections, but his erections were improved only after addition of a PDE5I on demand. I think that some patients with low testosterone levels do benefit from combination treatment; however, clinical trials are conflicting.

Case 3.
64 y/o Attorney with ED, unresponsive to PDE5Is

History
- Erectile Dysfunction:
  Dx: 9 years earlier, initially responsive to PDE5I, but not now
- Obesity: 180# in college to 350# at present; BMI 47
- T2DM: Rx: pioglitazone 45, metformin1000 bid, sitagliptin 100
- HTN: irbesartan 300, hctz 12.5, amlodipine 10
- Dyslipidemia: simvastatin 40/ezetimibe 10
- Sleep apnea: CPAP
- LUTS: alfuzosin 10
- Vitamin D deficiency: vitamin D 50,000 u 3x/month
- SH: Tobacco-never; Caffeine, 5/d; Wine, up to 1 L/d

Physical Examination
- VS: BP 141/73; P 73; Ht 6'; Wt 349; BMI 47
- General: generalized obesity
- GU: Penis and testes, WNL; prostate, moderately enlarged
- NS: Vibratory sensation intact in feet

Labs
Glucose 192 (65-100), A1c 9.0 (4.0-5.6), T cholesterol 198, Triglycerides 258 (<150), HDL cholesterol 42 (>39), LDL cholesterol 104 (<100), Testosterone 470 (241-827), SHBG 18 (15-49), Calculated free T 149 (34-194), Hematocrit 39 (37-49), PSA 1.8 (<4.0)

Framingham Risk Calculator
- Age: 58
- Gender: male
- Total Cholesterol: 198 mg/dL
- HDL Cholesterol: 42 mg/dL
- Smoker: No
- Systolic Blood Pressure: 140 mm/Hg
- On medication for HBP: Yes
- Risk Score* 13%

Means 13 of 100 people with this level of risk will have a heart attack in the next 10 years

Recent Labs:
eGFR 75 (>60), Glucose 112 (65-100), A1c 6.6 (4.0-5.6), GSH 2.4 (0.5-4.7), PSA 1.8 (<4.0), Hematocrit 39 (37-49), Albumin: Creatinine ratio 4 (<30)

Diagnostic Options
- Testosterone level
- Duplex Doppler study
- Treatment Options
- Stop or reduce alcohol intake
- Medication changes
- Weight loss
- Daily PDE5I
- Testosterone
- Vacuum constrictor device
- Penile injections
- Muse
- Combination of above
- Penile prosthesis

Answers:
Treatment options are being explored. A PDE5I was the first line treatment for this patient. It initially was effective, but now it is ineffective. I have requested an equilibrium dialysis free testosterone level. If it is low, I will consider adding testosterone treatment. If his free testosterone level is normal, I usually start with the vacuum erection device. There is some evidence that daily tadalafil can be effective when on demand treatment fails. Penile injections usually provide firm erections, but they are acceptable to fewer men. When these treatments are ineffective, a surgical prosthesis

can be offered to the highly motivated man.

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Low Testosterone in Men With Metabolic Syndrome/Diabetes: Evaluation and Management

M36
Monday, June 17
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Around 50% of ageing, obese men presenting to the diabetes clinic have lowered testosterone levels relative to reference ranges based on healthy young men. Many have symptoms consistent with androgen deficiency, but such symptoms can be nonspecific and overlap with comorbidities.

Therefore, the clinician is commonly faced with the question as to whether testosterone therapy should be considered, and there is vigorous debate about this issue. Only a small proportion of these men will have classical hypogonadism due to recognizable hypothalamic-pituitary-testicular axis pathology, an important diagnosis not to be missed.

In contrast, the risk-benefit ratio of testosterone therapy for the large proportion of men with metabolic disorders (defined here as type 2 diabetes or the metabolic syndrome), but without clear-cut classical hypogonadism is not known.

BARRIERS TO OPTIMAL PRACTICE

It is not clear to what extent low testosterone causally contributes to metabolic disorders, or whether low testosterone is a biomarker, coexisting because of in-common risk factors, or as a consequence of insulin resistance and obesity.

There is increasing evidence that lowered testosterone may respond to lifestyle measures, especially significant weight loss. However, achieving and maintaining the degree of weight loss required to normalize testosterone levels is difficult. Whether testosterone therapy has added metabolic benefits to lifestyle measures requires further study.

The testosterone cut-off level which favors testosterone therapy in men without pathological hypogonadism is controversial, and will vary among men.

The current evidence does not adequately inform about the risk-benefit ratio of testosterone therapy in men with metabolic disorders, because definitive randomized controlled trial (RCT) evidence regarding clinically meaningful endpoints is currently not available.

LEARNING OBJECTIVES

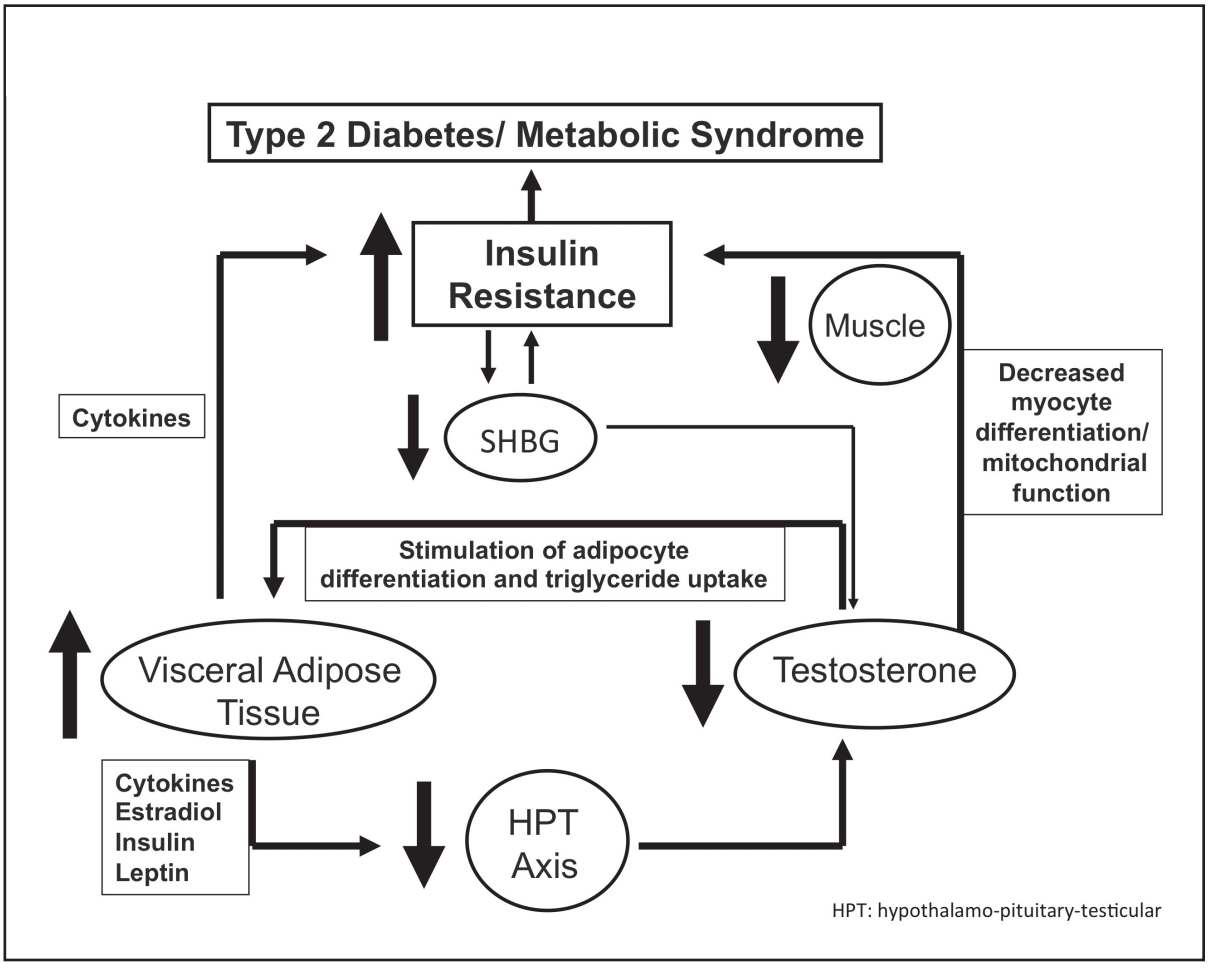
- Understand how to assess and to evaluate men for androgen deficiency in the setting of metabolic disorders.
- Recognize the mechanisms by which metabolic disorders are associated with lowered testosterone.
- To appreciate that the lowered testosterone state may be functional and reverse with lifestyle measures, especially with significant weight loss in obese men.
- Recognize that testosterone therapy modestly alters body composition in a metabolically favorable manner, and modestly reduces measures of insulin resistance in most but not all RCTs. Whether testosterone therapy improves glycemic control has not been established conclusively.
- To understand the limited evidence informing about the risk-benefit ratio with respect to patient-important outcomes when considering testosterone therapy in men with metabolic disorders.

SUCCINCT REVIEW- STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT: LOW TESTOSTERONE IN MEN WITH METABOLIC DISORDERS (TYPE 2 DIABETES OR THE METABOLIC SYNDROME)

1. Background

Population-based studies show a modest association (decrease of 2-3 mmol/L or 60-90 ng/dL) of total testosterone with diabetes and the metabolic syndrome, similar to what is seen in other chronic diseases[1]. This association is less consistent for free testosterone, because of the confounding effects of SHBG, itself a strong associate of insulin resistance. The relationship of low testosterone with insulin resistance is predominantly mediated via body composition, especially increased visceral adipose tissue[2]. This inverse relationship of testosterone with adipose tissue is bi-directional *(Figure 1)*: on the one hand, studies in men with prostate cancer receiving androgen deprivation therapy show that (very) low testosterone leads to metabolically unfavorable changes in body composition, termed "sarcopenic obesity", with associated increases in insulin resistance[3]. In addition, RCTs have shown that testosterone therapy reduces fat mass (by 1.6-2.0 kg) and increases muscle mass (by 1.6-2.7 kg)[4], and more significant fat loss has been observed in uncontrolled studies[5]. Preclinical studies have provided mechanistic evidence for such body-compositional changes *(Figure 2)*. On the other hand, there is also evidence for the reverse: In prospective studies, the metabolic syndrome predicts low testosterone, and weight gain and development of diabetes are major drivers of the age-related decline in testosterone levels[6,7]. Weight loss increases testosterone levels, suggesting that

FIGURE 1. Bi-directional Relationship between Visceral Fat and Testosterone: A Self-perpetuating Cycle Promoting Insulin Resistance



the lowered testosterone status is functional, and to a degree reversible[1].

2. Diagnosis

Men with metabolic disorders who present with features of androgen deficiency should have a thorough history and physical examination to identify the minority of men who have hypogonadism due to intrinsic hypothalamic-pituitary-testicular axis pathology[8]. There is insufficient evidence to recommend routine testosterone measurement in all men with metabolic disorders. However, men with features suggestive of androgen deficiency should have a serum fasting morning total testosterone quantified by a validated assay. Testosterone levels should not be measured during an acute illness. While a total testosterone level of > 12 nmol/L (> 350 ng/dL) is consistent with eugonadism, a lower level should be repeated, and gonadotrophins, SHBG and free testosterone should be determined. The majority of men with metabolic disorders and lowered testosterone will have low-normal gonadotrophin levels due to hypothalamic-pituitary inhibition (*Figure 1*)[9]. Further evaluation for underlying organic pathology should be individualized (*see Case Discussions 1&3*)[8].

3. Management

Priority should lie in the implementation of lifestyle measures, optimization of glycemic control and of cardiovascular risk factors using established pharmacotherapy with proven benefit. Small studies suggest that weight loss can increase testosterone levels, with larger effects seen in more obese men with greater degrees of weight loss *(Figure 3)*[1,5,10]. A retrospective analysis of men with impaired glucose tolerance from the diabetes prevention program (DPP) cohort showed that men randomized to lifestyle modification had a modest but significant +1.5 nmol/L (43 ng/dL) increase in their testosterone levels coincident with 7.8 kg weight loss (Dwyer et al, ENDO 2012 abstract OR28.3). Recent observational evidence from the EMAS cohort suggests that ≥ 15% of weight loss is required to reactivate the hypothalamic-pituitary-testicular axis[11].

Evidence for testosterone therapy

Current U.S. Endocrine Society guidelines state that "information about the risks and benefits of testosterone therapy in men with diabetes is either limited or not available"[8]. Recommended testosterone treatment thresholds for older men without classical hypogonadism due to testicular or pituitary

FIGURE 2. Mechanisms By Which Testosterone May Decrease Insulin Resistance

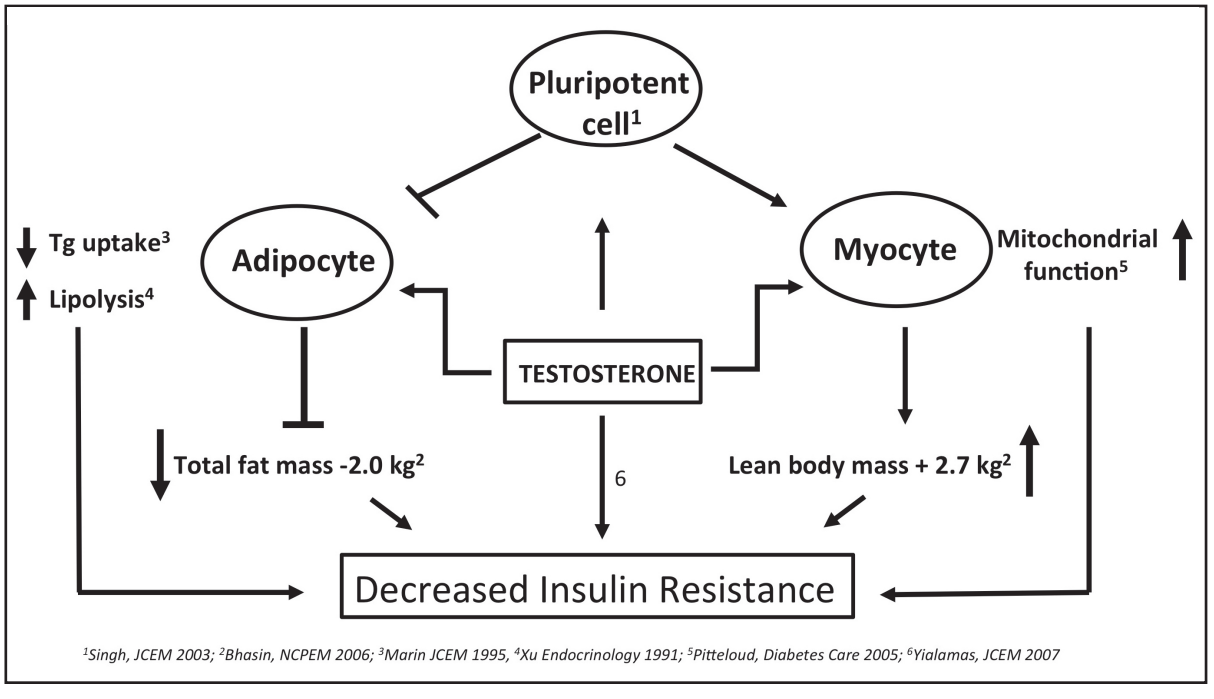
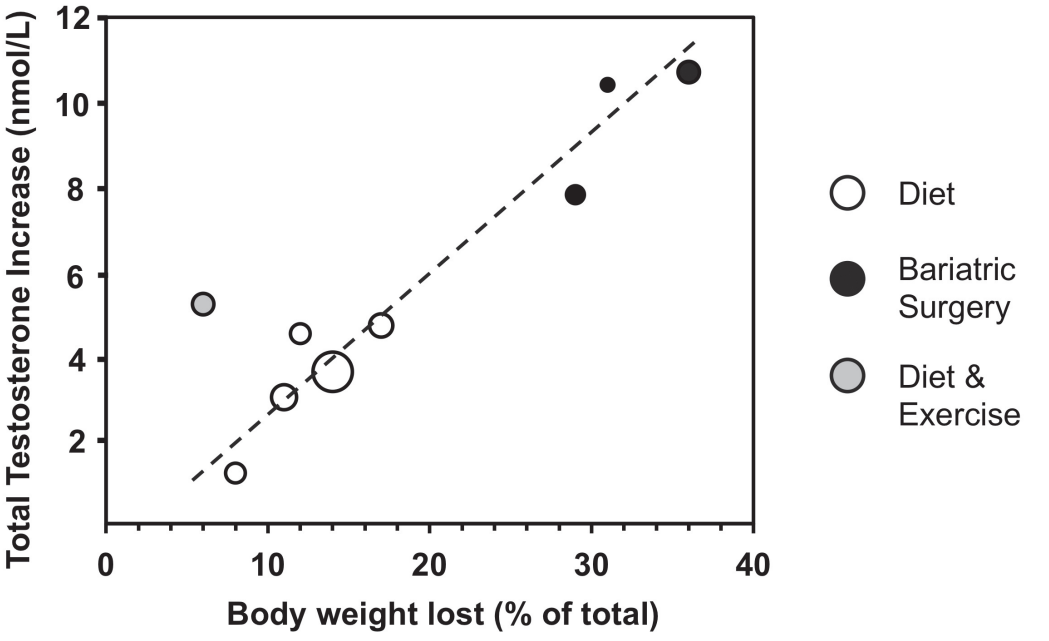


FIGURE 3. Effect of Weight Loss on Testosterone Levels



Each data point refers to an individual study, and the size of the data point is proportional to the size of the study

For individual references see Grossmann, JCEM 96:2341, 2011

pathology, not specific to diabetic men, range from 6.9–10.4 nmol/L (200-300 ng/dL), with considerable disagreement among members of the task force due to the lack of evidence[8].

Most, but not all RCTs in men with diabetes or the metabolic syndrome have shown small, but significant decreases in measures of insulin resistance, ranging from no significant change to a reduction of 60%[1,12]. Of the five RCTs that have reported effects of testosterone therapy on HbA1c, two small RCTs have reported a significant decrease (of -0.37 and -1.1%, respectively), whereas two did not find a significant change in the HbA1c level[1,2]. The largest RCT to date enrolled 220 men and found that 12 months of testosterone therapy reduced HbA1c at 9 months (-0.45%, p=0.034) but not at study end[13]. Testosterone therapy has not been directly compared metformin or TZD monotherapy. One small, non-placebo controlled study suggested that testosterone therapy has added benefit to lifestyle measures, but this finding requires confirmation[14]. Effects of testosterone therapy on lipid levels and blood pressure, arguably more important cardiovascular risk factors than glycaemia, have been minor[15]. However, existing trials have been small and hence (even when meta-analysed[15]) underpowered to provide conclusive evidence on such surrogate markers, let alone on diabetes-related complications.

Older men with metabolic disorders commonly have significant comorbidities and only modest reductions in testosterone levels. Therefore, they may be at higher risk of adverse outcomes of testosterone therapy compared to younger men receiving testosterone replacement for pathological androgen deficiency[16]. On the other hand, leaving such men untreated may deprive them of potential benefits of testosterone therapy on non-glycemic outcomes (*e.g.* improvements in androgen-deficiency symptoms, muscle strength, and bone density)[8, 12, 17]. Negative effects of testosterone on fertility should be considered in men who have not completed their family.

MAIN CONCLUSIONS

On the basis of current evidence, measurement of testosterone in men with metabolic disorders should not be performed routinely, but instead be targeted to men in whom androgen deficiency is suspected clinically.

While the association of low testosterone in men with metabolic disorders is partially mediated by SHBG, there is a bi-directional relationship with visceral fat, which promotes a self-perpetuating circle.

The key response to the aging, obese man with metabolic disorders and lowered testosterone should be implementation of lifestyle measures which, if successful, can increase testosterone levels and result in other health benefits.

Outside clinical trials, indications for testosterone therapy in men with metabolic disorders should be no different to those for men without diabetes or the metabolic syndrome. Testosterone therapy should currently be reserved for men with clinical features suggestive of androgen deficiency and unequivocally low testosterone levels. Such men require evaluation for an underlying pathological cause of hypogonadism, and it should not be assumed that the hypogonadism is a consequence of their metabolic disorder.

Given the multiple possible factors confounding both testosterone levels and symptomatology in these men, indications for testosterone therapy should be more stringent than those for younger men with pathological hypogonadism, in whom such confounders are absent.

The decision to treat with testosterone therapy will be guided by treatment goals, including other potential benefits not specific to men with diabetes, such as improved sexual function, bone density, and muscle strength, and by whether the physician and the patient place higher value on unproven benefits of therapy or on equally unproven harm.

Further clinical trials of testosterone therapy in men with metabolic disorders, preferably in combination with lifestyle intervention, are required to assess the effects of testosterone on glucose metabolism and non-glycemic outcomes.

CASES WITH QUESTIONS

Case 1

A 64-year old man presents to the diabetes clinic for review. His diabetes of 6 years duration is managed with metformin and a sulfonylurea, and a recent HbA1c was 8.9%. He is centrally obese with a BMI of 31 kg/m^2. Additional medications include an angiotensin 2 inhibitor for hypertension, a statin and low dose aspirin. He has microalbuminuria, background diabetic retinopathy, asymptomatic stable ischemic heart disease with one previous coronary stent, but no other known macrovascular complications.

Question 1. What is the probability that he has symptoms compatible with androgen deficiency and a low testosterone level?

Case 1 (cont.)

He reports poor libido and reduced sexual function and energy levels for the past year. He slowly, but steadily gained weight over the last 10 years. He reports poor dietary habits and does not exercise. He denied symptoms of sleep apnea. On physical exam, he had normal male pattern body hair, testes were 20 mls bilaterally, and there was no gynecomastia, no obvious loss of muscle bulk, or visual field defect. Because of his symptoms, a testosterone level was ordered. Morning fasting total testosterone was 7.4 nmol/L (215 ng/dL) [assay-specific reference range 10-27.6 nmol/L].

Question 2. What additional diagnostic studies would you order?

Case 1 (cont.)

Repeat total testosterone was 7.8 nmol/L (225 ng/dL). SHBG was 24 nmol/L [13-71 nmol/L] and free testosterone level was calculated to be 160 pmol/L (4.6 ng/dL), and 173 pmol/L (5.0 ng/dL) on repeat [230-610 pmol/L]. LH was 4.3 IU/L [1-10] and FSH 3.7 [1-10]. Prolactin was normal, ferritin mildly raised, but fasting transferrin saturation was normal. A pituitary MRI was not performed.

Question 3. How would you manage this man?

Case 1 (cont.)
A trial of lifestyle measures was recommended, with emphasis on weight loss. Over the next 10 months, he lost 11 kg of body weight. Repeat total testosterone was 11.1 (320 ng/dL) and 12.0 nmol/L (345 ng/dL). Energy levels improved, and he reports an improvement of sexual function with the use of a phosphodiesterase inhibitor. His HbA1c has decreased to 6.8%, and his sulfonylurea dose was reduced.

Case 2
A 62-year old man is interested to participate in a randomized clinical trial (ClinicalTrials.gov Identifier: NCT00613782) that examines the effects of testosterone therapy on body composition and glucose metabolism. He had type 2 diabetes for 4 years, managed with metformin. He is moderately symptomatic on a sensitive but nonspecific questionnaire (Aging Male Symptoms Scale 50/85), has moderate reductions in sexual function (International Index of Erectile Function Score 16/25), moderate urinary symptoms (International Prostate Symptom Score 14/25), and moderate risk of sleep apnea (Berlin Questionnaire 6/13). On examination, BMI is 32 kg/m^2, testes are 15 ml. Rectal exam reveals a smooth, mildly enlarged prostate. His HbA1c is 7.9%, total testosterone 7.6 nmol/L (215 ng/dL), repeat 7.1 nmol/L (193 ng/dL) calculated free testosterone 140 pmol/L (4.0 ng/dL), repeat 130 pmol/L (3.7 ng/dL), LH 2.5 IU/L, prolactin normal, PSA 2.88 mcg/L, and hematocrit 0.49 %.

Question 4. What advice would you give him regarding the metabolic benefit of testosterone therapy, and how would you discuss risks of therapy?

Case 2 (cont.)
Following informed consent, he was enrolled in the trial and randomized to active therapy with long-acting i.m. testosterone undecanoate (marketed in Australia as Reandron®, not currently available in the US) as per usual schedule (0, 6, and 18 weeks). After 42 weeks of testosterone therapy (study end) his trough testosterone was 19.2 nmol/L (550 ng/dL) (target 10-15 nmol/L) and LH < 0.1. He lost 4 cm of waist circumference. On DEXA, lost - 4.7 kg of fat mass and gained + 3.7 kg of lean mass. HbA1c, lipid profile remained stable. His AMS, IPSS, IIEF and Berlin scores were 47/85, 13/25, 17/35 and 6/13. Hematocrit increased to 0.56 %, and PSA to 9.2 mcg/L. He was referred to a urologist who recommended a prostate biopsy. This showed no evidence of prostate carcinoma. Testosterone therapy was ceased. He declined a sleep study.

Case 3
A 55 year-old man with the metabolic syndrome (waist 108 cm, blood pressure 148/85 mm Hg and impaired glucose tolerance) is referred for cardiometabolic risk assessment. He has been unable to engage in lifestyle measures, which he attributes to lethargy, muscle weakness, and depressive moods. He reports poor libido. Examination revealed mild gynecomastia and 12 ml testes, with normal visual fields and normal rectal exam. Total testosterone was 3.9 nmol/L (112 ng/dL), repeat 4.4 nmol/L (127 ng/dL), LH 1.8 IU/L, and prolactin 673 mIU/L (NR 86-324). Hemoglobin was 12.7 g/dl (NR 13-18).

Question 5. How would you assess this man?

Case 3 (cont.)
Pituitary function was otherwise normal, as were iron studies. MRI revealed a 16 mm pituitary cyst with anterior displacement of pituitary tissue. A pituitary neurosurgeon recommended conservative management. Follow-up MRIs remained stable, and visual fields normal.

Question 6. How would you manage him?

Case 3 (cont.)
Testosterone therapy was initiated with 5g of 1% testosterone gel and subsequently changed to testosterone undecanoate i.m. (trough total testosterone 13.8 nmol/L). Energy and libido improved markedly, and he commenced regular exercise and made dietary adjustments. 12 months later, he has lost 8 kg of body weight, and his metabolic syndrome has resolved. Peak grip strength improved from 33 kg to 41 kg.

DISCUSSION OF CASES WITH ANSWERS

Answer 1:
30-50% of men presenting to the diabetes clinic have testosterone levels below the reference range derived from healthy young men[9,18,19]. While up to 50% of such men may report symptoms reminiscent of those reported by men with pathologically-based hypogonadism, these symptoms were as strongly associated with older age as they were with low testosterone in a large cohort of men with type 2 diabetes[18]. In the general population, "late onset hypogonadism" (LOH) - defined as symptoms and signs consistent with androgen deficiency and low testosterone levels- occurs in 2-6% of men, and the presence of diabetes, obesity or metabolic syndrome is associated with a 2-3 fold increased odds ratio of LOH in these studies[20-22]. Thus while many men with metabolic disorders will meet the diagnostic criteria proposed for LOH[20], marked reductions in testosterone levels (< 5.2 nmol/L, (< 150 ng/dL)) are less common, and were found in 5% of men with type 2 diabetes in one large study[19].

Answer 2:
At least two low fasting morning total testosterone levels are required to provide biochemical evidence of androgen deficiency. Free testosterone levels should be quantified when alterations of SHBG are suspected although the biological superiority of free testosterone is not proven and total testosterone remains the mainstay of diagnosis[8]. SHBG is reduced in states of insulin resistance, and therefore a normal free testosterone level may help to reduce the probability of significant androgen deficiency in men with metabolic disorders, although reference ranges for free testosterone are not well validated.

Answer 3:
Given that there was no evidence of organic pituitary or testicular pathology, the low testosterone state may be functional and reversible with a successful lifestyle intervention leading to weight loss.

Answer 4:
See section on "Evidence for testosterone therapy" above.

Answer 5:
He needs a thorough evaluation for hypogonadotrophic hypogonadism.

Answer 6:
Testosterone replacement is indicated in the absence of contraindications.

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Klinefelter Syndrome: Clinical Management Issues

M4
Saturday, June 15
3:00–3:45 PM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Klinefelter syndrome (KS) is the most common chromosomal abnormality in men occurring in approximately one in 660 newborn boys (1). It has important clinical consequences at all stages of development. In the neonatal period, it can cause cryptorchidism. In childhood, it should be considered in the differential diagnosis of boys who present with language delay, learning disability and behavioral problems. However, in reality only 10% of cases are diagnosed before puberty (1) and the diagnosis is most commonly made in adulthood during the workup for gynecomastia, hypogonadism and/or infertility. KS is the most common genetic cause of primary gonadal failure accounting for 4% of cases of male infertility and 11% cases of azoospermia (2).

However, it is important for physicians taking care of patients with KS to be aware that the phenotypic spectrum of this disorder extends well beyond the reproductive system and includes cardiovascular, pulmonary, metabolic, oncologic, cognitive and psychiatric abnormalities. Men with KS have been shown to have increased morbidity and an increased mortality risk (hazards ratio 1.4 CI 1.13-1.74) with recent studies suggesting a lower medial survival of up to 6 years (3-5). The excess mortality is distributed between cardiovascular causes (30%), pulmonary causes (22%), and cancer (21%) (5). While the presence of the characteristic X chromosome may explain some of the increased disease burden associated with this disorder, the poorer socioeconomic status that accompanies KS is also thought to play a role (5).

BARRIERS TO OPTIMAL PRACTICE

- Reduced awareness of KS among health professionals
- Misconception that all patients with KS exhibit the classic textbook presentation while in reality the phenotype can be quite subtle especially in patients with mosaicism. Consequently, there is failure to make the diagnosis in 50-75% cases (1,6)
- Lack of randomized, placebo-controlled controlled trials to determine if early supplementation with testosterone can significantly improve outcomes and reduce morbidity and mortality in men with KS.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Appreciate the wide phenotypic spectrum of KS
- Perform a comprehensive evaluation of patients with suspected KS
- Manage both the testicular and extra-gonadal manifestations of the condition

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Diagnosis

The typical clinical presentation of KS often includes a history of developmental, psychosocial, behavioral and learning disabilities in childhood. Physical examination reveals small firm testes (typically <6 mL) in more than 95% of patients often associated with gynecomastia, tall stature, eunuchoidal proportions, and central adiposity (7,8).

From mid-puberty onwards boys with

KS show a gradual increase in FSH and LH to hypergonadotopic levels with FSH increasing earlier and to a greater degree than LH (9). Testosterone levels tend to be at or below the lower end of the normal range in the majority of patients, while estradiol and SHBG levels are usually increased. Serum inhibin B levels are usually undetectable (9). Given the phenotypic variability of KS it is recommended that all patients with hypergonadotopic hypogonadism have a karyotype.

While the diagnosis of KS can be suspected by the clinical features and hormone profile, it should be confirmed by determining the karyotype of the peripheral leukocytes. Approximately 80% will have the characteristic 47,XXY genotype, which results from nondisjunction of the sex chromosomes of either parent during meiotic division. A further 10% will have mosaicism with a mixture of 46XY and 47XXY thought to result from nondisjunction during mitotic division after conception. While many of the clinical features of KS are due to hypogonadism, others are due directly to the presence of an extra one or more X chromosomes. In general, the greater the number of extra X chromosomes, the greater the phenotypic consequences, both gonadal and extra-gonadal. The phenotype in KS patients also appears to be modified by the length of the CAGn polymorphism of the androgen receptor gene with some studies showing an association between a higher number of repeats and taller stature, lower bone density and gynecomastia (8).

Management

The optimal management of men with KS involves a multi-disciplinary approach with appropriate input where needed from primary care doctors, pediatric and adult endocrinologists, urologists, psychiatrists, psychologist and speech therapists.

Testicular Function

The diagnosis of KS is frequently made in adulthood because of symptoms of hypogonadism, gynecomastia and/or infertility. There is general agreement that androgen replacement should be instituted in KS men whose testosterone levels are in the hypogonadal range. However, some clinicians recommend instituting testosterone therapy at the start of puberty in boys with KS to optimize muscle and bone mass (8). At the moment however, there is no evidence base to support the hypothesis that such early intervention improves outcomes. Testosterone may be administered using transdermal or intramuscular formulations and treatment monitored as per the standard guidelines for androgen replacement in men (10).

Gynecomastia is a relatively common complaint in men with KS. In some cases it may improve with androgen replacement as endogenous LH levels are suppressed leading to a reduction in aromatase activity and thus an increase in the ratio of testosterone to estradiol. However, the most effective treatment for gynecomastia is surgery and good cosmetic results can be achieved by combining direct surgical excision of the glandular tissue with liposuction through a periareolar incision of any coexisting adipose tissue. However, it is important to remember that men with gynecomastia due to KS are at increased risk for breast cancer and yearly breast exams should be performed. A mammogram should be conducted if there are any features concerning for malignancy such as a nipple discharge, hard mass or tethering of the skin.

Traditionally, men with KS were considered to be infertile as the majority is azoospermic. However, recent studies have shown that as many as 8% of non-mosaic patients with KS have sperm in the ejaculate (11). In non-mosaic KS patients, pregnancy has been reported using intracytoplasmic sperm injection (ICSI) with ejaculated spermatozoa. For azoospermic KS men, advances in assisted reproduction now afford the possibility of genetic paternity, where previously options were limited to adoption or use of donor sperm. Using the technique of micro-dissection testicular sperm extraction (TESE), sperm recovery rates of up to 66% have been reported with up to 45% of these resulting in live births following ICSI (12). However in many centers, TESE is still not being offered because of lack of awareness and/or ethical concerns about the genetic risk

to the offspring.

Because of the concern that the likelihood of successful sperm retrieval decreases with age due to progressive hyalinization of the tubules, some groups are advocating that sperm retrieval be considered at the time of puberty (13). Some physicians are now counseling adolescents with KS for sperm banking if sperm are present in the ejaculate analogous to boys undergoing chemotherapy. At the more aggressive end of the spectrum, some centers propose micro-dissection TESE and cryopreservation in puberty and early adulthood, although this approach is not widely accepted and there are a number of ethical concerns.

Metabolic Syndrome

It has long been appreciated that KS is associated with insulin resistance and an increased prevalence of type 2 diabetes (8). In addition, recent studies suggest that almost 50% of KS patients fulfill criteria for metabolic syndrome. The mechanism underlying these metabolic abnormalities in KS is not fully understood but is likely to be mediated at least in part by the unfavorable body composition characteristically observed in these patients, namely an increase in central body fat and reduction in lean muscle mass. Thus, close attention should be paid to blood pressure, lipids and glucose tolerance with the importance of lifestyle changes emphasized, where appropriate.

Bone Health

Adults with KS have been shown to have reduced bone mineral density (BMD) and increased risk of fracture (8). Interestingly some studies show a better correlation between BMD and muscle strength in this population than with testosterone levels. It is therefore important to screen KS patients for osteoporosis and to ensure that their calcium and vitamin D status has been optimized.

Psychosocial Aspects

Many boys and men with KS have been shown to suffer from learning disabilities, scoring poorly on standardized testing especially with regard to verbal and executive functions (5). Many will have required input from speech and language therapists as children. As a result of these cognitive difficulties, the educational level achieved by these patients as well as their average income is significantly lower than controls. They may also suffer from social withdrawal and are less likely to find a partner and cohabitate. The impact of testosterone on these parameters is unclear with small, uncontrolled studies giving conflicting results. In addition, studies suggest that men with KS are more likely to suffer from a variety of psychiatric disorders including schizophrenia, depression, attention deficit hyperactivity disorder and autism. Thus, input from psychologists and psychiatrists can be critical to the optimal care of these patients.

Miscellaneous

As discussed earlier, men with KS have a predisposition to develop morbidities later in life that are unrelated to testosterone deficiency and are thought to be due to the effect of non-inactivated genes on the extra X chromosome. This non-reproductive phenotype includes an increased risk of pulmonary diseases (chronic bronchitis, emphysema, bronchiectasis), cancers (germ cell tumors with a predilection for the mediastinum, breast cancer), varicose veins and venous leg ulcers, and autoimmune diseases (systemic lupus erythematosus).

MAIN CONCLUSIONS

1. KS is a common but frequently under-diagnosed condition which should be ruled out in all patients presenting with primary gonadal failure.
2. Once the diagnosis of KS has been made, patients should have a comprehensive evaluation focused not only on the reproductive system but also on metabolic parameters, bone health, psychosocial issues with input sought from appropriate specialists as needed.
3. Significant advances have been made with regard to fertility options for KS patients in the last decade, but controversy exists with regard to the optimal timing of intervention
4. Placebo-controlled studies are needed to determine the impact of testosterone replacement on the myriad clinical features of KS to dissect the relative contributions

of hypogonadism versus the chromosomal abnormality *per se* to their etiology.

CASES WITH QUESTIONS

A 30-yr old man is referred for evaluation of decreased libido and difficulty both achieving and sustaining erections. He first noticed symptoms about one year ago and feels that they are getting progressively worse. He reports normal onset and progression through puberty with no history of cryptorchidism. He has a history of painless breast enlargement since puberty. He had surgery performed for the breast enlargement 18 months previously but had no work up at the time. Following an initial good cosmetic result. the breast tissue is now growing back.

On systems review he reports weight gain of over 50 pounds over the previous 3 years, which he attributes to poor diet and lack of exercise. He is especially concerned about his symptoms now as he recently got engaged and would like to start a family in the near future.

On examination his BMI is 35 kg/m^2 with a generalized distribution. He is 74 inches tall and has an arm span of 76 inches He has normal facial, axillary and pubic hair. He has bilateral gynecomastia, which is symmetrical and non-tender with no skin tethering and has peri-areolar scars from his previous surgery. His testes are 3 mL and firm in consistency. He is clinically euthyroid and has no stigmata of chronic liver disease.

POINTS FOR DISCUSSION

1. What hormonal work-up should have been performed on this patient prior to surgical correction of his gynecomastia?

All patients with gynecomastia should have a hormonal work prior to surgery to try to establish a treatable cause, such as hypogonadism or an estrogen-secreting tumor. In this case the gynecomastia had been present since puberty but the key factor which indicates that this is not persistent pubertal gynecomastia is the small testicular size. The presence of gynecomastia in association with eunuchoidal proportions and small testes should make one consider the diagnosis of Klinefelter syndrome. The appropriate work-up in this case includes measurement of testosterone, estradiol, LH and FSH. The patient's hormone profile indicated hypergonadotropic hypogonadism with a testosterone level of 164 ng/dL (5.7 nmol/L), an estradiol of 31 pg/mL (115 pmol/L), an LH of 18.8 U/L and FSH of 25.8 U/L. Karyotype confirmed that he was 47, XXY.

2. Does he need a mammogram?

Men with gynecomastia due to Klinefelter syndrome are at increased risk for breast cancer with some studies reporting a standardized mortality ratio of 57.8 (14), so a careful breast examination should be a key component of their annual physical. Mammography is not routinely recommended unless there are features on the examination concerning for malignancy such as a hard mass, tethering of the skin or nipple discharge. This patient had symmetrical, painless breast enlargement with no suspicious features so mammography is not indicated.

3. Does the fact that the patient is well virilized make the diagnosis of Klinefelter syndrome unlikely?

Many patients with Klinefelter syndrome have testosterone levels in the low normal range so the fact that this patient is well virilized in terms of body hair does not make this diagnosis less likely. Part of the reason that he only developed symptoms of hypogonadism in the previous year was that that was when he experienced the significant weight gain. It is likely that his current testosterone level of 164 ng/dL reflects not just Klinefelter syndrome but also his BMI of 35 kg/m2.

4. ***What factors would influence how you would counsel this patient with regard to his fertility?***

One of the key factors influencing the fertility potential of men with KS is their karyotype. In general, the greater the number of extra X chromosomes, the greater the phenotypic consequences, both gonadal and extra-gonadal. Thus, the 10% or so of men with mosaic KS are more likely to have sperm in their ejaculate and spontaneous pregnancies have been reported in this group (11). In the case described there was no evidence of

mosaicism, but it is important not to presume that all non-mosaic KS are azoospermic as studies indicate that up to 8% may have some sperm in the ejaculate. Thus, a knowledge of the patient's semen analysis is key to informing the discussion concerning his fertility. A history of cryptorchidism, which is more common in men with KS than in the general population, would be a negative prognostic indicator so its absence in this case is in the patient's favor. The final issue, as in any couple with infertility, relates to his partner in that factors such as her age and ovarian reserve need to be taken into account.

5. What fertility options are available to him?
Traditionally, the diagnosis of KS was considered an absolute barrier to biologic paternity and the only fertility options offered to patients were use of donor sperm or adoption. In the last decade or so, advances in assisted reproduction have led to success rates of over 50% in sperm retrieval using the technique of micro-dissection testicular extraction followed by intracytoplasmic sperm injection (11). Thus, while the likelihood of spontaneous conception is very low in these patients, there are effective options for assisted reproduction which should be discussed. However, there are a number of ethical considerations in this regard and it is important for KS patients to have the appropriate genetic counseling before embarking on assisted reproduction.

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Induction of Fertility in the Hypogonadotrophic Male

M30
Sunday, June 16
1:00–1:45 PM & 3:00–3:45 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Male infertility is the sole or contributory factor in half of the 1 in 7 couples presenting with infertility. Hypogonadotropic hypogonadism (HH) is relatively uncommon in fertility practice yet provides the best opportunity to restore natural fertility using evidence-based treatments. Conversely, congenital or acquired HH is frequent in endocrine practice and the patient's fertility concerns may evolve across the long association with their clinicians; the boy with Kallmann's syndrome becoming the 35 year man seeking to start a family.

Concomitant androgen deficiency is frequent and complete clinical evaluation is essential as other pituitary hormone deficiencies may co-exist resulting in significant non-reproductive consequences. The ability to successfully restore fertility when desired and to counsel patients about all their fertility options are key practice considerations. In addition to established causes of hypothalamo-pituitary (HP) dysfunction, various drug and lifestyle factors may impair the normal function of the hypothalamo-pituitary axis and required other approaches to improve fertility.

BARRIERS TO OPTIMAL PRACTICE

- Lack of understanding the hormonal requirements for the initiation and maintenance of spermatogenesis.
- Uncertainty about how to undertake time- and cost-effective evaluation of the male with possible HH related infertility.
- Unfamiliarity with the gonadotropin preparations and the convenient monitoring of treatment for HH.
- Knowledge gaps regarding empirical/ anecdotal treatment options and the need for evidence based on placebo-controlled RCTs.
- Lack of awareness of ART options for those HH men showing a suboptimal spermatogenic response to prolonged gonadotropin treatment.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to undertake the following:

- Systematic approach to the infertile couple; including a couples-based approach and investigation of both partners in developing the management plan aimed at achieving natural conception.
- Diagnosis of the male partner: specifically to identify that minority of infertile men with HH that is amenable to specific therapy.
- Time- and cost-effective investigation that reduces patient anxiety through expeditious diagnosis and treatment.
- Manage the induction of spermatogenesis in the HH male, including the initiation and monitoring of gonadotropin therapy.
- Knowledge of the evidence base supporting intervention: recognize settings in which efficacy/safety are known as opposed to 'off label' empirical approaches
- Assisted reproduction: consider the use of ART in settings where spermatogenic response and/or female factors mitigate against natural conception.

SUCCINCT REVIEW- STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Pathophysiology

Gonadotropins initiate and maintain normal sperm production: phases of pulsatile GnRH pulse activity during fetal and perinatal life stimulates gonadotropin release that drives (i) Sertoli cells and the germ cell lineage within the seminiferous epithelium, and (ii) Leydig cell androgen secretion that promotes sexual differentiation. At puberty sustained GnRH pulsatile release stimulates gonadotropin/androgen secretion and a final phase of Sertoli cell proliferation. Thus in prenatal-onset HH (e.g. Kallmann's) GnRH secretory phases are deficient resulting, in severe cases, in micropenis, cryptorchidism and small testes (<4ml) and a consequent reduction in adult Sertoli cell number and spermatogenic capacity. Conversely in post pubertal onset HH after prior fertility (e.g. post pituitary surgery), a prompt increase in sperm output is common.

Testosterone is essential for spermatogenesis; it acts via androgen receptors in Sertoli cells, peritubular myoid and Leydig cells, but not germ cells (1). Due to its local secretion, intra-testicular T (iTT) levels are 50-00 fold higher than those in serum (~300 vs 3 ng/ml). When LH is suppressed (in HH or by negative feedback during T therapy) iTT levels fall by 97% and spermatogenesis is inhibited. This is the basis for male hormonal contraception and a reminder to avoid testosterone treatment in men seeking fertility. Human chorionic gonadotropin (hCG) therapy (as an LH substitute) restores iTT levels while exogenous FSH acts via G protein-coupled receptors on Sertoli cells. Note that quantitatively normal sperm output requires both testosterone (T) and FSH action (2).

Clinical Evaluation

Infertile men require a complete medical history and examination including testicular volume estimation by orchidometry or ultrasound (normal 15-35ml) complemented by semen analyses and morning reproductive hormone testing (FSH, LH, T, prolactin). The causes of infertility should be identified and co-existent androgen deficiency or testicular cancer sought in this 'at risk' population.

The majority of male infertility relates to primary spermatogenic failure reflected in poor sperm density, motility and/or structure/function, and an elevated serum FSH, or obstructive lesions. HH accounts for ~1% of cases and is suggested by low normal-undetectable serum gonadotropin and testosterone levels and azoo-/severe oligozoospermia (< 5 million/ml). Normal range gonadotropin levels may be in inappropriate for the clinical setting (e.g. a low serum testosterone) (3).

HH has a wide range of causes and spectrum of severity. Many patients have an established diagnosis of congenital (e.g. Kallmann's syndrome) or acquired HH resulting from childhood or adult-onset disease (pituitary adenoma, surgery, radiotherapy, trauma, hemochromatosis) and

CAUSES OF MALE INFERTILTY

DISORDERS OF INTERCOURSE & EJACULATION

- **Intercourse frequency / timing**
- **Sexual dysfunction**: erectile/ejaculatory disorders

PRIMARY TESTICULAR FAILURE:

- **Idiopathic spermatogenic failure**
- **Testicular damage:** orchitis, torsion, varicocele, surgery
- **Drugs and toxins: c**hemotherapy, salazopyrine
- **Chromosomal anomalies: incl.** Yq microdeletions
- **Genetic:** single genes, e.g. myotonic dystrophy

MIXED PRIMARY AND SECONDARY

- **Non-reproductive illness:** acute, chronic
- **Iron deposition:** transfusion-dependent anemia

HYPOGONADOTROPIC HYPOGONADISM (HH)

- **GnRH deficiency:** Kallmann's, idiopathic isolated
- **Gonadotropin deficiency**
  - Sex steroid suppression- androgen use/ abuse
  - Sex steroid secreting neoplasia – Leydig cell, adrenal
  - Congenital adrenal hyperplasia
  - Hypothalamo-pituitary disorders
    - Prolactinoma, other adenoma
    - Trauma, infiltration, iron deposition

OBSTRUCTIVE AZOOSPERMIA

- Epididymal: post infective, surgery
- Vasal – vasectomy, congenital absence
- Ejaculatory duct obstruction

already be receiving T treatment. But HH may escape detection until presentation with infertility. Isolated HH displays only pubertal failure or adult androgen deficiency but other congenital or pre-pubertal onset pituitary disorders may feature other hormonal deficiencies and require specific therapy (e.g. drug, surgery, radiation).

- Congenital isolated HH is usually identified in childhood/adolescence but occasionally when partial, virilisation may have been sufficient so as to have not prompted earlier evaluation. In the case of Kallmann's syndrome, anosmia and olfactory bulb hypoplasia on MRI are apparent.
- Hyperprolactinemia of any cause (adenoma, drug related, idiopathic) may induce HH and effect fertility. Macroprolactinoma is the most common functional lesion, and presents with androgen deficiency (low libido, erectile dysfunction), mass effects (headache, visual field defects) but occasionally with infertility due to sexual dysfunction and/or oligozoospermia. Dopaminergic agents reduce tumor size and prolactin levels, and depending on stalk anatomy and gonadotropic cell mass, restore androgen secretion, spermatogenesis and fertility (4).
- Various sellar or parasellar neoplasms/cysts (e.g. macroadenoma, craniopharyngioma) can result in HH (with or without hyperprolactinemia) and infertility, as can their treatment (cranial surgery, radiation). Non-secretory microadenomas seldom, if ever, cause HH.

Induction of Spermatogenesis in HH

Natural fertility can often be restored with gonadotropin therapy (3, 5, 6). Positive prognostic factors for successful induction in prepubertal-onset HH include larger initial testicular volumes (>4ml implying incomplete HH with some 'spermatogenic infrastructure' development) and an absence of prior cryptorchidism (6). In adult onset cases, favorable factors include prior fertility and an absence of diseases or treatments that directly damage the testes. In both settings, prior successful gonadotropic induction therapy predicts a good and shorter time course of response (5).

Any pre-existing T treatment is ceased and hCG (1000-2000 IU 2-3 times per week sc) commenced with the aim of restoring normal serum T levels; the dose can be titrated to 3000 IU 2-times weekly in order to achieve this endpoint. Gynecomastia is the most common side effect: using the lowest hCG dose that maintains serum T in the lower end of the normal range is desirable. There is evidence that lower hCG doses fully restore iTT in normal men but the relevance of this observation to the clinical HH population is unclear (7). By virtue of co-incident marked rise in iTT, spermatogenesis may proceed, even in the face of low serum FSH: this is more likely in post-pubertal onset HH cases and/or in the presence of oligozoospermia at baseline.

In men remaining azoospermic after 4-6 months of hCG therapy alone (commonly those with congenital HH), FSH is co-administered, initially at 75 IU 3 times per week sc (3). Testicular growth, serum testosterone and sperm density and motility are monitored every 2 months. An increase to FSH 200 IU 3x times weekly should ensure that FSH is not response-limiting. There is no evidence of superiority between urinary and recombinant gonadotropins: patient convenience/compliance (e.g. pre-mixed pens delivery) and cost are considerations (effected by prevailing health system). Pulsatile GnRH administered by sc injection every 2 hours is an effective alternative with some evidence of improved efficacy in pituitary-intact HH but is available only in specialized centers (3, 8).

Prolonged therapy of up to 2 years may be needed to achieve optimal results. Testicular biopsy in order to determine the germ cell populations should be considered with azoospermia and/or poor testicular growth after 12-18 months; this will clarify whether treatment should continue or be abandoned (e.g. in the presence of co-existing Sertoli cell only syndrome or germ cell arrest during meiosis) in favor of discussion about donor gametes if acceptable to the couple.

Natural fertility occurs in ~70% and >90% of congenital and acquired cases, respectively; interestingly the average sperm density at conception is ~8 million/ml underscoring

the qualitative normality of spermatogenesis (9). ART/ICSI provides a 'backup' if semen quality is insufficient for timely natural conception. Gonadotropin therapy is continued into the second trimester at which stage sperm cryopreservation is considered and androgen replacement therapy re-instituted.

Special Settings

Sex steroid abuse

Exogenous androgen treatment suppresses gonadotropins and spermatogenesis. Azoo- or severe oligozoospermia are present often with normal-range testicular size. An undetectable serum LH and low SHBG level is typical while serum T may be high or undetectable (see below); in the latter case the picture may suggest HP pathology and further endocrine testing and imaging may be needed.

Testosterone therapy; iatrogenic secondary HH and infertility

Even in men with overt symptomatic androgen deficiency, T therapy should be deferred until fertility issues have been addressed or sperm cryopreservation undertaken. After testosterone replacement is ceased spontaneous recovery of pre-treatment fertility status may take > 6 months.

Combined primary failure and HH

Iron deposition associated with transfusions for chronic anemias, or hemochromatosis presents a particular challenge as gonadotropin therapy may not overcome testicular damage due to iron deposition (10). A poor serum T response to high dose of hCG is an ominous sign. Yet a few sperm may be achieved after prolonged therapy and permit ICSI (after due consideration of genetic issues).

Obesity and chronic illness

Severe obesity may reduce fertility by altered GnRH secretion and sex steroid feedback and impaired gonadotropin response. Reduced sperm density and quality is reported although inconsistently. A common presentation is the viscerally obese male presenting with infertility and impaired semen quality. Serum T, FSH/LH and SHBG are low-normal while serum E2 levels may be upper range normal. Does he have partial secondary HH? Clomiphene or aromatase inhibitors are appealing agents proposed to relieve estrogenic feedback and increase gonadotropin levels, and/or to reduce intra-testicular estrogen exposure (11). Adequately powered placebo-controlled RCT evidence is lacking; such studies are challenging as spontaneous improvements in semen quality (intrinsic variability and the 'regression to the mean' phenomenon) are readily misinterpreted as treatment effects and spontaneous conception occurs in ~30% of couples with sperm densities 1-5 million/ml over 2-3 year period. To be shown, effective treatment ought to, relative to placebo, lift the life table curve for pregnancy toward that of fertile couples, improving the cumulative pregnancy rate and shortening the time to pregnancy. Meta-analysis is problematic when it seeks to distil data from very different study populations, design, treatments and endpoints. Neither clomiphene nor aromatase inhibitors are approved for the indication of male infertility. Empirical therapies may have an intrinsic appealing and/or anecdotal or weak evidential support. A delay in the move to ART should be avoided, especially if female reproductive aging is a factor.

MAIN CONCLUSIONS

- HH represents an uncommon yet highly treatable cause of male infertility.
- Specific diagnosis permits address on non-reproductive health issues
- Gonadotropin therapy commences with hCG (LH substitute) restore serum and testicular T
- FSH acts synergistically to initiate and maximize sperm output
- If natural conception is not achievable, judicious use of ART permits fertility

CASES WITH QUESTIONS

Case 1

A 27 yr old bank manager presents with primary infertility of 2 years and oligospermia; intracytoplasmic sperm injection (ICSI) has been recommended. His wife is well with regular cycles. His sperm density has declined over the past year (77 → 0.1 million /ml). His

puberty was normal but he is much less hirsute than his brother and shaves only weekly. His erections are normal but he has reduced libido over past 2 year and increasing headaches. Examination: Youthful, little facial and stage 4 pubic body hair, 5cm bilateral gynecomastia, normal visual fields, 12ml testes. Initial blood results provided by local doctor: Se T 0.9 ng/ml, FSH 0.2 IU/L, LH 1.0 IU/L

What investigations are indicated? What are the potential non-reproductive considerations? What are the prospects for natural or ART-assisted fertility?

Case 2

A 39 yr man with b thalassemia major presents with primary infertility and azoospermia. His wife is 27yr G_0P_0, well and not a b thalassemia carrier. His lifelong transfusion dependency was complicated by many years of poor compliance with iron chelation therapy. He developed androgen deficiency requiring T therapy since age 26 yr. Examination: well virilised but testicular volumes ~3ml.

What is the basis of reproductive dysfunction? What can be done to help?

Case 3

A 43 yr old fitness instructor and his 42 yr old G0P0 partner presents with 1 yr primary infertility. She has a past history of tubal surgery. Until 2 months ago, he had long term use of anabolic regimens including nandrolone, testosterone and tamoxifen. Examination: muscular, well virilised, 15ml testes. Serum T 1 ng/ml, LH <0.1 IU/L, SHBG 9mM. Semen analysis: few non motile sperm seen in a concentrated sample.

What endocrine processes are at play? What are the prospects for natural fertility? What (if any) is the role of assisted conception?

DISCUSSION OF CASES AND ANSWERS

Case 1

The presentation strongly suggests secondary HH with longstanding androgen deficiency with the recent worsening of symptoms and a profound drop in sperm density. The key test is a serum prolactin which is grossly elevated at 17,000 IU/L (normal < 400); thyroid, cortisol and growth hormone testing was normal. MRI revealed a 1.5 cm macroadenoma extending toward right cavernous sinus. Dopamine agonist therapy rapidly suppressed prolactin to 200 IU/L, serum T rose to 4.8ng/ml with a month and semen quality normalized within 3 months allowing natural conception. Now 14 years since diagnosis, he remains well on low dose cabergoline therapy, had a second child, and has shown full virilisation.

Macroprolactinoma is a rare but eminently treatable cause of male infertility and should be excluded in all cases of suspected HH. Panhypopituitarism and visual field defects were excluded and his tumor size reduced but remains ~0.7cm diameter. Should dopaminergic therapy have not proven effective in restoring HPT axis function, then exogenous gonadotropin therapy, given his previous normal sperm density, would restore natural fertility. This case underscores the need for proper evaluation of the male partner in men referred for ART treatment. Unless there are coexisting spermatogenic disorders and/or female factors, ART is not appropriate.

Case 2

Hypothalamo-pituitary iron deposition results from chronic transfusion, especially with inadequate iron chelation therapy, and results in HH. In addition, T therapy will also suppress any residual function in his HPT axis. Furthermore testicular iron deposition may also affect the testicular response. T treatment should be ceased and hCG therapy commenced (1500 IU 2x weekly sc; as an LH substitute). His serum T was maintained at 4ng/ml indicating reasonable Leydig function but at 4 months he remained azoospermic. FSH 100 IU 3x weekly sc was added and increased to 200 IU per injection 9 months later. After a further 7 months, a few sperm were seen but he remained profoundly oligospermic over the next 2 years. The couple conceived in the second ICSI cycle and a healthy female infant was borne 4 year after presentation.

This case demonstrates the difficulty of spermatogenic induction in combined HH and

primary testicular failure, the patience required by physician and patient, and the judicious use of ART when sperm output limits natural fertility.

Case 3

Sex steroid use is usually admitted but may be denied even to the extent of seeking ART instead of ceasing. His undetectable serum LH and low SHBG is typical: the low serum T is due to suppression of endogenous T, the fact that synthetic androgens like nandrolone do not cross react in the testosterone immunoassay. The endocrine picture may be complicated by use of other drugs (e.g. tamoxifen), complex drug regimens and differing drug clearance rates. With cessation, there is gradual recovery of HH and sperm output over 3-12 months but transient symptomatic androgen deficiency is common.

In the great majority of infertility secondary to anabolic steroid abuse, management involves just cessation of usage and a basic review of couple and female factors. But in this case the prospects of natural fertility are diminished by the female age and fertility status. hCG treatment should promptly reinitiate spermatogenesis and allow early ART treatment. Anecdotal use of clomiphene citrate to reduce feedback and accelerate recovery is neither evidence-based nor an approved indication.

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MISCELLANEOUS

Sweating and Flushing: Evaluation and Management

M58
Tuesday, June 18
11:15 AM to 12:00 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Flushing describes episodic attacks of redness of the skin together with a sensation of warmth or burning of the face, neck, and less frequently the upper trunk and abdomen. Attacks are typically transient, contrasting with flushing from the persistent erythema of photosensitivity, sunburn or acute contact reactions. Repeated flushing can, over time, result in telangiectasia or occasionally facial rosacea.

Both flushing and sweating are frequently an exaggeration of a physiological process, and a biochemical work-up of every case of every presentation is neither practical nor cost-effective. While a thorough anamesis frequently identifies an obvious cause (e.g. vasomotor instability of the menopausal, alcohol induced flushing), often the diagnosis is far from obvious, and it becomes incumbent on the practitioner to exclude a potentially serious underlying cause of symptoms, which can have a profound effect on the patient's quality of life.

A structured anamnesis lies at the heart of accurate diagnosis, and coupled with physical investigations and targeted investigations, will generally lead to a high probability of a correct diagnosis.

The vasodilatation of flushing may be due to a direct action of a circulatory vasodilator substance, for example histamine, or it may be caused by dysregulated vasodilator autonomic neural activity to cutaneous vasculature of face (travelling with the trigeminal nerve), neck, and upper trunk, where flushing is most frequent. The neurological control of vascular tone is predominantly exerted by autonomic vasodilator nerve fibers. Autonomic nerve fibers also supply eccrine sweat glands, and neurally mediated flushing is frequently associated with sweating (wet flushing) as opposed to isolated (dry) flushing due to the actions of circulating vasodilator substances. The presence or absence of sweating may serve as a clinical guide to the mechanisms of flushing, though not an invariable one. Examples of wet flushing are physiological and menopausal flushing. Niacin-provoked flushing is an example of drug induced 'dry flushing.'

BARRIERS TO OPTIMAL PRACTICE

The causes of flushing and sweating are potentially myriad, but history and examination, may yield important diagnostic clues. In an age of defensive medical practice, the attending clinician may (reflexly) perform a bewildering number of complicated and often expensive investigations to rule out rare pathologies. Perseverance, and unhurried history taking are essential to eschew this pitfall. Patients with flushing and sweating may reach the endocrinologist 'to rule out an endocrine cause' having initially been referred to dermatologists, gastroenterologists, gynaecologists, neurologists, neuroendocrine tumor departments and even psychiatrists without a prior definitive diagnosis. An impoverished patient may then be desperate, and it behooves the endocrinologist, with common sense and a sound knowledge of internal medicine to elucidate the diagnosis.

LEARNING OBJECTIVES

- Learn the value of accurate anamnesis
- The key physical signs to be elicited to reach

a diagnosis
- To familiarize you with the range of disorders and drugs liable to cause flushing/ sweating
- To understand the place of botulinus toxin and endoscopic thoracic sympathectomy (ETS) in selected cases

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Diagnostic Evaluation of the Patient With a Flushing/Sweating

With flushing and sweating, several characteristics of these symptoms should be elicited prior to embarking on expensive laboratory evaluation. These include: (1) provocative and palliative factors, (2) morphology, (3) associated features, and (4) temporal characteristics.

Provocative or palliative factors

Certain agents that precipitate a flush may suggest an aetiological underlying systemic disease e.g., mastocytosis and carcinoid syndrome. Drugs are a particularly common cause of flushing *(see Table 1)*, as is alcohol, particularly in certain racial groups. A recent review has highlighted the fact that some 620 drugs have been associated with flushing!

Morphology of flush/ distribution of sweat
- Is it stereotyped and does it come and go? Can the patient provide photographic evidence ?
- Is the redness patchy or confluent?
- What is the color of the flush?
- Is there cyanosis?
- Is the flushing preceded or followed by pallor?
- Which parts of the body is affected by sweating?

The morphology of the flushing may suggest not only the cause of the flushing but also, in the case of carcinoid tumors, the anatomical origin of the disorder.

Associated features

These could include respiratory symptoms (e.g., wheezing), gastrointestinal symptoms (colicky pain and diarrhoea), headache, urticaria, facial oedema, hypertension, hypotension, palpitations, or sweating.

Temporal characteristics

What is the frequency and duration of the flush/sweat? Patients may not have thought carefully about these questions, and important information can be obtained from a 2-4 week diary in which the patient records qualitative and quantitative aspects of the flushing / sweating event and lists exposure to all exogenous agents. If the diagnosis remains obscure after evaluation of a 2-4 week diary, an exclusion diet can be suggested, paying attention to foods high in histamine, foods and drugs that affect urinary 5-HIAA tests, and foods and beverages that cause flushing. If the flushing reactions completely disappear, restoring the excluded items individually (rechallenge) can identify the causative agent. If the flushing/sweating reactions continue unabated, further metabolic work up may be mandated.

Physical examination of the patient with flushing/ sweating disorder

A thorough general examination of the patient should be undertaken, and vigilance paid to certain key physical signs: telan giectatic lesions, *urticarial pigmentosa*, venous pressures, right sided cardiac valvular signs, goitre and thyroid nodules (painful neck masses can occur with medullary carcinoma of the thyroid), lymphadenopathy in the neck, features of thyrotoxicosis, hepatosplenomegaly, Darier's sign.

Specific causes of flushing and sweating

Blushing

Embarrassment or anger may cause blushing in individuals with a low threshold for this response. The reaction itself may be unusually intense. Explanation and reassurance are usually sufficient. If necessary, propranolol or nadolol may be used to alleviate the symptom.[1]

Thermal stimuli

Heat provokes flushing in many, and overheating can lower the threshold to flushing due to other causes such as menopause. Overheating, such as after exercise or a sauna,

and hot drinks can induce physiological flushing due to the action of a rise in blood temperature on the anterior hypothalamic thermoregulatory center The temperature of hot coffee rather than its caffeine content causes flushing. A useful maneuver for patients faced with a brief thermal exposure is to suck on ice chips carried in an insulated cup, and this will attenuate flushing.

Menopausal flushing/sweating

About 80% of postmenopausal women experience flushing associated with sweating, and a similar syndrome may also occur in men with prostate cancer receiving treatment with gonadotropin-releasing hormone analogues such as buserelin. About 65% of post-menopausal women have hot flushes for 1 to 5 years, 26% for 6 to 10 years, and 10% for more than 11 years. There is considerable variation in the frequency, intensity, and duration of hot flushes within and among individuals. A typical hot flush begins with a sensation of warmth in the head and face, followed by facial flushing that may radiate down the neck and to other parts of the body; it is associated with an slight increase in temperature and pulse rate and followed by a decline in temperature and profuse perspiration over the area of flush distribution. Visible changes occur in about 50% of women, and each flush lasts for 1 to 5 minutes. Rapid oestrogen withdrawal rather than a low oestrogen level by itself is likely to induce hot flushes. A pulse of luteinizing hormone appears to be released at the onset of each flush, but this is not responsible per se for the hot flush since flushing can occur after hypophysectomy. Rather, the synchronization is likely to be with GnRH release. The anterior hypothalamus has oestrogen and progesterone receptors, and both hormones can be used effectively to treat hot flushes. $\alpha 2$ noradrenergic pathways appear participate in the pathogenesis of hot flushes since the $\alpha 2$-adrenergic agonist clonidine attenuates hot flushes by suppressing noradrenaline release. A number of drugs can induce a 'pharmacological menopause' with associated flushing including danazol, tamoxifen, clomiphene citrate and leuprolide.

Certain characteristics suggest the diagnosis of climacteric flushing: drenching perspiration, a prodromal sensation of overheating before the onset of flushing and sweating, and waking episodes at night with the typical symptoms. Alcohol can enhance a menopausal flush. Veralipride, a dopamine antagonist, can attenuate the frequency and intensity of menopausal flushing in premenopausal women pre-treated with goserelin (gonadotropin-releasing hormone agonist) for endometriosis.

Drug induced flushing

A large number of drugs can be associated with flushing *(Table 1)*. Other medications that can cause flushing are corticotrophin-releasing hormone, doxorubicin, niacin and calcium antagonists. Some 5-15% of patients taking PDE5 inhibitors (sildenafil, vardenafil, tadalafil) complain of flushing also. Systemic administration of morphine can cause histamine mediated flushing of the face, neck, and upper thorax. Some patients develop facial flushing and/or generalized erythema after epidural or intra-articular administration of triamcinolone; this is counter-intuitive, as glucocorticoids are usually vasoconstrictors.

Alcohol induced flushing

Certain Asian genotypes evince extensive flushing in response to modest alcohol exposure, due to higher plasma levels of

TABLE 1. Some Causes of Drug-Induced Flushing

All vasodilators (e.g., nitroglycerine, prostaglandins)
Calcium channel blockers (nifedipine etc.)
Nicotinic acid (not nicotinamide)
Morphine and other opiates
Amyl nitrite and butyl nitrite
Cholinergic drugs
Bromocriptine used in Parkinson's disease
Thyrotropin releasing hormone (TRH)
Tamoxifen, clomiphene
Cyproterone acetate
Oral triamcinolone
Cyclosporin
Rifampin
Sildenafil citrate, vardenafil, tadalafil

acetaldehyde caused by deficiency of an isoenzyme of liver aldehyde dehydrogenase. This population can be detected by using an ethanol patch test which produces localized erythema. A special type of alcohol flush is also associated with chlorpropamide. Even small amounts of alcohol provoke intense flushing within a few minutes of ingestion. This flushing is not associated with sweating, but in some cases tachycardia, tachypnoea, and hypotension may be seen. The flush is mediated by elevated acetaldehyde plasma levels and possibly by release of prostaglandins.

Alcohol ingestion can trigger flushing in carcinoid tumors, mastocytosis, medullary thyroid carcinoma, and certain lymphoid tumors. Trichloroethylene, a chemical that has been abandoned in recent years because of carcinogenic potential, can cause flushing. When inhaled following ingestion of alcoholic beverages, a striking cutaneous reaction results, consisting in the sudden appearance of erythema of the face, neck, and shoulders—a reaction that has been termed "degreaser's flush." Nausea and vomiting may also occur.

Food associated flushing/sweating

Eating spicy or sour foods can cause gustatory facial flushing, due to a neural reflex involving branches of the trigeminal nerve. The flushing may curiously be unilateral. The flushing of monosodium glutamate (MSG: sino-cibal syndrome) is controversial. Oral challenge with MSG often fails to induce flushing in volunteers with a history of MSG flushing, and it may be appropriate to look at other dietary agents, such as red pepper, other spices, nitrites and sulphites (additives in many foods), thermally hot foods and beverages, and alcohol. Scromboid fish poisoning (tuna and mackerel) is due to the ingestion of fish that was left in a warm temperature for hours. In addition to flushing, patients with scromboid fish poisoning have sweating, vomiting, and diarrhea. These symptoms are due to intoxication with histamine, which is thought to be generated by histidine decarboxylation by bacteria in spoiled fish.

TABLE 2. Factors That Can Precipitate Flushing in the Carcinoid Syndrome

Hot food/beverage
Spicy food
Chocolate
Cheeses
Tomatoes
Avocados
Red plums
Walnuts
Eggplant
Alcohol
Emotional Stress
Valsalva maneuver: Straining and vigorous coughing
Sudden direct pressure on a large carcinoid tumor

Carcinoid Syndrome

Manifestations of carcinoid tumors include flushing, bronchoconstriction, gastrointestinal hypermotility, and valvular (usually right sided) cardiac disease. Four types of flushing have been described in the literature: erythematous, violaceous, prolonged and bright red. The sudden, diffuse erythematous flush usually affects the face, neck and upper chest and lasts 1-5 minutes and is reported in 20-70% of patients with midgut tumors. Carcinoid tumors can produce a variety of peptides, hormones, and neurotransmitters many of which are vasoactive. 'Carcinoid syndrome' occurs in about 10% of patients with these tumors, and in 75%, episodes of severe flushing are precipitated by exercise, alcohol, stress, and certain foods (spices, chocolate, cheese, avocados, plums, walnuts, red sausage, and red wine) *(Table 2)*; flushing may however appear without provocation. Foregut tumors (stomach, lung, pancreas) are said to be associated with a bright-red "geographic" flush of a more sustained duration, as well as lacrimation, wheezing, sweating, and a sensation of burning. In ileal tumors, the flush is patchier and more violaceous, intermingled with areas of pallor, and does not last as long. Both may be associated with facial oedema that may progress to telangiectasia and even facial rosacea. Pellagra-like skin lesions can result from excessive utilization of tryptophan by the carcinoid tumor, leaving little for the daily

niacin requirement. These lesions include hyperkeratosis; xerosis; scaling of the legs, forearms, and trunk; angular cheilitis; and glossitis. 70% of patients also have watery diarrhoea, and 35% develop right-sided endocardial fibrosis leading to congestive heart failure. Diarrhoea and other gastrointestinal manifestations may precede or coexist with the flushing.

Ninety-five percent of all carcinoids are found in the appendix, rectum, or small intestine, the remainder arising outside of the intestinal tract (e.g. ovary, testis, lung). In general, the larger the primary tumor, the greater the likelihood of metastasis, which provides prognostic implications. Carcinoids of the appendix and rectum rarely present with the carcinoid syndrome. 40- 50% of patients with carcinoids of the small intestine or proximal colon have manifestations of the carcinoid syndrome. Tumors that secrete their hormonal product into the portal venous system do not cause flushing because the released amines are inactivated by the liver. In contrast, liver metastases may escape hepatic inactivation and deliver their product directly into the systemic circulation and hence cause flushing. Pulmonary or ovarian carcinoids release pharmacological products directly into the venous circulation, bypassing the portal system, and can therefore cause symptoms without metastasizing to the liver. Bronchial carcinoids are associated with the more prolonged type of flushing, lasting several hours to sometimes days.

Pathophysiology

The flushing seen with foregut carcinoids is due to release of histamine. Flushing seen with ileal carcinoids is unlikely to be explained solely by serotonin production, since serotonin may or may not be released into the circulation during flushing, intravenous infusion of serotonin does not cause flushing, and moreover flushing is unaffected by serotonin antagonists such as methylsergide, cyproheptadine, and ketanserin). Foregut carcinoids do not generally secrete serotonin but, instead, its precursor, 5-hydroxytryptophan. Screening should therefore seek this product if the other metabolites are not elevated. Other likely mediators of flushing include prostaglandins and the tachykinins. Tachykinins are believed to be mediators of the flushing in tumors of the midgut. They exert vasodilation and contraction of various types of smooth muscle. These peptides include substance P, substance K, and neuropeptide K. Their release is usually partially blocked by somatostatin analogues. Urine excretion of histamine is usually increased in patients who have gastric carcinoid.

Diagnosis

Clinical diagnosis is not difficult in patients with flushing episodes associated with systemic symptoms (diarrhoea, wheezing, and weight loss) and hepatomegaly. It is more difficult in patients who have occasional flushing and no associated symptoms. Only when there is reasonable clinical suspicion should biochemical testing be done, and localization studies must be reserved for those cases proven biochemically.

Provocative Tests

When in doubt, a carcinoid flush can be provoked by alcohol ingestion (4 mL of 45% ethanol) or the infusion of 6 μg noradrenaline, an effect blocked by phentolamine (5 to 15 mg intravenously). Calcium gluconate, 10 to 15 mg/kg, administered intravenously over 4 hours, may produce a flush mimicking a spontaneous attack. Epinephrine reverses flushing in patients with mastocytosis but provokes flushing in patients with the carcinoid syndrome. The procedure should only be performed in a controlled environment. A 1 μg/mL solution of epinephrine in normal saline is administered by intravenous bolus beginning with an initial dose of 0.05 μg. The dose is doubled at intervals of 10 minutes until flushing appears or a until a maximum of 6.4 μg is given. When flushing occurs, it usually begins within 60 seconds after epinephrine administration and dissipates after 3 or 4 minutes.

Biochemical Diagnosis

The diagnosis is confirmed by determining urinary excretion of 5-hydroxyindoleacetic

acid (5-HIAA), the major metabolite of serotonin, normally excreted at 2 to 10 mg (10 to 50 μmol) per 24 hours. A value of more than 150 μmol/24 hours (30 mg/24 hours) is usually diagnostic, and in carcinoid syndrome it is often above 200 μmol per day. This test has a sensitivity of 75% and a specificity of up to 100%. The degree of elevation of 5-HIAA does not always correlate with the severity of flushing, and other vasoactive substances are clearly at play (vide infra). As excretion may be variable, repeated estimations are mandatory. Some patients with carcinoid cannot convert serotonin to 5-HIAA, and have high blood levels of serotonin but normal urinary 5-HIAA. Dietary factors may cause confusion and patients should receive a diet free of the culprit items for 3 days before the urine collection. Measuring blood serotonin is helpful when urinary 5-HIAA is equivocal. Patients with carcinoid syndrome usually have very high blood levels of serotonin. Measurement of serotonin and its metabolites permits the detection of 84% of neuroendocrine tumors. Even carcinoids that predominantly secrete 5-hydroxytryptophan are associated with increased urinary excretion of 5-HIAA because the released 5-hydroxytryptophan is converted to serotonin in other tissues and is subsequently metabolized to 5-HIAA. Chromogranin A (CgA), an acidic glycoprotein of 439 aminoacids, is co-secreted with serotonin, and is elevated in most patients with carcinoid tumors. CgA can be cleaved into smaller fragments at dibasic cleavage sites, generating multiple bioactive fragments such as vasostatins, chromostatin, and pancreastatin. In the evaluation of flushing with an equivocal 24-hour urinary 5-HIAA, a normal plasma CgA value suggests non-endocrine causes. This test is sensitive but not specific, and its predictive value in carcinoid is still uncertain. Flushing was associated with a rise in circulating substance P in 80% of patients with gastric carcinoid. Neurokinin A levels are elevated in certain patients.

Management

Corticosteroids, phenothiazines, and bromocriptine are sometimes effective in suppressing flushing in patients with bronchial carcinoid tumors, as may cyproheptadine, a serotonin antagonist. Combined administration of H1 and H2receptor antagonists may prevent attacks of flushing in patients with foregut carcinoid tumors that produce histamine. Alpha-interferons may control symptoms of carcinoid syndrome and produce objective biochemical responses (greater than 50% suppression of 5-HIAA) that have a median duration of about 4 weeks. Since catecholamines are known to precipitate attacks, a trial of clonidine is worthwhile. Long acting somatostatin analogues such as octreotide/lanreotide have a much longer half-life, making subcutaneous therapy possible. Octreotide lowers plasma levels of serotonin and tachykinins and relieves both flushing and diarrhoea. Amelioration of these manifestations is accompanied by a marked reduction in the urinary excretion of 5-HIAA. The patient should receive an adequate niacin supplement (nicotinamide rather than nicotinic acid, since the latter causes flushing) and should avoid foods, agents, and activities that precipitate symptoms.

In some patients, failure of medical treatment may necessitate carrying out hepatic artery embolization. This treatment is based upon the dependence of metastatic malignant tissue but not healthy liver parenchyma on an intact hepatic arterial blood supply. Anti-tumor chemotherapy remains experimental. Alpha-interferon causes symptomatic relief accompanied by lowering of urinary 5-HIAA.

Prognosis

About one-fifth of patients with the carcinoid syndrome undergo a protracted course. In the remainder, deterioration can be rapid. The mean survival is about 8 years with some surviving up to 20 years. Mean survival is 36 months after the first flushing episode. Targeted radionuclide therapy may in future extend duration of remission in inoperable cases.

Mastocytoses: Aetiology

Mastocytoses are benign, indolent proliferative disorders of the reticuloendothelial system and due to a hyperplastic rather than a neoplastic process, although some forms are aggressive.

TABLE 3. Factors That Produce False-Positive Results With Urinary 5-HIAA Determination

Foods	Drugs
Avocado	Paracetamol (acetaminophen)
Banana	Acetanilid
Chocolate	Caffeine
Coffee	Fluorouracil
Eggplant	Guaifenesin
Pecan	L-Dopa
Pineapple	Melphalan
Plum	Mephenesin
Tea	Methylamphetamine
Walnuts	Methocarbamol
	Methysergide
	Phenmetrazine
	Reserpine
	Salicylates

Most patients have evidence of cutaneous involvement, most commonly multiple, small, pigmented lesions that produce urticarial on stroking with a blunt object (Darier's sign). They are often self-limited, especially in childhood. Mast cells possess the enzyme histidine decarboxylase which enables them to synthesize and store histamine. Other preformed mediators include tryptase, chymase, and carboxypeptidase. Serotonin has not been detected in the human mast cell.

Histopathology

There are increased numbers of normal-looking mast cells in the dermis. These cells may be predominantly perivascular or may show a nodular distribution. The epidermis is normal, apart from increased melanization.

Biochemical Markers

Symptoms of mastocytosis are mainly the result of release of products of mast-cell activation. Plasma histamine levels are frequently raised in patients with systemic symptoms, and elevated urinary excretion of histamine and its metabolite methyl imidazole acetic acid (MIAA) can also be seen. Plasma tryptase levels can also be elevated. Prostaglandin D2 (PGD2) is another product of mast-cell activation. Urinary excretion of this substance and its major metabolites can be elevated several-fold in patients with mastocytoses. Urine should be collected within a few hours of an attack.

Clinical Presentation

Episodic bright-red flushing occurs either spontaneously or after rubbing the skin or exposure to alcohol or mast-cell degranulating agents. Attacks may be accompanied by headache, dyspnoea and wheezing, palpitations, abdominal pain, diarrhoea, and syncope and may closely resemble the flushing episodes of the carcinoid syndrome, especially the foregut variety, also mediated by histamine. Rosacea may develop rarely. PGD_2 might be associated with the symptoms of flushing and diarrhoea. The flushing of cutaneous mastocytosis typically lasts more than 30 minutes, unlike the typical carcinoid flush which lasts less than 10 minutes. In *urticaria pigmentosa*, the diagnosis is established by demonstrating that gentle rubbing of the lesional skin causes local itching, redness, and whealing (Darier's sign). This reaction is due to local histamine release. Darier's sign may also be demonstrated in non-lesional skin. Bone involvement may manifest as osteoporosis or osteosclerosis, and the systemic form of the disease can involve the GI tract with mucosal nodules in the ileum, stomach and large bowel. Haematological abnormalities include mast cell infiltration of the bone marrow, anaemia, leucocytosis, eosinophilia and occasional lymphadenopathy. A subgroup of patients has mastocytosis secondary to a primary haematological disorder. More than 80% of patients with systemic mastocytosis have activating mutations (D816V) in the tyrosine kinase domain of KIT that alter mast cell growth and differentiation.

Confirmation of the diagnosis is obtained by skin biopsy. In patients with systemic symptoms, bone-marrow biopsy and liver and spleen scans are usually performed. Bone scans should only be carried out in the presence of localized bone symptoms.

Treatment

Treatment of non-localized forms of mastocytosis is mainly symptomatic.

Patients should avoid known histamine-degranulating agents. Antihistamines remain the preferred treatment for most patients with uncomplicated urticaria pigmentosa. Human skin blood vessels possess H1 and H2 receptors, involved in both vasodilation and increased vascular permeability evoked by histamine. Thus, combination treatment with an H1 antihistamine (hydroxyzine, 10 to 20 mg, or cetirizine 10mg tid) and H2antihistamine (cimetidine, 200 to 500 mg) is logical and sometimes effective at controlling the flushing episodes. Oral administration of the mast-cell stabilizing agent disodium cromoglycate has proved effective in some patients. The drug does not decrease urinary excretion of histamine and the histamine metabolite MIAA. Some experts recommend using this agent only in patients with systemic mastocytosis suffering from gastrointestinal symptoms. Photochemotherapy has been reported to cause symptomatic relief as well as objective reduction in the population of mast cells and the urinary excretion of MIAA.

Medullary Thyroid Carcinoma

The range of substances secreted by medullary carcinoma of the thyroid is considerable, whether sporadic or familial and the most common symptom after diarrhoea. Occurring in one-third of the patients with diarrhoea, there is pronounced episodic flushing, which, as in the carcinoid syndrome, may be induced by alcohol ingestion. Calcitonin-gene related peptide, an extremely powerful peripheral vasodilator, is a likely mediator of flushing. The other possible explanation is that calcitonin stimulates prostaglandin secretion which in turn, cause the symptoms. A mass is usually evident in the neck, with evidence of lymph node metastases. In all cases the diagnosis can be confirmed by positive immunostaining of tumor tissue for calcitonin and CEA.

Phaeochromocytoma

Flushing is rare in patients with pheochromocytoma. If flushing occurs at all, it is seen after a paroxysm of hypertension, tachycardia, palpitations, chest pain, severe throbbing headaches, and excessive perspiration. Pallor is typically present during the attack, and mild flushing may occur after the attack as a rebound vasodilation of the facial cutaneous blood vessels.

TABLE 4. Factors That Can Cause False-Negative Results

Corticotrophin
P-chlorophenylalanine
Chlorpromazine
Heparin
Imipramine
Isoniazid
Methenamine mandelate
Methyldopa
MAOI
Phenothiazine
Promethazine
(adapted from Kjell Oberg Williams Textbook of Endocrinology Pages 1809-1828 12th Edition)

Spinal cord lesions above T6

Facial flushing and headache can occur along with sweating of the face, neck, and upper trunk in patients with spinal cord lesions above T-6, particularly as an exaggerated response to bowel or bladder distention.

Miscellaneous causes of flushing

Other causes are certain pancreatic tumors (VIPOMAS), insulinoma, and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes). Transient flushing of the face, chest, or arms has been noted after neurological deterioration secondary to rapid rise in intracranial pressure.

Other endocrine causes of hyperhydrosis

Acromegaly, thyrotoxicosis, hypoglycaemia constitute other causes of sweating *(see Table 4)*.

Idiopathic hyperhidrosis

It is estimated that 0.6 to 1 percent of the population has idiopathic hyperhidrosis, or excessive sweating. The condition may be focal or more generalized. To diagnose idiopathic hyperhidrosis, there must be excessive sweating

for at least six months duration with two of the following criteria:

- Bilateral symmetric sweating
- Impairment of daily activities
- At least one episode per week
- Onset before 25 years of age
- Family history of idiopathic hyperhidrosis
- Focal sweating that stops during sleep

Idiopathic hyperhidrosis is underreported for various reasons. Patient may be too embarrassed to report the symptom or may not even realize the condition is treatable. The Primary Care Physician may also be dismissive of the symptom.

Topical and oral medications that can be used to treat idiopathic hyperhidrosis. Procedures such as Botox and iontophoresis may also be used. When these interventions fail and hyperhidrosis continues to be a debilitating condition, a minimally invasive endoscopic thoracic sympathectomy may help.

MAIN CONCLUSIONS

1. Flushing and sweating are common clinical symptoms.
2. The key to optimal management relies on a thorough anamnesis and clinical examination.
3. Targeted investigation is preferable to a shot-gun approach.
4. Effective treatment is available for most causes of flushing if the correct diagnosis is made.

CASES WITH QUESTIONS

Case 1

A 29-year-old male patient of Irish origin, a nonsmoker and nondrinker, gave a 14 month history of an erythematous skin rash after intake of aspirin. He presented to A and E with abdominal pain, vomiting, and a diffuse erythematous skin rash. OE he was alert and afebrile with no abdominal tenderness. Initially, blood pressure was 170/90 mm Hg and pulse rate was 70/min, but hemodynamic parameters rapidly deteriorated despite fluid infusion. Laboratory investigations revealed acute renal failure (creatinine 211 μmol/L), hypokalaemia (2.6 mmol/l) haemoconcentration (protein 92 g/L), and clotting tests showed prolonged activated partial thromboplastin time (aPTT) (187" versus 30" control value) and prothrombin time (17"2 versus 11"8 control value). Blood count showed leucocytosis (18 × 109/L) with neutrophiia (16 × 109/L) and a normal platelet and eosinophil count. Haemoglobin level was 12.6 g/dL. C-reactive protein was only slightly elevated (14 mg/L). The patient was transferred to the intensive care unit of the university hospital because of anuria and unexplained abnormalities of clotting tests. On admission a diffuse skin rash was still present. Blood pressure fell to 80/60 mm Hg, pulse rate 130/mn, anuria and agitation ensued. Orotracheal intubation was thus performed, and mechanical ventilation and continuous hemofiltration were started. An epinephrine infusion corrected the haemodynamic status, and the skin rash quickly disappeared. Septic or toxic shock were the first hypotheses investigated, but no infection was documented, and there was no evidence for disseminated intravascular coagulation, since the platelet count remained normal. Repeated clotting tests showed however an aPTT up to 200", a prothrombin time raised up to 90", and anti-Xa activity was 2.5 UI/mL. Fibrinogen was 1.8 g/L, antithrombin level was 56%.

Questions

What is your differential diagnosis?
Can you explain the haemostatic abnormalities?
What management would you consider?

Case 2

A 32 year old polish man reports onset of a livid discoloration of the cheeks within 5 minutes of ingesting white wine, and certain spirits. There is a past history of anxiety state but his general health is otherwise good. He takes no recreational drugs and is on no regular medication. He is distressed by this socially disabling symptom.

Questions

1. What is the differential diagnosis?
2. How should he be managed?

Case 3

A 28 year old beautician complains of excessive armpit sweating brought on by

minimal exertion. Recently, her hands have become cold and clammy, so that she has to keep drying them. Her mother suffered from a similar condition. Her general health is good, her weight constant and appetite good. She does not drink alcohol and is on no medication.

Questions
1.What is the differential diagnosis?
2. How is she best managed?

DISCUSSION OF CASES AND ANSWERS

Case 1

Systemic mastocytosis, confirmed by a serum tryptase level up to 200 µg/L (normal < 13) and a bone marrow biopsy showing multifocal infiltrates of spindle-shaped mast cells. The patient was initially treated with fresh frozen plasma and red cell transfusions, and then protamine was infused at a rate of 1200 UI/h combined with IV glucocorticoids, enteral H1 and H2 antihistamines, and imatinib mesylate (400 mg/d). aPTT and prothrombin time were normalized within four days. On clinical examination in the internal medicine unit, urticaria pigmentosa with Darier's sign (urtication reaction at the site of the papulo-macular lesions when scratched) demonstrated on the trunk.. Complementary workup revealed long bones involvement on radiology, diffuse bone abnormality on technetium scintigraphy, diminished bone mineral density (lumbar T-score -1.4; femoral T-score -0.8), and the presence of mastocytic infiltrates in the oesophageal wall. No skin biopsy was performed. C-kit mutation D816V was demonstrated. The patient was discharged on ranitidine, cetirizine, glucocorticoids, alendronate, and imatinib mesylate (200 mg/d). On his last follow-up visit in June 2012, he remained asymptomatic under the same treatment at the exception of steroids which had been discontinued.

Case 2

Most likely a deficiency of isoenzyme of alcohol dehydrogenase.

Case 3

Idiopathic focal hyperhidrosis.

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Growth Hormone Therapy in Prader Willi

M34
Monday, June 17
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Prader-Willi syndrome (PWS) is a genetic, multisystemic disorder, characterized by short stature, muscular hypotonia, developmental and cognitive impairments, behavioral and psychiatric difficulties and frequently hypogonadism and impaired growth hormone (GH) secretion (1, 2). The prevalence of the syndrome is 1/10,000 to 1/30,000 individuals. PWS is caused by loss of function of paternally expressed, imprinted genes from the chromosome 15 q11-q13 (1, 2). In newborns and infants the syndrome is dominated by muscular hypotonia and nutritional difficulties, which from early childhood typically is replaced by hyperphagia often leading to progressive obesity if a strict diet and regular exercise is not implemented. With increasing age the behavioral and psychological problems increase while the muscular hypotonia improves (1, 2). The signs and symptoms of PWS indicate a hypothalamic-pituitary dysfunction, but a structural lesion in this area has not yet been fully identified.

Short stature, muscular hypotonia, altered body composition with more body fat than lean body mass and low energy expenditure resembles features seen in GH deficiency without PWS. The aetiology of impaired GH secretion in PWS is not known and the often present obesity complicates the evaluation of GH stimulation tests. The GH response to stimulation tests varies in all ages, but serum levels of IGF-I are reduced in the majority (3, 4).

BARRIERS TO OPTIMAL PRACTICE

- PWS is rare limiting the knowledge and understanding of this condition
- A simple definition of clinical outcome and non-responsiveness of GH therapy is difficult
- Fear of side effects

LEARNING OBJECTIVES

As a result of participating in this session learners should be able to:

- Feel confident establishing GH treatment in PWS
- Manage GH treatment in PWS
- Identify patients at risk of developing side effects

SUCCINCT REVIEW- STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Strategies for Diagnosis of GH Deficiency in PWS

More than 50% of infants and children with PWS are or will become GH deficient as evaluated from routine testing (3, 4). GH testing in children with PWS is generally not recommended, but is requested for reimbursement in some countries. In studies reporting the results from GH testing in adults with PWS, GH deficiency was demonstrated in 50% or more (5). However, all available studies suggest that some degree of insufficient GH secretion is intrinsic in PWS and it can be argued if GH stimulation tests are clinically indicated. In both infants, children and adults with PWS IGF-I should be analyzed as part of the evaluation for GH deficiency.

Considerations Before Starting GH Treatment in PWS

The major contraindications for GH treatment

are active cancer, proliferative retinopathy, severe obesity and uncontrolled diabetes and these should of cause also be considered before starting GH treatment in PWS. There are however a number of additional issues in PWS that has to be taken into account.

Concerns were raised after case reports of sudden deaths during GH treatment in children with PWS(6, 7), but it was later shown that the rate of death in children with PWS with or without GH treatment did not differ. Children and adults with PWS have a high incidence of central apnoea and obstructive apnoea (8, 9). GH treatment can theoretically lead to lymphoid tissue growth in children. Therefore, polysomnography should be performed before starting GH treatment in children with PWS and GH treatment not started during an acute respiratory infection. Data regarding GH treatment and sleep apnoea is not available in adults with PWS.

Scoliosis occurs in 30-80% with PWS, and GH treatment has not been shown to affect neither incidence nor rate of progression (10, 11). Therefore, scoliosis is not a contraindication, but because of the high prevalence regular x-ray controls are recommended.

Central adrenal insufficiency has recently been hypothesized to be responsible for increased risk of sudden death in PWS (12). Available data indicate that some degree of central adrenal insufficiency may be part of PWS phenotype, although clinically relevant adrenal failure in PWS appears to be rare (13, 14). GH accelerates the shift from active cortisol to the inactive cortisone and adrenal insufficiency and hydrocortisone treatment during GH treatment should be considered when clinically indicated.

Patients with PWS are more insulin sensitive than patients with simple obesity. Physiologically GH treatment will raise insulin and glucose levels increasing the risk for type 2 diabetes, especially in obese patients and in patients with heredity for diabetes (15). It is therefore recommended that glucose and HbA1C are analyzed regularly during GH treatment in all ages.

When and How to Start GH Treatment

Observational studies have shown that GH treatment is started at a mean age of 7 years, but starting GH treatment in infancy is of benefit. However, the optimal age at which to begin GH treatment is controversial and needs to be further investigated. This also applies when deciding whether or not all adults with PWS should be treated with GH.

Infants and children. A GH dose of 1.0 mg/m^2/day has been used in clinical trials (16). The dose should be titrated according to levels of IGF-I, which are recommended to be between 0 to 2 SD scores for age-matched controls. However, in most children with PWS, GH treatment generates IGF-I levels >2SD scores but with a stable IGF-I to IGF binding protein-3 ratio, suggesting that bioactive IGF-I is not increased. IGF-I levels>3 SD scores necessitates adjustment of the GH dose.

Adults. GH doses between 0.2 and 1.6 mg have been used in studies in adults with PWS (5). In the individual patient a dose resulting in IGF-I values between 0 to +2 SD scores for age-matched controls is recommended.

Monitoring and Clinical Outcome

As in other conditions with GH insufficiency the goal of GH replacement in PWS is to normalize growth and optimize metabolism and body composition as well as mental and motor development and quality of life.

Although, tolerability of GH treatment by children and adults with PWS is high the frequently present obesity and the intellectual disability and behavioral problems bring about a number of management issues during GH replacement.

First of all it is important to obtain the patient's and the legal guardian's acceptance and consent of the treatment. This is rarely a problem. Cognitive impairment should not be a barrier or contraindication to GH treatment but in the majority the injection procedure has to be supervised.

Central hypothyroidism occurs in PWS (17) and as GH increases the peripheral conversion of T4 to T3, thyroid function should be followed during GH treatment, especially as any impairment in metabolism will have large consequences in this particular group of patients.

Incomplete sexual development is frequently seen in PWS and clinical and laboratory measurements demonstrate hypogonadism in the majority. Central and peripheral factors are involved in both genders with primary gonadal dysfunction being the major contributor whereas severe gonadotropin deficiency is rare (18, 19). It is likely that both genders would benefit from treatment with sex-steroids. In relation to GH treatment it is important to remember that oestrogen has a negative and testosterone might have a positive effect on IGF-I generation which should be considered if these are introduced during GH treatment.

Responses to GH vary according to age, pubertal status, degree of growth retardation and duration of therapy. In children with PWS a successful first year response to GH treatment includes a delta height SD score >3 cm, a first year height velocity increment of ≥3 cm/year or a height velocity SD score≥+1. There are in addition limited reports of positive effects on cognitive and motor development.

In adults BMI, waist and hip circumference and bio impedance give useful information in the routine clinical setting, while more detailed analysis can be obtained with Dual Energy X-ray Absorptiometry (DXA) scanning. For monitoring GH's psycho-social and physical effects no feasible tests have yet been identified, but some studies have shown an improvement in quality of life and physical performance. In adults a successful treatment response is difficult to define in a simple way but an unchanged or improved body composition is positive.

For risk of respiratory problem, risk of deterioration of scoliosis and the risk of diabetes please see above.

MAIN CONCLUSIONS

Strict diet and regular physical exercise are cornerstone treatments, also during GH treatment. GH treatment should be considered in PWS patients with a genetically confirmed diagnosis. Cognitive impairment is not a barrier to treatment. Exclusions to GH treatment are severe obesity, uncontrolled diabetes mellitus, proliferative retinopathy, untreated severe obstructive sleep apnoea and active cancer. GH treatment normalizes skeletal growth and improves body composition. GH treatment in PWS is safe but glucose metabolism and changes in respiration must be evaluated continuously. Treatment should be continued as long as benefits outweigh the risks.

CASES WITH QUESTIONS

28 year old man (methylation positive). He was born by Caesarean section and weighted 2001 g and was 50 cm long, cryptorchid testes. The first years of life was complicated by muscular hypotonia and feeding problems. During early childhood the appetite increased but BMI was normal to slightly overweight. Fortunately the family proved rather resourceful and investigated a lot of time and effort in following the recommendations given by the multidisciplinary team. During childhood it was also noticed that he had scoliosis. Cognitive and motor development were delayed and impaired and the patient went to a special educational class. Growth was slow and insufficient and at the age of 10 the patient started on GH treatment (0.33 mg/kg/day). He managed the injections himself and hardly missed any of them. The GH dose was gradually increased and during the following years he grew 6-12 cm/year. Weight was stable (+/- 0SD) and no adverse effects occurred. The scoliosis was checked regularly and it was noticed to increase.

Question 1.
Is he a good candidate for GH treatment? Should GH treatment been considered earlier? Before starting GH treatment are there other investigations to be considered? How should GH treatment be monitored?

At the age of 11 years the patient underwent an uncomplicated orchiopexy. However, the post-operative period was complicated by aggressive behavior and temper outbursts. At the age of 13 years he had developed pubertal signs: hairiness stadium 3, genital development stadium 2.

At the age of 16 years he grew 2.2 cm/year and the GH dose was increased. The scoliosis was causing symptoms and had progressed

significantly and the patient was operated (fixation). The operation went well but again the patient got aggressive for a long period postoperatively. During the following years the patient's mood fluctuated. He refused blood tests to be taken and he requested to manage the GH injections himself without help.

A transition meeting between the pediatrician and the adult endocrinologist was organized when the patient was 18 years old. He had reached his final height and his parents asked if further GH treatment was necessary. It was agreed that a GH stimulation test should be performed before he was referred to the endocrinologist.

At the age of 19 years the patient came for the first visit with the adult endocrinologist. For several reasons a GH stimulation test had not been performed. The patient was feeling fine. He was in the last year of "high school" and was living with his parents. His height was 172 cm, weight 64.6 kg, BMI 21.6 kg/m2, fat mass 16 kg (24%). He was on 1.8 mg GH/day. IGF-I was 830 µg/L (160-420). HbA1C was normal.

Question 2.
What do we do now?
After some discussions and arguing GH treatment was discontinued and after two month ITT was performed. Peak GH was 2.97 µg/L (glucose nadir 1.7 mmol/L). IGF-I was 86 µg/L (-3.2 SDS)

Question 3.
Would you resume GH treatment?
The patient restarted on GH treatment. Routine visits every year to the endocrinologist were without any remarks, and physical condition stable. However, he had large fluctuations in his mood that he was seeing a psychiatrist for.

At 24 years of age the patient moved to a group home and got a job in a day care for dogs, where he is still working. He is most of the time pleased with life but has reoccurring periods with bad mood and aggressiveness. He is on a firm diet and besides the exercise he gets by working he also swims and dances. Weight is stable. He is on a GH dose of 0.6 mmol/day and he is injecting it under supervision.
At latest visit weight was 69.5 kg, BMI 23.2 kg/m2.
IGF-I was normal (298 µg/L (150-390)), Testosterone low (5.4 nmol/L (10-30)), LH 1.9 U/L, FSH 7.6 U/L
HbA1C 30 mmol/mol (27-42), total cholesterol 4.6 mmol/L, HDL cholesterol 1.4 mmol/L, LDL cholesterol 3.2 mmol/L

Question 4.
How should GH treatment be monitored? For how long should GH treatment be continued? Any other lab tests to be considered?

DISCUSSION OF CASES AND ANSWERS

1. This patient is a good candidate for GH treatment. Growth was slow and he responded very well to GH treatment. The scoliosis although increasing is not a contraindication. Studies indicate that it is of benefit to start GH treatment in infancy. Monitoring of height, weight, BMI, body composition, IGF-I (IGFBP-3), glucose metabolism, lipids, TSH, free T4, Cortisol, pubertal status, spine X-ray and side effect is recommended every 6-12 months. Polysomnography should be performed before starting GH treatment and during respiratory infections.
2. The patient has to discontinue GH treatment and a GH stimulation test performed.
3. He should continue. He fulfills the criteria for GH treatment in adults and has no contraindications. It has to be agreed that blood tests are taken as well as supervision of the injections if he wants to continue.
4. Monitoring of weight, BMI, body composition (bio impedance), IGF-I (IGFBP-3), glucose metabolism, lipids, TSH, free T4, Cortisol, FSH, LH. Sex-steroids and side effect is recommended every 12 months. DEXA-scan every 2-5 year, when indicated. Polysomnography when clinically indicated. GH treatment should be continued as long as benefits outweigh.

In this case the patient had started treatment with risperidon causing a rise in prolactin (84

μg/L) and a decrease in testosterone.

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Nutraceuticals: Sorting Fact From Fantasy

M8
Saturday, June 15
3:00–3:45 PM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Clinical endocrinologists are frequently faced with a patient encounter in which dietary supplements (DS) and nutraceuticals (DSN) are used. The major driver for the DSN use is to optimize health but other factors include notions of self-healing, fear of pharmaceuticals, and purported benefits of natural compounds. Though many DSN have medical indications grounded in scientific substantiation, the majority of health-related claims are based on weak or no clinical evidence. This pitfall in the widespread consumption of DSN is compounded by adverse interactions with medications, unknown risks, ever-rising costs, and an unfortunate shortage of physicians with formal training in nutritional medicine who can offer expert and objective opinions to patients.

BARRIERS TO OPTIMAL PRACTICE

In general, clinical endocrinologists have not received formal training in nutritional medicine and therefore continuing medical education programs in various aspects of nutrition are needed. One important area of nutritional medicine for continuing medical education involves DSN and the impact on endocrine, metabolic, and nutritional disorders.

LEARNING OBJECTIVES

As a result of participating in the session, learners should be able to:

- Understand the emerging role of DSN as confounders in routine physician-patient encounters and
- Understand the important evidence based role some DSN play in specific endocrine, metabolic, and nutritional disorders.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

A DS is defined by the Dietary Supplement Health and Education Act of 1994 as a vitamin, mineral, herb, phytochemical, amino acid, glandular, dietary substance that increases total dietary intake, or derivative, and is not a food in its natural form, nor is it a meal substitute. A nutraceuticals is simply a highly concentrated form of a DS. A functional food is a natural food with nutrients that confer a physiological effect beyond energy or protein provision. An example of a functional food, dietary supplement, and nutraceuticals would be soybean, soy protein, and ipriflavone, respectively. Alternative medicine is a type of healthcare delivery system that incorporates unproven therapies (i.e., those without sufficient levels of scientific substantiation), methods not taught in US medical schools, and/or interventions that target complaints without diagnoses. Important issues surrounding the use of DSN include: balancing unproven risks with unproven benefits; adulteration of commercial products; errors in labeling, interactions with other DSN, medications, and foods; being part of a larger alternative care healthcare paradigm with possible profiteering and quackery by a provider and covert use of other DSN or even pharmaceuticals. Nevertheless, there is still an imperative to respect a patient's rights and autonomy with decision-making. Therefore, when a DSN discussion evolves, effective

communication is paramount. There are four types of DSN clinical encounters: (1) routine – ask about all nonprescribed medications, supplements or remedies; examine labels, look up information, and advise based on the evidence; (2) second opinion regarding a specific DSN – express your personal opinion after reviewing the data and objectively assessing risks and benefits, and describing potential interactions in layperson terms; (3) incidental discovery – address the specific issues for that particular DSN when the issue arises; and (4) confrontational – where the patient and physician clearly differ in opinion regarding the role of certain DSN or even alternative care in general; here, clearly state your position, establish effective dialogue, and if unsuccessful, consider concluding the encounter.

Cardiometabolic targets for DSN are also discussed with respect to insulin resistance and type-2 diabetes, hypertension, obesity, dyslipidemia, and atherosclerosis and vascular biology. Specific DSN mentioned are chromium, vanadium, magnesium, carnitine, taurine, b-complex vitamins, alpha-lipoic acid, fiber, omega-3 polyunsaturated fatty acids, probiotics, soy, and various botanicals such as cinnamon and those containing polyphenols.

MAIN CONCLUSIONS

The inappropriate use of DSN is prevalent but many patients can benefit from compassionate, objective, and expert care. Physician nutrition education is critical to improve healthcare delivery and familiarity with DSN is an integral component to this approach.

DISCUSSION OF CASES WITH QUESTIONS AND ANSWERS

The patient is a 30 year-old woman referred for evaluation of "brain fog". Two years earlier she had weakness and fatigue, weight gain, "not herself", and saw her primary doctor. She was found to have multiple endocrine problems and treated with thyroid, adrenal, and pituitary hormones. She is still not better and now complains of swelling also. She has relocated to New York City and was told by a friend to see an endocrinologist.

She brings with her an extensive notebook of detailed medical records. In the thyroid section and prior to any intervention with thyroid extract, she had a normal TSH, total and free T4, and anti-TPO and –TG, but with a low total T3 (normal free T3) and elevated reverse T3. Several months after treatment, her TSH was suppressed. In the adrenal section, she had an extensive biochemical evaluation of serum and urine steroids and metabolites, all essentially normal with the exception of a mildly low DHEA. She reports that she was treated with intravenous "cortisone" and DHEA pills but these were stopped after a few weeks and she was switched to prednisone by mouth (5 mg a day) along with another "adrenal supplement". In the pituitary section, she had an MRI report that was normal and baseline biochemical profiling for prolactin, GH, and IGF-1 were normal. Yet, the patient reports that she was treated with GH injections for a few weeks. She also reports she takes bromocriptine and her current prl was < 1. In the "supplements" section there were many pages of listings of over 20 different supplements that periodically varied, including CoQ10, B-complex, C, D, carnitine, chromium, thyroid preparations [containing tyrosine and kelp], adrenal preparations [containing vitamins], fish oil, and various herbs.

What other information would you want and how would you ask for it?

I generally begin with the original complaint, drilling down to determine whether there was some other true organic condition that may have been missed. I use open-ended questions first and then specific closed-ended questions about each organ system being addressed. It is important to establish whether the patient truly believes she improved with these interventions as most have not, or even became worse, and then there is an avenue to pursue to change the therapeutic paradigm.

How would you direct the exam?

I would focus on potential organic disease states that may have been missed as well as potential DSN toxicities.

What biochemical tests would help you?

These would be limited to suspected potential underlying organic disorders and potential toxicity states or adverse reactions to the therapies started.

How would you approach the therapeutic component of the encounter?

First, I would clearly state that her initial clinical data provided did not support any of the endocrine diagnoses that were being treated, and that since she wasn't improving anyway, and that they may be harmful, that we should discuss ways to taper off the drugs and DSN. Unless there is an immediate threat, I generally do this gradually earning the patient's trust and confidence in my care. I deliberately try not to reveal my frustrations. I would go through her list of supplements and discuss/indicate which must be stopped due to potential harm, which are optional, and which she should continue.

This particular patient was able to taper off the thyroid extract, bromocriptine, and prednisone with gradual down-titration of dosing, lab monitoring, and lots of verbal discussion. She was also able to stop all of her unnecessary supplements and is back at work at "90%" of her usual healthy state.

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Multiple Endocrine Neoplasia Type 1 (MEN1): Update and Case Presentation

M19
Sunday, June 16
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Multiple Endocrine Neoplasia type 1 (MEN1) is characterized by the occurrence of parathyroid, pancreatic islet and anterior pituitary tumors *(Table 1)* (1-6). Some patients may also develop carcinoid tumors, adrenocortical tumors, facial angiofibromas, collagenomas and lipomas (1-6). MEN1 is an autosomal dominant disorder, due to mutations of the tumor suppressor gene *MEN1* which encodes a 610 amino acid protein, Menin (1,7,8). Thus, the finding of *MEN1* in a patient has important implications for family members because first-degree relatives have a 50% risk of developing the disease and can often be identified by *MEN1* mutational analysis (1,3). Patients with MEN1 have a decreased life-expectancy, and the outcomes of current treatments, which are generally similar to that for the respective tumors occurring in non-MEN1 patients, are not as successful because of multiple tumors which may be larger, more aggressive, and resistant to treatment, and the concurrence of metastases (1, 9-12). The prognosis for *MEN1* patients might be improved by pre-symptomatic tumor detection and undertaking treatment specific for MEN1-tumors (12) *(Table 1)*.

BARRIERS TO OPTIMAL PRACTICE

- Non-availability of genetic testing.
- Lack of multi-disciplinary teams, comprising relevant specialists with experience in the diagnosis and treatment of patients with endocrine tumors.

LEARNING OBJECTIVES

To identify:

- Who should be tested for *MEN1* mutations?
- When should testing for *MEN1* mutations be undertaken?
- What approach should be undertaken for *MEN1* tumor screening?

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT STRATEGIES FOR DIAGNOSIS AND SCREENING FOR TUMORS

MEN1 Mutational Analysis in Clinical Practice

MEN1 mutations are diverse in their types and are scattered throughout the 1830-bp coding region of the *MEN1* gene with no evidence for clustering (1,7). Correlations between the *MEN1* mutations and the clinical manifestations of the disorder appear to be absent (1,7). More than 10% of the *MEN1* mutations arise de novo and may be transmitted to subsequent generations (1,7). It is also important to note that between 5% and 10% of *MEN1* patients may not harbor mutations in the coding region of the *MEN1* gene, and that these individuals may have mutations in the promoter or untranslated regions, which remain to be investigated (1,7). Tumors from *MEN1* patients and non-MEN1 patients have been observed to harbor the germ line mutation together with a somatic loss of heterozygosity (LOH) involving chromosome 11q13, as expected from Knudson's model and the proposed role of the *MEN1* gene as a tumor suppressor (1,7).

MEN1 mutational analysis is helpful in clinical practice in several ways *(Table 2)* that include: 1) confirmation of the clinical diagnosis; 2) identification of family members

TABLE 1: Multiple Endocrine Neoplasia (MEN) Syndromes and Their Characteristic Tumors and Associated Genetic Abnormalities

Type (Chromosome Location)	Tumors (estimated penetrance)	Gene; Most frequently mutated codons
MEN1 (11q13)	Parathyroid adenoma (90%)	*MEN1*
	Entero-pancreatic tumor (30-70%)	83/84, 4-bp del (≈4%)
	- Gastrinoma (40%)	119, 3-bp del (≈3%)
	- Insulinoma (10%)	209-211, 4-bp del (≈8%)
	- Non-functioning & PPoma (20-55%)	418, 3-bp del (≈4%)
	- Glucagonoma (<1%)	514-516, del or ins (≈7%)
	- VIPoma (<1%)	Intron 4 ss, (≈10%)
	Pituitary adenoma (30-40%)	
	- Prolactinoma (20%)	
	- Somatotrophinoma (10%)	
	- Corticotrophinoma (<5%)	
	- Non-functioning (<5%)	
	Associated Tumors/	
	- Adrenal cortical tumor (40%)	
	- Phaeochromocytoma (<1%)	
	- Brochopulmonary NET (2%)	
	- Thymic NET (2%)	
	- Gastric NET (10%)	
	- Lipomas (30%)	
	- Angiofibromas (85%)	
	- Collagenomas (70%)	
	- Meningiomas (8%)	
MEN2 (10 cen-10q11.2)		
MEN2A	MTC (90%)	*RET*
	Phaeochromocytoma (50%)	634, missense
	Parathyroid adenoma (20-30%)	e.g. Cys®Arg (~85%)
MTC only	MTC (100%)	*RET*
		618, missense (>50%)
MEN2B (also known as MEN3)	MTC (>90%)	*RET*
	Phaeochromocytoma (40-50%)	918, Met®Thr (>95%)
	Associated abnormalities (40-50%)	
	Mucosal neuromas	
	Marfanoid habitus	
	Medullated corneal nerve fibres	
	Megacolon	
MEN4 (12p13)	Parathyroid adenoma*	*CDKN1B*
	Pituitary adenoma*	No common mutations identified to date
	Reproduction organ tumors* (e.g. testicular cancer, neuroendocrine cervical carcinoma)	
	?Adrenal + renal tumors*	

*Autosomal-dominant inheritances of the MEN syndromes have been established. del, deletion; ins, insertion; PPoma, pancreatic polypeptide–secreting tumor; VIPoma, vasoactive intestinal polypeptide–secreting tumor; MTC, Medullary Thyroid Cancer, * insufficient numbers reported to provide prevalence information. Reproduced from Thakker RV et al (2012). J Clin Endocrinol Metab 97: 2990-3011.*

who harbor the *MEN1* mutation and require screening for tumor detection and early/appropriate treatment; and 3) identification of the 50% of family members who do not harbor the familial germ line *MEN1* mutation and can therefore be reassured and alleviated of the anxiety burden of developing future tumors (1,2,8). This latter aspect cannot be over-emphasized as it helps to reduce the cost to the individuals and their children, and also to the health services in not having to undertake unnecessary biochemical and radiological investigations. Thus, *MEN1* mutational analysis can be useful in clinical practice.

MEN1 mutational analysis should be undertaken *(Table 2)* in: 1) an index case with two or more *MEN1*-associated endocrine tumors (i.e. parathyroid, pancreatic or pituitary tumors); 2) asymptomatic first degree relatives of a known *MEN1* mutation carrier; 3) a first-degree relative of an *MEN1* mutation carrier expressing familial MEN1 (i.e. having symptoms, signs, biochemical or radiological evidence for one or more MEN1-associated tumors); or 4) in patients with suspicious or atypical MEN1, which includes individuals with parathyroid adenomas occurring before the age of 30 years or multigland parathyroid disease, gastrinoma or multiple pancreatic neuroendocrine tumors (NETs) at any age, or individuals who have two or more MEN1-associated tumors that are not part of the classical triad of parathyroid, pancreatic islet and anterior pituitary tumors (e.g. parathyroid tumor plus adrenal tumor) (1,2,7,8).

Such mutational analysis may be undertaken in children within the first decade because children with MEN1-tumors have been reported by the age of 10 years, and appropriate intervention in the form of biochemical testing or treatment or both has been considered (1,13). For example, the earliest reported age of onset for a MEN1-associated pituitary tumor, parathyroid tumor, insulinoma and nonfunctioning pancreatic NET >2cm in size, are 5, 8, 8 and 12 years, respectively (1,2,3). Further, one study of 12 children under the age of 20 years from MEN1 families has reported that >40% of children will have developed one or more MEN1-associated tumors (13). These studies suggest that that early identification of at risk individuals through mutation testing may be beneficial. Thus, a DNA test identifying an individual, who may be an asymptomatic relative of a patient with MEN1, as a mutant gene carrier is likely to lead to earlier and more frequent biochemical and radiologic screening rather than to immediate medical or surgical treatment *(Figure 1)* (1,2,3). In contrast, those relatives who do not harbor the *MEN1* mutation have their risk of developing MEN1-associated endocrine tumors markedly decreased from 1 in 2 for an autosomal dominant disorder, to that of the general population, thereby freeing these

TABLE 2: Suggested approach for *MEN1* mutation analysis in a clinical setting

MEN1 Mutational Analysis
Value in Clinical Setting: • Aid in confirming the diagnosis • Identify mutation carriers in a family for screening and development of tumors, thereby facilitating early treatment • Identify the 50% of family members who do not harbor the *MEN1* mutation, thereby alleviating the anxiety and burden of disease from them and their progeny
Who should be tested? *In an Index case:* • meeting the clinical criteria for MEN1 (i.e. two or more MEN1-associated tumors or a diagnosis of familial MEN1) • suspicious (i.e. multiple parathyroid adenomas before the age of 40 years; recurrent hyperparathyroidism; gastrinoma or multiple pancreatic NETs at any age) or atypical for MEN1 (i.e. development of two non-classical MEN1-associated tumors, e.g. parathyroid and adrenal tumor) *A first degree relative of family member with known MEN1 mutation:* • Asymptomatic first degree relative • First degree relative with familial MEN1 (i.e. one MEN1-associated tumor)
When should testing be undertaken? • As early as possible (e.g. <5 years of age for asymptomatic individuals)
Where should test be performed? • In accredited department/laboratory undertaking DNA testing of *MEN1* gene
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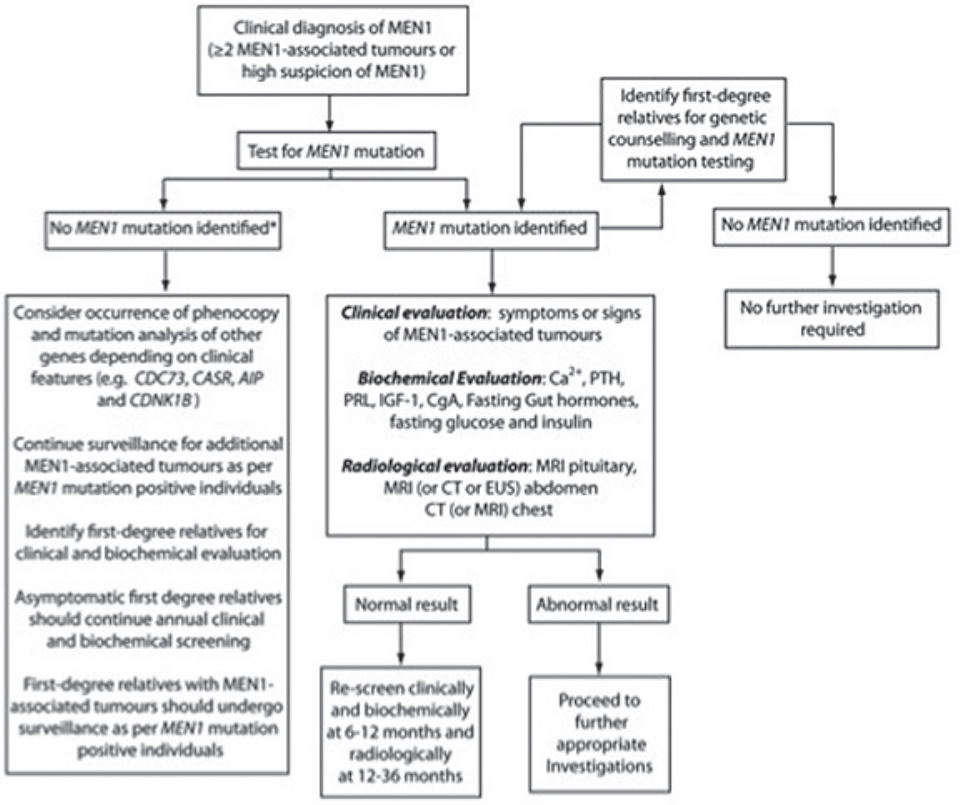
FIGURE 1



An approach to screening in MEN1. Index cases, or individuals in whom there is a high suspicion of clinical MEN1 (e.g. multigland parathyroid disease, parathyroid + adrenal tumor), should be offered genetic counseling and MEN1 mutation testing. Mutation testing should also be offered to those with familial MEN1 (i.e. individual with one MEN1-associated tumor and a first-degree relative with a known MEN1 mutation). The identification of a germline MEN1 mutation should prompt entry into a periodic clinical, biochemical and radiological screening programme. At the same time, first-degree relatives should be identified and offered genetic counselling and MEN1 mutation testing. Individuals who have inherited the MEN1 mutation should enter periodic screening, even if asymptomatic. First-degree relatives who have not inherited the MEN1 mutation require no further follow up and may be alleviated of the anxiety associated with the development of MEN1-associated tumors. For index cases, in whom a MEN1 mutation, which includes testing for partial or whole genome deletions (asterisked), is not identified, additional genetic testing may be required depending on the specific clinical features. This may include examination for mutations in genes associated with familial parathyroid syndromes including CDC73 associated with the Hyperparathyroidism-Jaw tumor syndrome (HPT-JT) and the Calcium Sensing Receptor (CASR) associated with familial benign hypocalciuric hypercalcaemia (FBHH); or cyclin dependent kinase 1B (CDKN1B) and aryl hyrdrocarbon receptor interacting protein (AIP) which are rarely identified in those with clinical MEN1. Up to 10% of kindreds with clinical MEN1 may harbour phenocopies emphasising the importance of accurate genetic evaluation. For MEN1 kindreds in whom no MEN1 mutation is identified a pragmatic approach is to offer clinical, biochemical and radiolical screening to those with clinical manifestations of disease and to offer annual clinical and biochemical screening to asymptomatic first-degree relatives. Abbreviations: Ca2+, Calcium; PTH, parathyroid hormone; PRL, prolactin; IGF-1, insulin-growth-factor-1; CgA, chromogranin A; MRI magnetic resonance imaging; CT, computer tomography; EUS, endoscopic ultrasound

relatives without the MEN1 mutation from the requirement for further repeated clinical investigations (1,2). Thus, identification of *MEN1* mutations may be of help in the clinical management of patients and their families with this disorder. Finally, *MEN1* mutational analysis in a symptomatic family member (i.e. an individual already showing a clinical manifestation of MEN1), from a family with a known MEN1mutation, has been challenged as being unnecessary to establish the diagnosis of MEN1. However, studies have reported that 5-10% of MEN1 kindreds have the occurrence of phenocopies, which may confound the diagnosis, and therefore MEN1 family members with one MEN1-associated tumor should be offered MEN1 mutation analysis (1,14).

MEN1 germ line mutational analysis should be considered in those presenting at an early age with a single, apparently sporadic MEN1-associated tumor. However, the occurrence of germ line MEN1 mutations in all patients with sporadic, non-familial parathyroid adenomas is 1%, in gastrinomas is 5%, in prolactinoma is 1%, and in foregut carcinoids is 2% (1,2,7). Investigations by studies for germ line *MEN1* mutations in patients developing non-familial (i.e. sporadic) parathyroid tumors below the age of 40 years has found the occurrence of such mutations in only 3 of 36 patients. All 3 of these patients had multi-gland parathyroid disease, whereas the majority (~95%) of the patients without *MEN1* mutations had solitary parathyroid adenomas. *MEN1* mutational testing should be offered to patients who are below 40 years of age and have primary hyperparathyroidism due to multi-gland disease (1). The occurrence rates of germ line *MEN1* mutations in individuals presenting with a single apparent non-familial (i.e. sporadic) pancreatic NET at similarly younger age, has not been established, and at present *MEN1* mutational analysis should also be considered in those with gastrinoma or multiple pancreatic NETs.

SCREENING FOR MEN1 TUMORS

Detection of MEN1 Tumors

Biochemical screening for the development of MEN1 tumors in asymptomatic members of families with MEN1 is likely to be of benefit in as much as earlier diagnosis and treatment of these tumors may help reduce morbidity and mortality (1). Age-related penetrance (i.e., the proportion of gene carriers manifesting symptoms or signs of the disease by a given age) has been ascertained, and the mutation appears to be non-penetrant in those younger than 5 years (1,2,5,15). Thereafter, the mutant *MEN1*gene has a high penetrance, > 50% penetrant by 20 years of age and > 95% by 40 years. Screening for MEN1 tumors is difficult because clinical and biochemical manifestations in members of any one family are not uniformly similar (1,5). Attempts to screen for development of MEN1 tumors in the asymptomatic relatives of an affected individual have depended largely on measuring serum concentrations of calcium, gastrointestinal hormones (e.g. gastrin), prolactin and insulin-like growth factor (IGF-1), as well as on abdominal and pituitary imaging *(Table 3)*. Parathyroid overactivity causing hypercalcemia is almost invariably the first manifestation of the disorder and has become a useful and easy biochemical screening investigation. In addition, hyperprolactinemia, which may be asymptomatic, may represent the first manifestation in ~15% of patients and may thus also be a helpful and an easy biochemical screening investigation. Pancreatic involvement in asymptomatic individuals has been detected by measuring fasting plasma concentrations of gastrin, pancreatic polypeptide, glucagon, and chromogranin A and by abdominal imaging (1).

The current guidelines suggest that individuals at high risk for MEN1 (i.e., mutant gene carriers) undergo biochemical screening *(Figure 1)* at least once per annum and also have baseline pituitary and abdominal imaging (e.g., MRI or CT), which should then be repeated at 1- to 3-year intervals *(Table 3)* (1). Screening should possibly commence in early childhood because the disease has developed in some individuals by the age of 5 years, and it should be repeated throughout life because the disease may not manifest in some individuals until the eighth decade. Screening history and physical examination should be directed toward eliciting symptoms and signs

of hypercalcemia, nephrolithiasis, peptic ulcer disease, neuroglycopenia, hypopituitarism, galactorrhea and amenorrhea in women, acromegaly, Cushing's disease, and visual field loss and the presence of subcutaneous lipomas, angiofibromas, and collagenomas. The current guidelines suggest that biochemical screening should include estimations of serum calcium, PTH, gastrointestinal hormones (e.g., gastrin, insulin with a fasting glucose, glucagon, VIP, and PP), chromogranin A, prolactin, and IGF-1 in all individuals, and more specific endocrine-function tests should be undertaken in individuals who exhibit symptoms or signs suggestive of a clinical syndrome *(Table 3)* (1). Radiologic screening should include an MRI (or CT scanning) of the pancreas, adrenal glands, and pituitary, initially as a baseline and then every 1 to 3 years, as well as imaging for thymic and bronchial carcinoids using CT or MRI every 1-2 years *(Table 3)*.

MAIN CONCLUSIONS

MEN1 is an autosomal dominant disorder characterized by the occurrence of tumors of the parathyroid gland, pancreas, and anterior pituitary gland. In addition, some patients may also develop adrenocortical tumors, foregut carcinoids, lipomas, collagenomas, and facial angiofibromas. The *MEN1* gene, which consists of 10 exons, encodes a 610-amino acid nuclear protein, referred to as Menin, that has roles in transcriptional regulation, genome stability, cell division, and proliferation. The application of *MEN1*mutational analysis, which can identify individuals at high risk for biochemical and radiological screening programs, has helped to target earlier, appropriate interventions (e.g. surgery for non-functioning pancreatic NETs), thereby preventing the later sequalae of the tumors.

CASES WITH QUESTIONS

Case 1

A 32-year-old man was referred with a history of recalcitrant hypercalcemia due to primary hyperparathyroidism that had not been successfully treated by partial parathyroidectomy (3). He had been well until the age of 24 years, when he presented at another center with renal colic and haematuria. He passed several renal stones per urethra, and investigations revealed him to have hypercalcemia with increased plasma PTH concentrations, and hypercalciuria, consistent with a diagnosis of primary hyperparathyroidism. He was referred for surgery; a subtotal parathyroidectomy was performed, and histology revealed the presence of parathyroid hyperplasia. Over

TABLE 3: Suggested Biochemical and Radiological Screening in individuals at high risk of developing MEN1

Tumor	Age to begin (yr)	Biochemical test (plasma or serum) annually	Imaging test (time interval)
Parathyroid	8	Calcium, PTH	None
Pancreatic NETs			
Gastrinoma	20	Gastrin (± gastric pH)	None
Insulinoma	5	Fasting glucose, insulin	None
Other Pancreatic NET	<10	Chromogranin-A; pancreatic polypeptide, glucagon, vasoactive intestinal peptide	MRI, CT, or EUS (annually)
Anterior pituitary	5	Prolactin, IGF-1	MRI (every 3 years)
Adrenal	<10	None unless symptoms or signs of functioning tumor and/or tumor >1cm identified on imaging	MRI or CT (annually with pancreatic imaging)
Thymic and Bronchial carcinoid	15	None	CT or MRI (every 1-2 years)

CT, Computed tomography; MRI, magnetic resonance imaging; EUS, endoscopic ultrasound. Reproduced from Thakker RV et al (2012). J Clin Endocrinol Metab 97: 2990-3011.

the next 8 years, he continued to have renal stones, was observed to remain hypercalcemic with raised plasma PTH concentrations, and was referred for further consultation. A detailed medical history revealed that he did not suffer from dyspepsia, ulcers, diarrhea, neuroglycopenia or impotence. However, his mother had died of pancreatic cancer, and his elder brother had recurrent peptic ulcers and hypercalcemia. Physical examination revealed no abnormalities other than a neck scar and facial angiofibromas. A presumptive diagnosis of familial MEN1 was made and appropriate biochemical and radiological investigations undertaken *(Figure 1* and *Table 3)*. These revealed that in addition to the primary hyperparathyroidism, he had hyperglucagonemia, and a CT scan showed the presence of a pancreatic tumor located in the tail. The recurrent primary hyperparathyroidism was treated by a total parathyroidectomy, and he was given oral calcitriol (1,25 dihydroxy vitamin D3) replacement. He also had a distal pancreatectomy, and histology revealed the pancreatic tumor to immunonstain for chromogranin and glucagon. He has been screened annually *(Table 3)* for the development of MEN1-associated tumors. For the past 17 years he has remained well and normocalcemic and has not suffered from renal stones or recurrence of the pancreatic NET. MEN1 mutational analysis revealed that he and two of his asymptomatic children, a daughter aged 12 years and a son aged 9 years, had a MEN1mutation (3).

Questions:

Is this a typical history for an MEN1 patient?
Will the children get the same tumors as their father?
At what age are they likely to get tumors?
What should the plan be for the children?

DISCUSSION OF CASE AND ANSWERS

The history of this young man is typical of a patient with MEN1. The occurrence of primary hyperparathyroidism in a young individual, especially a male; the involvement of multiple parathyroid glands; the persistence of hypercalcemia following partial parathyroidectomy; and the family history, which is often inadequately ascertained by doctors, are all frequent features in patients with MEN1. The value of thorough investigations for other tumors is also illustrated by this case, as this revealed the presence of a glucagonoma, which does not present in MEN1 patients with the characteristic manifestations of a skin rash (necrolytic migratory erythemia), weight loss, and anemia, but may instead be silent and asymptomatic (2).

The children may not get the same tumors as their father, as there is variability of tumor development within a family, and there is no genotype-phenotype correlations (5,7). The age at which tumors develop is also variable, as there is an age-related penetrance for MEN1 with ~50% of individuals, harboring an *MEN1*mutation, having tumors by age 20 years and >95% by age 40 years (5). In view of this, screening should be undertaken for all the MEN1-associated tumors *(Tables 1* and *3)* in the children and this was undertaken in these children. Two years later, at screening, the youngest daughter, aged 14 years, was found to have developed MEN1-associated tumors (13). She denied symptoms, but detailed questioning revealed she had oligomenorrhea. She was found to have hyperprolactinemia, and MRI of the pituitary gland showed the presence of a microprolactinoma; treatment with cabergoline restored a regular menstrual cycle and normoprolactinemia. She also had mild hypercalcemia with an inappropriately normal plasma PTH concentration, consistent with early primary hyperparathyroidism. In addition, MRI of the abdomen revealed a 2cm mass in the neck of the pancreas, in keeping with a pancreatic NET, although her fasting gut hormones were normal. This suggested that this was a non-functioning pancreatic NET, which has been reported to be the most common cause of death in patients with MEN1 and to be associated with a worse prognosis than that for functioning pancreatic NETs (13). Surgery was therefore undertaken and partial pancreatectomy performed. Histology and immunology revealed features consistent with those of a non-functioning pancreatic NET. She remains well at 3 years

follow-up with normal glucose tolerance (13).

The case histories from this family with MEN1 help to illustrate the importance of undertaking combined genetic analysis with regular screening for tumors *(Figure 1)* by using plasma biochemistry and radiological imaging *(Table 3)* and in potentially reducing the harmful effects of metastatic disease and hormonal over secretion.

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NEURO-ENDOCRINOLOGY

Cushing Disease: Evaluation and Management

M22
Sunday, June 16
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Cushing's disease (CD) is caused by a corticotroph pituitary adenoma that secretes adrenocorticotroph hormone (ACTH) resulting in chronic overproduction of cortisol by the adrenal glands. This chronic state of hypercortisolism is associated with significant morbidity which severely impairs quality of life. (1, 2). The clinical phenotype is characterized by features of the metabolic syndrome (central obesity, diabetes mellitus, dyslipidemia, and hypertension), hirsutism, easy bruisability, muscle weakness, cognitive dysfunction and mood alterations including depression (1, 2). When untreated or insufficiently treated, CD can lead to an increased mortality with cardiovascular disease as leading cause of death (2, 3). Because of the gradual development of symptoms and the overlap in features of the metabolic syndrome, it can take years before the diagnosis is established (4). At present, transsphenoidal adenomectomy is the first choice of treatment for CD and remission rates vary between 60 and 90 % (5). Treatment modalities for patients with persistent or recurrent disease include repeat surgery, radiotherapy, medical therapy and bilateral adrenalectomy (5). Importantly, morbidity of CD is not or only partially reversible in a substantial number of patients which is possibly related to the duration of pre-existing hypercortisolism (2). Therefore, after diagnosis cortisol production should be rapidly normalized with concomitant careful treatment of (cardiovascular) co-morbidity.

BARRIERS TO OPTIMAL PRACTICE

The diagnostic work-up of a patient with (possible) CD can be challenging for several reasons. First, the spectrum of clinical presentation of CD is broad, and it can be difficult to detect mild cases based on clinical symptoms. Second, first-line screening tests to determine endogenous hypercortisolism each have limitations with respect to sensitivity and/or specificity and several confounding factors can influence test results. These screening tests can be false-positive in conditions accompanied by overactivity of the hypothalamic-pituitary-adrenal axis, e.g. psychiatric disorders, and the subsequent differentiation between these so-called pseudo Cushing states and (mild) true CD can require additional testing. Interpretation of test results can further be difficult in patients with a cyclical pattern of cortisol overproduction. If ACTH-dependent hypercortisolism is ultimately established but pituitary imaging is negative, the next challenge is to differentiate a non-visible pituitary adenoma from ectopic ACTH production. With respect to long-term management of CD patients after unsuccessful pituitary surgery, it is very important to prepare a tailor-made treatment strategy where the pros and cons of adjuvant treatment modalities must be weighed in relation to relevant patient characteristics and potential side effects.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to apply and interpret (differential-) diagnostic tests for CD, should be aware of potential pitfalls and confounding factors and should be informed on postoperative treatment modalities for patients with persistent hypercortisolism, in

particular the efficacy and potential side effects of available medical treatment options.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Diagnosis

Considering the heterogeneous clinical presentation of CD and the overlap of part of its symptoms with those of the highly prevalent metabolic syndrome, deciding to initiate diagnostic procedures to establish hypercortisolism can be difficult. In general, it is important to examine whether so-called sensitive symptoms of CD are present as plethora, muscle and skin atrophy, haematomas and striae of recent onset. These symptoms have a higher discriminatory index, although their prevalence is variable. The Endocrine Society Guideline recommends further evaluation in case of: (a) multiple and progressive features; (b) unusual symptoms for age (e.g. hypertension, osteoporosis); (c) an adrenal incidentaloma and (d) a decreasing height percentile and weight gain in children (4). In certain risk populations, e.g. patients with poorly controlled diabetes, obesitas or osteoporosis, a higher incidence of Cushing's syndrome (CS) has been found. Screening for CS in these conditions can be considered but it is not recommended (yet) to perform this on a routine basis (4).

After exclusion of exogenous glucocorticoid exposure, three first-line screening tests are available to identify patients with CS, i.e. 24 h urinary free cortisol excretion (UFC), the overnight 1 mg dexamethasone suppression test (DST) and measurement of midnight salivary cortisol levels.

Urinary free cortisol excretion

UFC is an integrated measure of cortisol secretion during 24 h. Because non-CBG bound cortisol is measured, factors that increase CBG levels, e.g. estrogen use, do not influence UFC values. It is important that a complete 24 urine volume is collected with simultaneous measurement of urinary creatinine levels. UFC can be false-negative in patients with mild or cyclical disease and in patients with renal impairment. Because in patients with CD cortisol production rate can vary from day to day, UFC should be measured in at least two 24 h urine collections. False positive UFC levels can be found after high fluid intake and in conditions accompanied by HPA-axis activation *(Table 1)* (4).

1 mg Dexamethasone suppression test

The 1 mg DST is based on the absence (or decrease) of negative feedback inhibition on ACTH production after administration of low-dose dexamethasone. The recommended cut-off value for post-dexamethasone cortisol levels have been decreased in the past years from 5 μg/dl (140 nmol/l) to 1.8 μg/dl (50 nmol/l), thereby increasing sensitivity but decreasing specificity of the test. Some centers prefer the long (48 h) 2 mg DST because of a higher specificity compared to the 1 mg DST (4). DST can give false-positive results in women using oral contraceptives (estrogen-induced CBG synthesis) and when drugs are used that accelerate dexamethasone metabolism like phenytoin and rifampicin (induction of Cyp 3A4). False-negative results can occur with concomitant use of drugs that impair dexamethasone clearance, e.g. itraconazole and fluoxetine (inhibition of Cyp 3A4) (4).

Midnight salivary cortisol

Measurement of the midnight salivary cortisol (MSC) concentration has recently been emerging as a primary screening test. This test makes use of the loss of cortisol circadian rhythm as occurs in (most) patients with CD. As a result, higher salivary cortisol levels are measured at midnight compared to healthy controls. The variety of used assays has yielded different reference ranges. Overall, sensitivity and specificity range from 92 to 100 %, more or less comparable to the performance of UFC and 1 mg DST (4, 6). Saliva can be collected using a so-called salivette at home which makes it a convenient test. Another advantage is that salivary cortisol levels are not influenced by CBG levels. False-positive results can be caused by blood contamination, a disturbed sleep-wake rhythm (e.g. shift workers) and smoking (4). In addition, age over 60 years and co-morbidity like hypertension and diabetes is associated with

higher salivary cortisol levels (7).

If clinical suspicion is high but first-line screening tests are negative, a cyclical pattern of cortisol overproduction may be present. Repeated measurement of UFC and midnight cortisol levels, rather than DST, and careful follow-up should ultimately establish the diagnosis in these patients. Preliminary data show that measurement of cortisol in scalp hair can reveal episodic cortisol overproduction (8). Depending on the hair length, a retrospective time line of cortisol exposure can be created that may detect peaks in cortisol secretion (8). In patients with mild hypercortisolism and possible presence of other factors that activate the HPA-axis *(Table 1)*, a so-called pseudo Cushing syndrome should be excluded. For this purpose second-line screening tests are used, i.e. measurement of midnight serum cortisol levels and the dexamethasone-CRH test. Similar to salivary cortisol, serum cortisol levels are higher at midnight in patients with CD compared to healthy subjects and patients with pseudo Cushing syndrome. Cut-off values have been proposed for midnight serum cortisol levels sampled when patients are sleeping (1.8 µg/dl, 50 nmol/l) and are awake (7.5 µg/dl, 207 nmol/l) respectively (4). The dexamethasone-CRH test, a 48 h 2 mg DST extended with a CRH test, is based on the fact that patients with CD are still able to mount a pituitary-adrenal response after administration of exogenous CRH despite pre-treatment with dexamethasone. Patients with pseudo Cushing's syndrome, however, are usually unresponsive to CRH stimulation while suppressed by dexamethasone. Although the first exploring study showed a high sensitivity using a post-CRH cortisol cut-off value of 1.4 µg/dl (38 nmol/l), sensitivity values were lower in subsequent studies (4).

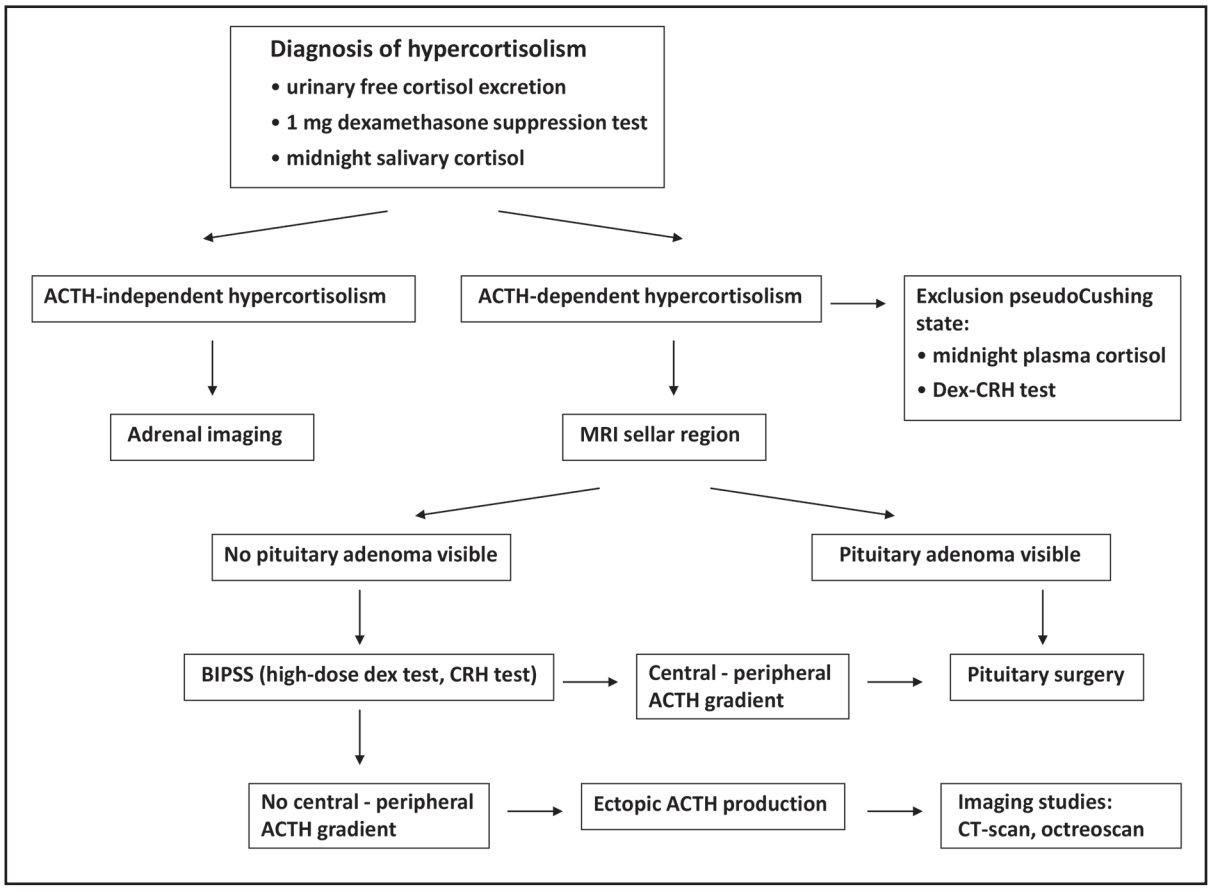
TABLE 1. Conditions Associated with Endogenous Hypercortisolism in the Absence of Cushing's Syndrome

Chronic stress
Chronic disease
Psychiatric disorders, e.g. depression
Chronic alcohol abuse
Alcohol and drugs withdrawal
Malnutrition, anorexia nervosa
Poorly regulated diabetes mellitus
Morbid obesity
Glucocorticoid resistance

After establishing ACTH-dependent hypercortisolism, the next diagnostic step is imaging of the sellar region with gadolinium-enhanced MRI as a pituitary adenoma is the most prevalent cause of CS. However, in approximately 20 % of patients with CD no pituitary adenoma can be visualized. Bilateral inferior petrosal sinus sampling (BIPSS) is the gold standard to differentiate a pituitary cause from ectopic ACTH production in patients with ACTH-dependent hypercortisolism and a negative MRI (1). A central to peripheral ACTH gradient (ratio > 2.0 for basal ACTH levels and ratio > 3.0 for CRF-stimulated ACTH levels) is indicative for a pituitary adenoma as underlying cause (1). BIPSS can show false-negative results in case of insufficient cannulation of the inferior petrosal sinus and false-positive results due to ectopic CRH production and cyclic ectopic ACTH production in a quiescent phase, conditions that both allow for a central to peripheral ACTH gradient. BIPSS is an invasive procedure performed in specialized centers. Dynamic testing with the CRH test and high dose DST can also be used to differentiate a pituitary from an ectopic cause of CS, although both tests have a lower accuracy than BIPSS (1). The concept of these dynamic tests is that most pituitary adenomas retain sensitivity to CRH stimulation and to negative feedback inhibition by high dose dexamethasone in contrast to most causes of ectopic ACTH production. There is, however, a considerable overlap in test results (1). In particular brochial carcinoids can mimick typical responses of a pituitary adenoma with a cortisol response to CRH stimulation and cortisol suppression after high dose dexamethasone administration.

The (differential) diagnostic procedures for CS are summarized in *Figure 1*.

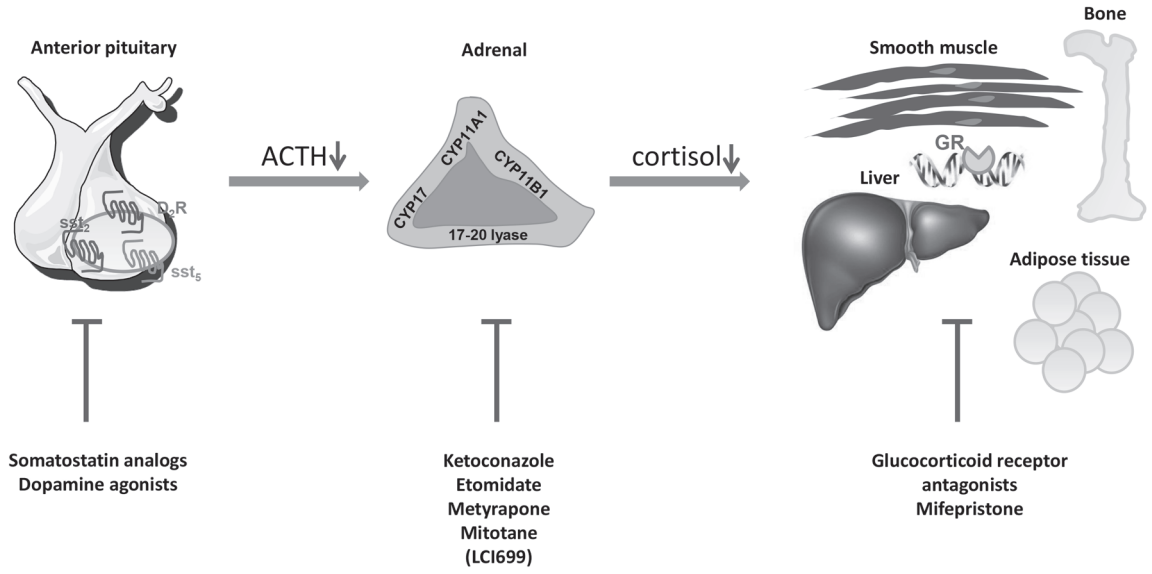
FIGURE 1



Therapy

The first-line treatment of Cushing's disease is transsphenoidal resection of the pituitary adenoma. Reported immediate remission rates for this procedure vary between 60 and 90 % (5). However, in patients with non-visible adenomas and patients with macroadenomas these remission rates are considerably lower. In addition, recurrent CD occurs in up to 20-25 % of patients (5). Thus, in a substantial number of patients additional treatment is indicated considering the morbidity and mortality risks of persistent hypercortisolism. What are the treatment modalities to induce definite remission? Repeat surgery is an option for patients with persistent or recurrent CD, but remission rates are lower with also a higher risk on hypopituitarism (5). Radiotherapy can induce biochemical remission in the majority of patients. However, it can take years for radiotherapy to become effective, leaving patients exposed to the toxic effects of cortisol excess. In addition, 30-40% of patients develop pituitary insufficiency after pituitary irradiation (5). Laparoscopic bilateral adrenalectomy is an option in patients with acute complications of severe hypercortisolism such as acute psychosis or sepsis and in patients who are severely disabled by complications of hypercortisolism and in whom other treatments have proved ineffective (5). After bilateral adrenalectomy direct control of hypercortisolism is obtained but patients need lifelong gluco-and mineralocorticoid replacement therapy with a permanent risk on adrenal insufficiency when precipitating factors are present. Finally, patients with persistent or recurrent CD can be treated with medical therapy (9). Medical treatment can also be indicated in patients with acute complications of hypercortisolism and patients with a high surgical risk (9). Medical therapy can be classified into pituitary-targeted drugs, adrenal-blocking drugs and glucocorticoid receptor antagonists (9) *(see also Figure 2)*.

FIGURE 2



Reproduced from Reference 9.

Pituitary-targeted drugs

Dopamine and somatostatin receptors have been identified as targets for pituitary-targeted drug therapy (9). Approximately 80% of ACTH-secreting pituitary adenomas expresses the dopamine receptor subtype 2 (DA_2) (9). Several studies show that the DA_2 agonist cabergoline, at doses between 1 and 7 mg/week, can normalize cortisol production by 25-40% of patients with CD (9, 10). Treatment escapes can occur, though, at the long-term.

Of the 5 known somatostatin receptor subtypes (sst), corticotroph pituitary adenomas predominantly express sst5, whereas sst_2 expression is low due to down-regulating effects of high cortisol levels (9). Pasireotide is a somatostatin analog with affinity for sst1, sst_2, sst_3 and sst_5. Recently, a phase III trial was published in which 162 patients with CD were treated with pasireotide in a dose of 600 or 900 µg s.c. twice daily (11). UFC levels decreased by more than 50 % in about half the patients, and normalized in up to 26% of patients (11). Hyperglycemia is an important side effect of pasireotide, induced by inhibition of postprandial incretin release. Glycemic regulation should be assessed and, if necessary, optimized, before pasireotide is started and glucose levels should be monitored during pasireotide treatment. Pasireotide was recently approved in Europe and the United States for treatment of patients with CD after unsuccessful surgery or for whom surgery is not an option.

Adrenal blocking drugs

Adrenal blocking drugs directly suppress the production of cortisol by inhibition of steroidogenic enzymes in the adrenal cortex (12). Although these drugs have been used for decades they are not officially approved for the treatment of CD. Ketoconazole and metyrapone are most widely used to inhibit steroidogenesis in patients with CD. Ketoconazole, originally an antimycotic drug, is effective as monotherapy at doses between 600 and 1200 mg per day. Gastrointestinal complaints and hepatotoxicity are the most important side effects (12).

Metyrapone selectively inhibits the enzyme 11-β-hydroxylase and suppresses cortisol production at doses between 0.5 and 4.5 g / day. The strong cortisol-lowering effect of metyrapone can result in an increase

in ACTH secretion which in turn can lead to an increased production of adrenal androgens (hirsutism) and mineralocorticoids (hypertension and edema) (12).

Mitotane has, in addition to its inhibitory effect on steroidogenic enzymes, also selectively toxic effects on the adrenal cortex and is therefore most frequently used in the treatment of adrenocortical carcinoma (12). Etomidate, finally, is an anesthetic drug with a strong inhibitory effect on cortisol synthesis and can be used in patients with severe complications of CD, e.g. sepsis, in an intensive care setting (12).

Glucocorticoid receptor antagonists

Mifepristone is an antagonist of the glucocorticoid receptor and blocks the effects of cortisol at tissue level (9). Mifepristone has a rapid onset of action which can be useful in patients with acute complications of hypercortisolism, e.g. psychosis (9). In a recent open-label trial (the SEISMIC study), 50 patients with CS (mainly pituitary-dependent) were treated for six months with mifepristone in a dose range of 200-1200 mg/day (13). This treatment resulted in a significant improvement of clinical symptoms and glycemic control. Mifepristone has, however, some drawbacks that may limit long-term treatment. First, no biochemical parameter is available to adjust mifepristone dose and patients are at risk to develop clinical adrenal insufficiency if the dose is (relatively) too high. Second, ACTH and cortisol levels can strongly increase during mifepristone treatment resulting in (worsening of) mineralocorticoid effects. Finally, mifepristone can induce endometrial hyperplasia and in female patients periodic monitoring of the endometrium is necessary during prolonged mifepristone treatment. Mifepristone was recently approved in the United States for treatment of patients with CS and hyperglycemia who are not eligible for surgery or in whom surgery is not successful.

Combination therapy

In most patients with moderate to severe hypercortisolism biochemical remission can only be achieved by medical combination therapy. Since the majority of corticotroph adenomas expresses DA_2 and sst5 there is a rationale to combine DA_2 and sst5 targeting compounds which may have additive or synergistic effects (9). This concept has been studied in a recently published multicenter trial in which patients with CD were treated in a stepwise approach with pasireotide, cabergoline and ketoconazole (14). If UFC levels did not normalize after 4 weeks of pasireotide monotherapy, cabergoline and eventually ketoconazole were added resulting in biochemical remission in almost 90 % of patients within three months (14). The severity of hypercortisolism at baseline determined the number of drugs needed to control cortisol production (14).

Combining drugs may allow for lower doses, concomitantly reducing the risk of developing side effects. One study e.g., shows that the combination of cabergoline and low-dose ketoconazole (200-400 mg instead of 800-1200 mg as monotherapy) can be effective (15).

Finally, in a recently published study, patients with life-threatening complications of severe hypercortisolism were treated with a combination of three adrenal blocking agents, i.e. ketoconazole, metyrapone and mitotane (16). This combination induced a rapid normalization of cortisol production and was well tolerated. Aggressive cortisol-lowering therapy may therefore be an alternative to bilateral adrenalectomy in patients with severe complicated CD.

MAIN CONCLUSIONS

CD is associated with severe morbidity and, if not successfully treated, an increased mortality. It can be difficult to diagnose CD in patients with mild or cyclical disease. The primary treatment for CD is a transsphenoidal adenomectomy. Medical therapy, whether or not combined with radiotherapy is indicated in patients who are not operated successfully or are not eligible for surgery. Available medical treatment options include pituitary-targeted drugs, adrenal-blocking drugs and a glucocorticoid receptor antagonist. The choice of (combinations of) drugs should be tailored based on patient-related characteristics (severity of hypercortisolism, acute complications etc.) and drug characteristics (efficacy, onset of action, potential side effects, etc.). Apart from correction of hypercortisolism, cardiovascular

risk factors should carefully be treated given the cardiovascular morbidity in CD.

CASES WITH QUESTIONS

A 45-year old female is evaluated for possible Cushing's syndrome (CS). Her weight had increased with 6 kg in the past 18 months with development of central obesity. She reports muscle weakness and difficulty in climbing up stairs. Amenorrhoea exists since 1 year. Her medical history includes hypertension, treated with nifedipine, and depression, possible as part of a bipolar disorder, for which she is treated with paroxetine and carbamazepine.

Physical examination reveals a mild Cushingoid appearance with moderate facial plethora and central obesity and some degree of muscle atrophy, no hirsutism and easy bruisability are present. BMI is 28 kg/m2 and blood pressure is 140/90 mmHg.

Endocrine evaluation for hypercortisolism showed the following results:

- Urinary free cortisol excretion (2 collections): 0.9 and 1.6 x upper limit of normal
- 1 mg dexamethasone suppression test: cortisol 5.8 µg/dl (160 nmol/l)
- ACTH (8.00 a.m.) 55 pg/ml (12 pmol/l)

1. Which of the used medications could have influenced test results?

a. nifedipine, paroxetine and carbamazepine
b. paroxetine and carbamazepine
c. carbamazepine
d. none of the above mentioned medication

2. Which test could be used to exclude a pseudo Cushing syndrome?

a. midnight salivary and/or serum cortisol concentration
b. CRH-test
c. dexamethasone-CRH test
d. none of the above mentioned tests

Additional testing showed a midnight salivary cortisol level of 0.87 µg/dl (24 nmol/l) and a midnight plasma cortisol level of 10.3 µg/dl (284 nmol/l) suggesting CS rather than pseudo CS. Subsequently an MRI of the sellar region was performed but no pituitary adenoma could be identified.

3. What would be the next diagnostic step?

a. CT-scan of thorax and abdomen
b. ^{111}In-pentetreotide scintigraphy
c. Bilateral inferior petrosal sinus sampling (BIPSS)
d. FDG-PET scan

An uncomplicated BIPSS procedure was performed and demonstrated a central to peripheral ACTH ratio of 1.8 under basal conditions and of 4.2 after CRH stimulation.

4. These results:

a. indicate pituitary-dependent CS
b. indicate ectopic ACTH production
c. indicate catheter malposition
d. are inconclusive

Subsequently the patient underwent a transsphenoidal exploration of the pituitary. A small lesion in the midline region was resected. Pathological examination shows a basophilic adenoma with a positive ACTH staining. A postoperative morning cortisol concentration showed a value of 4.7 µg/dl (130 nmol/l).

5. Would this patient be at risk for recurrent CD?

DISCUSSION OF CASES AND ANSWERS

1. *Correct answer:* C. Carbamazepine induces hepatic clearance of dexamethasone via CYP 3A4 resulting in lower dexamethasone concentrations which can lead to insufficient suppression of normal corticotroph cells and a false-positive test result.
2. *Correct answer:* A. Midnight salivary and/or serum cortisol levels can be used to differentiate between CS and pseudo CS in this patient. The dexamethasone-CRH test can also be used for this purpose but can be disturbed by carbamazepine.
3. *Correct answer:* C. When MRI shows no pituitary lesion in patients with ACTH-dependent hypercortisolism, a pituitary adenoma is still the most likely cause. Bilateral inferior petrosal sinus sampling (BIPSS) can differentiate between a pituitary adenoma and ectopic ACTH production. When BIPSS shows no central to peripheral ACTH gradient, imaging studies (CT-scan of thorax and abdomen, 111In-pentetreotide scintigraphy etc.) should be performed to localize the source

of ectopic ACTH production.

4. *Correct answer:* A. A central to peripheral ACTH ratio of > 2.0 in basal conditions and/or > 3.0 after CRH stimulation indicates a pituitary cause of ACTH-dependent hypercortisolism.
5. A postoperative morning cortisol level of < 1.8 μg/dl (50 nmol/l) can be predictive of long-term remission, whereas most patients with a relapse have a postoperative morning cortisol level > 1.8 μg/dl (50 nmol/l).

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Pituitary Incidentalomas

M50
Monday, June 17
1:00–1:45 PM & 3:00–3:45 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

A pituitary incidentaloma is a previously unsuspected pituitary lesion that is discovered on an imaging study performed for an unrelated reason. Pituitary incidentalomas are common, as autopsy data and imaging studies show a prevalence of 10 to 20%. The majority of such tumors are microlesions (less than 1 cm). Given the high prevalence of such lesions, it is critical that clinicians have a thorough understanding of the differential diagnosis, the potential pituitary function abnormalities, and the natural history of these lesions in order to formulate a clinical approach.

BARRIERS TO OPTIMAL PRACTICE

First, the anatomic description of the lesion is critical, including a detailed description of the lesion appearance, location, and association/compression of local structures. A MRI scan is superior to a CT scan. Therefore, access to a MRI scanner is important, and both the availability of a MRI scanner and financial coverage of the cost of the scan may be barriers to the diagnosis and management. Another barrier may include access to validated hormone assays, and a thoughtful and standardized approach to the biochemical characterization of these lesions necessitates the availability of validated assays.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Describe the causes of a pituitary incidentaloma
- Identify the biochemical tests used to characterize the incidentaloma for hypersecretion and the presence of hypopituitarism.
- Identify the management options for the clinical approach to a pituitary incidentaloma.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

A pituitary incidentaloma is a previously unsuspected pituitary lesion that is discovered on an imaging study performed for an unrelated reason. In this case, the scan is not performed for a sign or symptom related to a sellar lesion, such as visual loss, hypopituitarism or hormone excess, but instead for the evaluation of another problem, such head trauma, headache, or another neurologic concern.

Prevalence/Cause

In autopsy series, a pituitary adenoma has been detected in approximately 11% of cases. In MRI and CT series, pituitary lesions are detected in 5-40% of cases (1, 2). Micro (<1cm) lesions are found in the majority of such cases, although some series suggest a higher frequency of macrolesions (> 1 cm). Because incidentalomas infrequently come to surgery, the underlying pathological diagnoses are estimated based on sellar masses that require surgery. In a series of sellar masses that required surgery, 91% were pituitary adenomas and about 9% were nonpituitary in origin, of which most were cystic lesions including craniopharyngiomas and Rathke's cleft cysts (3)(4). Of the non-cystic-appearing incidentalomas, most are pituitary adenomas, and the majority of clinically nonfunctioning pituitary adenomas

are of gonadotrope origin as determined by immunocytochemical studies (5).

Clinical Evaluation

Patients with a pituitary incidentaloma should undergo a complete history and physical examination that includes an evaluation for evidence of hypopituitarism and a hormone hypersecretion syndrome. Patients with clinical suggestion of either of these conditions should undergo an appropriately directed biochemical evaluation. This is especially the case if a patient has clinical findings to support either acromegaly or Cushing's syndrome.

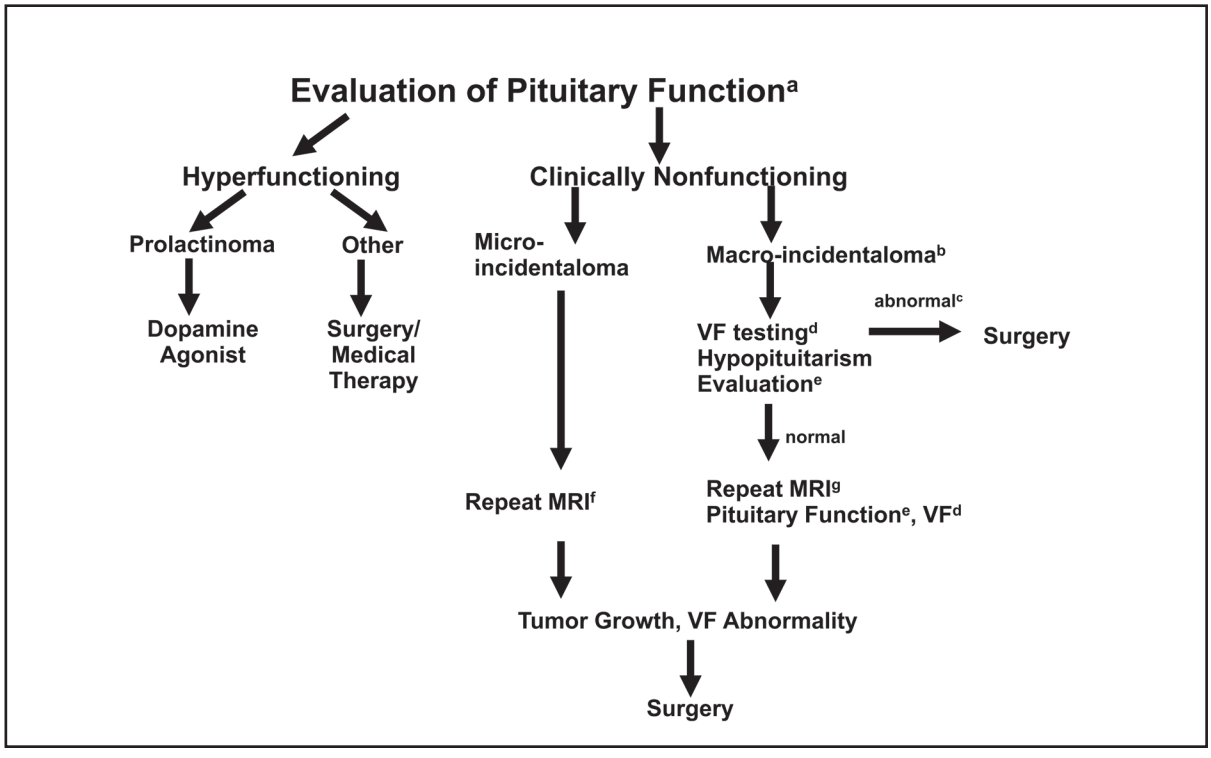
Biochemical Assessment

The evaluation for hypersecretion should include an assessment for prolactin, GH, and ACTH hypersecretion. Prolactin level should be measured in all (6). If a patient does not appear clinically to have acromegaly or Cushing's syndrome, then there is controversy over the utility of biochemical assessment of either of these disorders. In a microincidentaloma, the chance of a silent GH secreting lesion is very low, and this author does not routinely measure IGF-1 in this setting. In a macroincidentaloma, then an IGF-1 measurement is reasonable. Screening for glucocorticoid excess due to a possible corticotroph tumor may also be considered when this is suspected clinically. Some clinicians measure an ACTH value to screen for a silent corticotroph tumor, although the recent Endocrine Society Task Force did not recommend this as a routine test (7). Evaluation for hypopituitarism should be routinely performed in all subjects with a macroincidentaloma. Though hypopituitarism is uncommon in patients with microlesions of the sella, hypopituitarism can be detected, including GH deficiency in up to 50% of subjects, so biochemical screening for hypopituitarism should be pursued based on clinical assessment in the setting of a microincidentaloma (8).

Natural History of Pituitary Incidentaloma

It is important to understand the natural history of pituitary lesions in order to determine a clinical approach. Based on a compilation of follow-up studies, macroincidentalomas enlarged in approximately 24% of subjects, including

FIGURE 1. Evaluation and Treatment of Pituitary Incidentalomas



new visual field (VF) abnormalities in 8% of patients and apoplexy in 2% (9, 10). In microincidentalomas, tumor growth was noted in 11% in up to 7 yr follow-up. Of note, none of the patients with microincidentalomas developed new VF abnormalities that would have necessitated surgery.

Further Testing

Baseline VF testing is recommended for all patients with an incidentaloma abutting the optic nerves or chiasm, even without visual symptoms. If a CT scan had been performed, then a MRI scan is recommended to visualize better both the anatomy and the characteristics of the lesion.

Management

If the subject has a hypersecretory syndrome, such as prolactinoma, then medical therapy can be utilized. Otherwise, the management usually involves a choice of surgery or follow-up.

Figure 1: Flow diagram for the evaluation and treatment of pituitary incidentalomas. a, Baseline evaluation in all patients should include a history and physical exam evaluating for signs and symptoms of hyperfunction and hypopituitarism and a laboratory evaluation for hypersecretion. b, This group may also include large microlesions. c, The recommendation for surgery includes the presence of abnormalities of VF or vision and signs of tumor compression; surgery is also suggested for other findings. d, VF testing is recommended for patients with lesions abutting or compressing the optic nerves or chiasm at the initial evaluation and during follow-up. e, Evaluation for hypopituitarism is recommended for the baseline evaluation and during follow-up evaluations. This is most strongly recommended for macrolesions and larger microlesions. f, Repeat MRI in 1 yr, yearly for 3 yr, and then less frequently thereafter if no change in lesion size. g, Repeat the MRI in 6 months, yearly for 3 yr, and then less frequently if no change in lesion size. This figure is used with permission from Freda et al. (7), (*Copyright 2011, The Endocrine Society*).

Follow-up Monitoring: Patients with incidentalomas who do not meet criteria for surgical resection should receive nonsurgical follow-up, including MRI scan in 6 mo after the initial scan with a macroincidentaloma and 1 yr after the initial scan if it is a microincidentaloma. In patients whose incidentaloma does not change in size, the MRI may be repeated annually for macroincidentalomas and every 1–2 yr in microincidentalomas for the following 3 yr and gradually less frequently thereafter. VF testing should be repeated in patients with an incidentaloma that enlarges to abut or compress the optic nerves or chiasm. Clinical and biochemical evaluations for hypopituitarism should be performed at 6 mo then yearly in patients with a pituitary macroincidentaloma, although hypopituitarism typically develops with evidence of growth of the lesion. In the recent TES guidelines, repeat pituitary function testing was not recommended in patients with pituitary microincidentalomas whose clinical picture and MRI did not change over time (7).

Surgical Indications: Surgery is recommended if the lesion abuts or compresses the optic nerves or chiasm, there is a VF deficit or ophthalmoplegia, there is pituitary apoplexy with visual disturbance, or there is a hypersecreting tumor other than prolactinoma that requires surgery. Surgery is suggested but not mandated if there is clinically significant growth of the pituitary incidentaloma without chiasmal compression, loss of pituitary function, the lesion is close to the optic chiasm and the patient plans to become pregnant, or the patient has unremitting headache (7).

MAIN CONCLUSIONS

Pituitary incidentalomas are a common finding, and a thoughtful clinical approach that characterizes the lesion and determines potential consequences of the lesion with regard to hormone and neurologic function is important. Knowledge of the natural history of pituitary incidentalomas is important for deciding on therapeutic approaches.

CASES WITH QUESTIONS

Case 1

A 29 yo male is referred for a new sellar mass. He was in a MVA three weeks before. There

was no loss of consciousness, and he did not need to see a physician. Because of fatigue the next day, he underwent a brain MRI scan "to be on the safe side." The MRI scan was normal except for an 8 mm sellar lesion without chiasmal compression. He denies headache and dizziness. His past medical history is benign, and he is on no medications. On further history, he describes normal sexual function, energy, weight, and activity level prior to event. His fatigue has resolved by the time of this consultation.

Physical examination is normal. Laboratory testing includes prolactin 18.3 ng/mL and free T4 1.2 ng/dL.

Which one of the following is the best next step in the care of this patient?

1. Radiation therapy
2. Visual field testing
3. Selective endocrine assessment and serial monitoring
4. Transsphenoidal surgery
5. Administer cabergoline therapy

Case 2

67 yo male with increasing memory loss. MRI scan shows cortical atrophy and an incidental 12 mm pituitary lesion that is solid, hypoenhancing, and is abutting the optic chiasm. He has been well except for hypertension and arthritis. Normal libido and erectile function. Examination unremarkable, with BP 142/90. Testing shows prolactin of 26.1 ng/mL, a testosterone of 323 ng/dL, a Free T4 of 1.0 ng/dL, fasting serum cortisol 21 mcg/dl, and a serum IGF-1 125 ng/ml. Visual fields are normal.

Which one of the following is the best next step in the care of this patient?

1. Transsphenoidal surgery
2. Radiation therapy
3. Serial follow-up with imaging and pituitary function testing
4. Administer cabergoline therapy

DISCUSSION OF CASES AND ANSWERS

Case 1

Answer: 3

This patient has a lesion that is less than 10 mm, consistent with a microincidentaloma. Given the radiographic characteristics, this is likely a microadenoma of the pituitary gland. The evaluation consists of an endocrine assessment for pituitary hypersecretion and hypofunction. The normal serum prolactin and physical examination rule out prolactinoma, Cushing's syndrome, and acromegaly. Measurement of IGF-1 and cortisol values for subclinical hyperfunction is controversial in a patient with a microincidentaloma. Because hypopituitarism is unusual in this setting, further endocrine assessment for pituitary dysfunction is specific to the subject: in this case, not necessary. Further management including serial imaging is warranted to assess for tumor growth, as surgery, radiation therapy, and medical therapy are not indicated.

Case 2

Answer: 1

In this case, the lesion is a macroincidentaloma, although borderline so. The appearance on scan is described as solid, so this is not a cystic disease and hence likely to be a pituitary adenoma. The evaluation shows normal anterior pituitary gland function except for possible growth hormone deficiency, given the low IGF-1. A GH provocative test would be necessary to assess GH reserve. Given the proximity of the lesion to the chiasm, surgery would likely be recommended. The visual field testing is normal, so a non-surgical approach including serial follow-up with repeat imaging and hormone assessment is reasonable, although the fact that the tumor abuts the chiasm pushes us towards surgery. The prolactin level is borderline elevated, and this likely reflects stalk compression. A trial of a dopamine agonist, such as cabergoline, is unlikely to be of benefit in this situation as the tumor is probably not a prolactinoma: one would expect a higher serum prolactin in the setting of a macroprolactinoma. Radiation therapy is not necessary for this situation, and may well lead to optic chiasmal damage given the proximity of the tumor to the chiasm anyways.

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Craniopharyngioma: Diagnosis and Management

M61
Tuesday, June 18
12:15–1:00 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Craniopharyngiomas (CP) are partly cystic embryogenic malformations of the sellar and parasellar region. With an overall incidence of 0.5 to 2.0 new cases / million population / year, approximately 30 to 50% of all cases represent childhood CP. Typical manifestations at diagnosis are headache, visual impairment, polyuria/polydypsia, growth retardation, and significant weight gain. Therapy of choice in patients with favorable tumor localization is complete resection with the intention to maintain optical nerve and hypothalamic-pituitary functions. In patients with unfavorable tumor localization (hypothalamic involvement), a limited resection followed by local irradiation is recommended. The overall survival rates are high (92%). Recurrences after complete resection and progressions of residual tumor after incomplete resection are frequent post-surgical events. Accordingly, the appropriate time point of irradiation after incomplete resection is currently under investigation in a randomized multinational trial (KRANIOPHARYNGEOM 2007). Quality of life is substantially reduced in approximately 50% of long-term survivors due to sequelae, notably morbid hypothalamic obesity (1). Both, childhood CP and adult onset CP should be recognized as chronic diseases requiring constant monitoring of the consequences and appropriate medical resources for treatment in order to provide optimal quality of survival for patients (2).

BARRIERS TO OPTIMAL PRACTICE

- An improvement in prognosis of CP patients will require the development of risk adapted neurosurgical and radiooncological treatment strategies in a multidisciplinary approach.
- One of the biggest challenges in treating CP is identifying the best candidates for the radical versus the conservative approach.
- In clinical practice, the timing of postoperative residual tumor irradiation is both unclear and inconsistently regarded.
- Despite the availability of "more or less" promising therapeutic approaches for hypothalamic obesity, it must be emphasized that there is currently no generally accepted pharmacological therapy for obesity in CP patients that has been shown to be effective in controlled studies.

LEARNING OBJECTIVES

- Differential diagnosis of sellar / parasellar masses / CP
- Appropriate risk-adapted treatment strategies
- Grading systems for hypothalamic involvement of CP
- Treatment options for hypothalamic obesity
- Recommendations for follow-up

As a result of participating in this session, learners should be able to:

- interpret imaging of sellar / parasellar masses
- identify CP patients at risk for hypothalamic sequelae
- choose risk-adapted treatment strategies
- monitor follow-up

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Strategies for diagnosis

The diagnosis of CP is often made late, sometimes years after the initial appearance

of symptoms. The clinical picture at the time of diagnosis is often dominated by non-specific manifestations of increased intracranial pressure, such as headache and nausea. Further leading manifestations include visual impairment (62% to 84%) and endocrine deficits (52% to 87%). The latter involve the hypothalamic-pituitary axis and affect the secretion of growth hormone (75%), gonadotropins (40%), adrenocorticotropic hormone (ACTH) (25%), and thyroid-stimulating hormone (TSH) (25%). Neurohormonal diabetes insipidus is present preoperatively in 17% of patients. A study of the history of CP patients before diagnosis revealed that the initial symptoms often occur long before the diagnosis is made. The clinical combination of headache, visual impairment, decreased growth rate, and polydipsia/polyuria should arouse suspicion of CP in the differential diagnosis.

Both computerized tomography (CT) and magnetic resonance imaging (MRI) reveal CP as a usually cystic tumor of the intra- and/or suprasellar region. CT is the only way to detect or exclude calcification, which is found in approximately 90% of tumors. The signal intensity of CP in MRI is highly variable, as it depends on the protein content of the cysts. The most common localization is suprasellar, with an intrasellar portion. 20% of tumors are exclusively suprasellar, 5% exclusively intrasellar. The combination of solid, cystic, and calcified tumor components is an important radiological clue to the diagnosis. MRI before and after gadolinium application is the standard imaging for detection of CP. A sellar or parasellar mass detected on MRI should be further imaged by native CT for detection of calcifications. After preoperative detection of calcifications and complete resection confirmed by postoperative MRI, a postsurgical native CT of the sellar / parasellar area is recommended for reconfirmation of complete resection (3).

Strategies for therapy

Surgery

Before surgery, a tumor-related impairment of cerebrospinal fluid (CSF) flow often causes hydrocephalus, which can be of varying severity. Although resection of the tumor is the preferred treatment for restoration of normal CSF flow, a pre-excision shunt operation may be required. For larger cystic CP, particularly in infancy or early childhood, the endoscopic guided or open implantation of an intracystic catheter is a valuable treatment option, both for the relief of pressure and, in some cases, for a possible intracystic instillation of sclerosing substances. In particular for patients with large cysts exerting mass effect and consequent marked preoperative visual impairment, a two-staged approach is proposed: cyst drainage to relieve pressure and improve vision, followed by resection. Once surgical resection has been decided and the timing deemed appropriate, the operative approach is generally dictated by the localization and extent of the childhood CP. A right frontotemporal approach is standard, but intrasellar tumors can be operated on by the transsphenoidal route. However, CPs arising in childhood usually extend to the suprasellar area and must be removed through a transcranial approach in most cases. For topographical-anatomical reasons, transsphenoidal surgery has the advantage of not disturbing hypothalamic function, which is pivotal to childhood CP patients whose growth maturation and pubertal development are dependent on hypothalamic-pituitary functions.

Besides classic fronto-pterional approaches, neuroendoscopic procedures are claiming an increasing neurosurgical significance. Neuroendoscopic routes to CP are known as transnasal-transsphenoidal, transventricular, as well as the supra-orbital approach. That said, endoscopic transsphenoidal surgery is mostly used for smaller, primary intrasellar CPs, of which only 5% are exclusively intrasellar.

For favorably localized tumors, the preferred treatment of choice is an attempt at complete resection with preservation of visual, hypothalamic, and pituitary function. For unfavorably localized tumors (with hypothalamic involvement), a planned limited resection (biopsy, partial/subtotal resection) followed by irradiation should be performed instead (4).

Experiential expertise in large centers in

western countries has increased the possibility of safe gross total resection, evidenced by two reports representing historically different attitudes: the first at Necker Hospital, which is more surgically oriented; and the second in North America, which is more oriented towards a conservative approach. The North American experience shows that most recent cases now receive moderate to aggressive surgery and only 42% have limited surgery before irradiation. The Necker authors show in a contemporary series that 96% of their recent cases achieve complete (23%) or subtotal resection (73%), and that radiotherapy is performed in 50% of cases after subtotal resection. It appears there is a trend towards radiotherapy in centers with past prevalent surgical approaches, and towards more radical surgical treatment strategies in centers historically conservative-oriented. A recent report showed that especially tumor involvement and surgical lesions of posterior parts of hypothalamic structures predisposes to adverse late effects such as obesity and consecutively impaired quality of life.

Irradiation

Optimal techniques must be used. The target volume should be defined according to the visible tumor in the CT and/or MRI images. The resolution of current imaging techniques permits the use of a small safety margin, which may not be greater than 5 mm, depending on the precise configuration of the tumor. A smaller safety margin may be chosen in the vicinity of important structures, such as the optic chiasm, as long as the less than perfect precision of radiological localization as well as possible difficulties in the interpretation of images, of both physical and medical nature, are taken into account. A larger safety margin is required if the hypothalamus is involved, even when MRI-based planning is used. Three-dimensional planning with individual field configurations should be used to protect radiosensitive structures and to provide a maximal dose fall-off between the tumor and the adjacent normal structures.

Preliminary experiences with proton beam therapy applied to CP are very promising, offering a more protective radio-oncological option for low malignant brain tumors than conventional external irradiation, especially for tumors localized in the vicinity of the optic nerve or chiasm, pituitary gland, or hypothalamus.

Only limited experience has been gained to date with stereotactic gamma-radiotherapy (Gamma Knife) in the treatment of primary or recurrent CP. For reasons relating to radiation biology, single-dose convergence irradiation seems to be of little value in the treatment of CPs. Another experimental treatment option, the stereotactic instillation of radioisotopes, is mainly applicable to monocystic recurrences of CP. This method can be used for cystic tumors and should be considered for tumors that recur after both surgery and percutaneous radiation therapy (5).

In clinical practice, the timing of postoperative residual tumor irradiation is both unclear and inconsistently regarded. Some favor immediate postoperative irradiation in the event of life-impairing clinical conditions, proactively preventing tumor progression. On the other hand, some favor a wait-and-see procedure, delaying irradiation in order to reduce both its necessity and the negative consequences associated with radiation therapy. Inarguably, immediate postoperative irradiation significantly delays tumor progression. However, progression-contingent irradiation has proved effective, as overall survival is statistically unaffected by this wait-and-see strategy.

KRANIOPHARYNGEOM 2007, a prospective, European multinational trial, is currently evaluating CP patients' prognoses (QOL, event-free, and overall survival rates) following defined therapeutic strategies. A stratified randomization of two treatment arms is conducted with respect to timing of postoperative irradiation (immediate irradiation versus irradiation at the time of progression) for the subgroup of patients ≥5 years of age at the time of incomplete resection. The trial is open for international recruitment. Trial information and protocol are available at www.kraniopharyngeom.net

Strategies for follow-up

Hypothalamic syndrome

Symptoms related to hypothalamic dysfunction, such as obesity, fatigue, behavioral changes, circadian rhythm and sleep irregularities and imbalances in regulation thirst, body temperature, heart rate or blood pressure, are common in childhood CP and have been found at diagnosis in 35% of patients. The rate of hypothalamic dysfunction dramatically increases after treatment; in some series up to 65–80%. Based on a recently published MRI grading system for pre-surgical hypothalamic tumor involvement and surgical hypothalamic lesions in childhood CP patients, the impact of surgical lesions of posterior hypothalamic areas on postoperative weight gain and quality of life could be demonstrated.

Treatment of hypothalamic obesity

Due to disturbances in energy expenditure, central sympathetic output, and appetite-regulation, CP patients with hypothalamic obesity typically develop morbid obesity that is mainly unresponsive to conventional lifestyle modifications (diet and exercise). Based on impairment of sympatho-adrenal activation and epinephrine production manifesting as a reduced hormonal response to hypoglycemia, treating this disorder with central stimulating agents (amphetamine derivates, methylphenidate, modafinil) has been suggested.

Childhood CP patients with hypothalamic obesity have a "parasympathetic predominance" of the autonomic nervous system induced by vagal activation and manifesting as daytime sleepiness, and reduced body temperature and heart rate. Parasympathetic stimulation causes insulin secretion by way of direct activation of β cells as well as promotes adipogenesis. As insulin is an anabolic hormone, it has been suggested as an important driver of weight gain in hypothalamic obesity. Octreotide is a somatostatin analogue and thus causes reduction in insulin secretion. Lustig and colleagues used octreotide in a double blind randomized controlled study in children with hypothalamic obesity and demonstrated moderate reductions in weight gain and showed that insulin levels during a proof-of-concept oral glucose tolerance test decreased without leading to major changes in glucose tolerance.

Bariatric surgery

Initial experiences with bariatric surgery in severely obese childhood CP patients achieved sufficient tolerability and short-term weight reduction. An instant improvement of binge-eating behavior in patients with childhood CP immediately after laparoscopic adjustable gastric banding (LAGB) was observed, but failed in long-term weight reduction. Treatment with invasive, non-reversible bariatric methods such as gastric bypass is controversial in the pediatric population because of medical, ethical, and legal considerations.

Despite the availability of these promising therapeutic approaches, it must be emphasized that currently no generally accepted (pharmacological or bariatric) therapy for hypothalamic obesity in CP has been shown to be effective in randomized studies (6).

MAIN CONCLUSIONS

For favorably localized CP, the preferred treatment of choice is an attempt at complete resection with preservation of visual, hypothalamic, and pituitary function.

For unfavorably localized CPs with close proximity to optical and/or hypothalamic structures a radical neurosurgical strategy attempting complete resection is not recommended in order to prevent severe sequelae.

Hypothalamic CP involvement and neurosurgical hypothalamic lesions have major negative impact on quality of life in survivors, mainly due to hypothalamic obesity.

Irradiation is effective in preventing recurrences and progressions.

The appropriate time point of irradiation in CP patients with residual postoperative tumor is currently under investigation in a randomized multinational trial (KRANIOPHARYNGEOM 2007) (7).

Currently no generally accepted (pharmacological or bariatric) therapy for hypothalamic obesity in CP has been shown to

be effective in randomized studies.

Perspectives
Risk-adapted surgical strategies at initial diagnosis should aim at a maximal degree of resection keenly focused on respecting the integrity of optical and hypothalamic structures to prevent severe sequelae. Because initial hypothalamic tumor involvement has an a priori effect on the clinical course, childhood CP should be recognized as a chronic disease requiring constant monitoring of the consequences and medical resources for treatment in order to provide not only optimal QoL for patients, but also to garner additional information with the intent of minimizing what at present are severe consequences of both the disease and its treatment.

CASES WITH QUESTIONS

1. Cases of sellar/parasellar masses: Differential diagnosis based on MRI / CT

Langerhans cell histiocytosis (LCH)	pituitary adenomas	hypothalamus and optical tract gliomas
Rathke cleft cysts	xanthogranuloma	thrombosis arachnoid cysts
epidermoid tumors	germinomas	inflammatory variations
germ cell tumors	aneurysmata	colloidal cysts of the third ventricle

2. Cases with different degrees of hypothalamic involvement/surgical lesions *(Figure 1)*

3. Cases with different treatment approaches
a.) limited surgery, b.) intracavitary Interferon alpha instillation, c.) Protonbeam therapy

4. Late effects
a.) hypothalamic obesity, b.) disturbed circadian rhythm/increased daytime sleepiness

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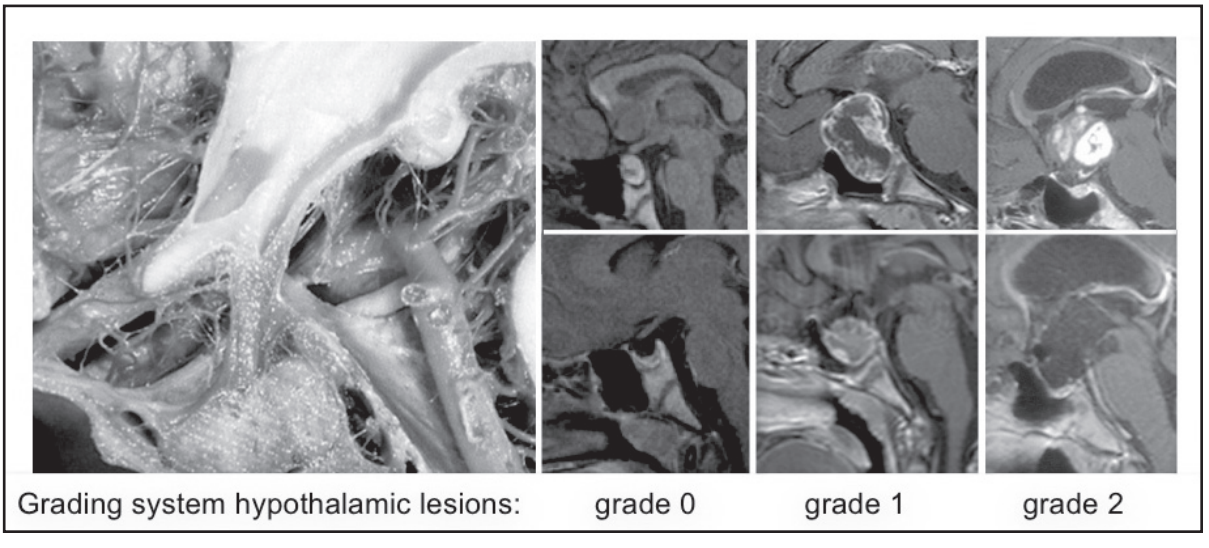
FIGURE 1



Acromegaly: Diagnosis and Management

M1
Saturday, June 15
3:00–3:45 PM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Approximate incidence of 5 cases per million per year. Prevalence of 60 cases per million.

Aetiology

99% pituitary adenomas
>70% macroadenomas

Rarely ectopic secretion of growth hormone releasing hormone (GHRH) or somatroph hyperplasia. Most cases are sporadic.
Familial syndromes:

- Multiple endocrine neoplasia type 1
- McCune Albright syndrome
- Familial acromegaly and Carney's syndrome
- Aryl hydrocarbon receptor interacting protein (AIP) gene mutations
- Increased morbidity and premature mortality, reduced if disease is controlled.

BARRIERS TO OPTIMAL PRACTICE

- Delay in diagnosis
- Access to specialist pituitary surgeon
- Cost of medical therapy

LEARNING OBJECTIVES

- Limitations of assays
- Importance of input of a multi-disciplinary team including laboratory, pituitary surgeon, radiotherapist and specialist nurse

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Diagnosis

Greatest challenge in the diagnosis of acromegaly is for the disease to enter the differential diagnosis of the presenting manifestations. Typically a decade lapsing between development of symptoms and confirmation of diagnosis. Once considered, the diagnosis is usually rapidly confirmed.

Biochemical confirmation

GH

- Undetectable (<0.3 mcg/l) random GH measurement good evidence against acromegaly
- 75 gm oral glucose tolerance test and serum IGF-I
  - º normal individuals, GH levels falls, at least one value <0.3 mcg/L
  - º failure of suppression or a paradoxical rise in GH indicative of acromegaly
  - º results usually unequivocally

GH can fail to suppress in uncontrolled diabetes mellitus, liver or renal disease, patients receiving estrogen, during pregnancy and late adolescence, malnutrition and anorexia, but in combination with IGF-I measurement and examination of the patients there is rarely a problem. Not difficult to distinguish anorexia from acromegaly!

IGF-I

IGF-I within the reference range in newly diagnosed acromegaly is very rare utility hindered by concerns over the quality of some commercial assays and reference ranges levels may vary, typically being low in liver and renal dysfunction and uncontrolled diabetes mellitus.

Nutrition, circadian rhythm, estrogen, insulin, glucocorticoid therapy and thyroxine levels can affect IGF-I levels.

The limitations of assays

Application of international consensus criteria statements poses various challenges.

GH & IGF-I assays have improved in terms of simplicity to perform, elimination of radioactive isotopes and lower limitations of quantification, however the bias between assays has increased, i.e., significant variation is seen between assay kits.

Diagnostic/therapeutic 'cut-offs' provide convenient guidance but are artificial and lack biological significance and may lack an evidence base.

These factors and others, for example prior radiotherapy and the use of oestrogens, results in discordance between GH and IGF-I values. The commonest scenario being 'normal' serum GH with an elevated IGF-I.

Imaging

Magnetic resonance imaging (MRI) with gadolinium contrast

- >70% pituitary tumour >10 mm
- Hyperplastic gland in rare cases of ectopic GHRH or somatotroph hyperplasia

Pituitary function testing

As per standard protocols

Therapy

Goals of therapy/criteria for remission

Random GH level of <1 mg/L

or

Nadir GH of <0.3 mg/L on OGTT

and

IGF-I in the age-adjusted normal range

- Exception pegvisomant therapy
- GH cannot be used – rely on IGF-I

Surgery

- Choice of the surgeon is crucial
- Transsphenoidal microsurgical approach is initial treatment in the great majority of patients
- In expert hands, approximately 80% and 50% of patients with micro- and macroadenomas, respectively, achieve normal IGF-I levels
  - morbidity and mortality lower in the hands of specialist pituitary surgeons

Radiotherapy

Effective at controlling tumour growth

Slow to control GH secretion and normalize IGF-I

Conventional multi-fractionated (3-field 4500 cGy)

- Out of favor, particularly in younger people, because of the risk of cerebrovascular accidents but still has a place in the treatment of patients with large and growing residual tumour after surgery.
- Hypopituitarism - most common complication
  - 10 years deficiencies; 27% TSH, 18% FSH/LH, 15% ACTH

Stereotactic high dose irradiation

- In many centres supplanted conventional radiotherapy
- Most frequently being delivered by the Gamma Knife®.
- Require precise delineation of the tumour to ensure minimal surrounding tissue exposure
- Suitable for smaller volumes residual tumour beyond reach of surgeon
- Tumour control attained in 97%
- Hormonal remission rates varying from 17-96%
- Hypopituitarism is the most common side effect

Medical treatment

Dopamine Receptor Agonists

- Act through D2 receptor
- Continue to have a place in its treatment
  - often in combination with somatostatin analogues
- Twin virtues of relatively inexpensive and orally administered

Cabergoline long-acting ergot-derived dopamine agonist - superseded bromocriptine

- More potent and better tolerated
- Doses of up to 1 mg per day normalize IGF-I in up to 30% patients
- Probably most effective in patients with prolactin co-secretion
  - likely to induce tumour shrinkage

Cabergoline is not licensed for the treatment of acromegaly

- Large scale prospective studies have not

been undertaken
- Therefore value not fully explored

Side-effects
- Gastrointestinal discomfort, nausea, vomiting, dizziness, headache and postural hypotension manageable by slow dose titration.
- Depression or mania - often in patients with a prior history
  - very rarely development of gambling, alcohol and sex addiction

Cardiac valve fibrosis
- Evidence in Parkinson's disease with ergot-derived dopamine agonists
- Lack of convincing evidence in pituitary disease
- Related to cumulative dose
  - doses in endocrine patients smaller than Parkinson's
- Annual echocardiograms recommended

Somatostatin analogues

Somatostatin regulatory peptide produced by neuroendocrine, inflammatory and immune cells in response to specific stimuli.
- Actions mediated by 5 subtypes of receptors (SST1-5)
- Somatostatin cannot be used for therapy of acromegaly: very short plasma half-life (2-3 minutes), lack of specificity (binds all five receptor subtypes)

Somatostatin analogues

Octreotide and lanreotide are somatostatin analogues with prolonged plasma half-lives and high affinity for the SST2 and SST5 receptors responsible for regulation of GH secretion from somatotrophs.

Treatment of choice for most patients not cured by surgery

Prospective clinical trials - biochemical disease control achieved in 60-70%
- Results being better in patients with milder disease
- 'Real-Life' normalization rate in an unselected patient population of nearer 50%

Addition of cabergoline may result in a further fall in GH and IGF-I levels accompanied by relief of symptoms.

Increasing interest somatostatin analogue therapy pre-operatively, either as a short-term measure in the hope that surgical outcomes are improved or as a long-term alternative to surgery.
- Impressive tumour shrinkage in patients as first line therapy
- Little objective data that pre-operative somatostatin analogue therapy improves the outcome of subsequent surgery

Octreotide and lanreotide monthly depot injections - similar efficacy

Pasireotide (SOM 230)

Novel analogue - high affinity for SST1, 2, 3 and 5.

May be of value in patients with an inadequate response to octreotide

Significantly higher rate of impaired glucose tolerance and diabetes

Side-effects
- Gastro-intestinal symptoms
- Biliary tract abnormalities
- Hyperglycaemia
- Asymptomatic sinus bradycardia

Pegvisomant

Genetically engineered analogue of human GH

GH receptor antagonist

IGF-I main measure of disease activity (serum GH should not be measured)

Normalized IGF-I in 89% at dose of 20 mg per day

Normalization of IGF-I in 97% using doses up to 40 mg per day

Data from the post-marketing surveillance database - IGF-I normalization rate is only around 70% probably due to a failure of adequate dose titration

Long half-life (>70 hours) of pegvisomant means probably a once weekly, rather than daily medication

Place of pegvisomant in treatment algorithm: persisting symptoms and elevated IGF-I despite surgery, possibly radiotherapy, and maximum doses of somatostatin analogues.

Monotherapy or combination with somatostatin analogue both expensive but little to choose between the two in terms of cost

Combination with cabergoline offers a more cost-effective option

Side effects

- Elevation of liver enzymes
- MR Imaging initially six monthly and ultimately annual
- Lipohypertrophy

MAIN CONCLUSIONS

- Delay in diagnosis remains a frustration
- Surgery by an experienced pituitary transsphenoidal surgeon is the appropriate initial treatment and only opportunity for cure
- With appropriate pharmaceutical manipulations it should be possible to achieve biochemical and tumour control in the great majority of patients
- Radiotherapy still has an evolving place in the treatment
- All assays have limitations

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OBESITY

Management of Morbidly Obese Adolescents

M44
Monday, June 17
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Pediatric obesity is widespread in developed countries around the world (and worsening in developing countries) and threatens to shorten the lifespan of the current generation. At highest risk for comorbidities of obesity such as Type 2 diabetes mellitus, non-alcoholic fatty liver disease and dyslipidemia is a subset of children with morbid obesity, typically defined as a BMI percentile >99th percentile. The route to morbid obesity is diverse and usually involves some combination of genetic predisposition and maladaptive lifestyle choices. While these unhealthy lifestyle characteristics—ultimately resulting in excess caloric intake and/or insufficient energy expenditure—may not be different from the lifestyle of less severely affected children around them, among morbidly obese children this lifestyle have resulted in a dangerous accumulation of fat mass. Intervention is critical to halt the worsening of BMI and when possible reverse it. Clinical approaches toward lifestyle change can be successful when children and parents are motivated. Treatment with medications such as metformin and orlastat has had limited success in clinical trials. Surgical treatment may be the best option for some severely affected children who are motivated to adhere to the long-term treatment needs. As a final option, some children may benefit from removal from hostile environments refractive to the changes needed to help these children avoid serious sequelae.

BARRIERS TO OPTIMAL PRACTICE

- Children with morbid obesity are likely to have genetic backgrounds that require more stringent lifestyle modification—and likely longer-term following—than most children.
- Children with morbid obesity are more likely to have a degree of family disarray that is refractive to needed changes and requires additional attention to parenting practices toward healthier family lifestyle choices.
- One potentially-useful treatment option—bariatric surgery—also requires a degree of commitment in order to provide long-term success.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Discuss with families the potential reasons behind their child's morbid obesity and the urgency behind weight loss.
- Plan an approach of lifestyle changes with a morbidly-obese child targeting improved activity and weight loss.
- Formulate criteria needed prior to referral for bariatric surgery.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Introduction

Morbid obesity in childhood, frequently defined as a BMI >99th percentile for age and sex, poses particularly worrisome threats to future health. Unfortunately, it can be difficult to overcome the unhealthy patterns that led to the weight accumulation in the first place and lifestyle intervention has had mixed effects in the long-term. As we will see, the optimal approach involves a multi-disciplinary team, patience, and a critical eye toward surgery as a

possible intervention.

Prevalence of morbid obesity and associated risks

The problem of morbid obesity in childhood is unfortunately not a rare one. Approximately 2% of preschoolers are classified as morbidly obese,[1] and this proportion rises to >4% during adulthood.[2] These numbers have worsened since 1998 but the childhood prevalence has shown a recent slight improvement.[1] Despite this improvement, it bears noting that children who are obese in childhood have a 37-51% chance of being morbidly obese in their 30's,[3] raising the importance of optimizing efforts toward obesity treatment as well among children who are obese but remain below the 99th percentile—to prevent continued progression.

Childhood obesity is associated with a two-fold higher risk of earlier death[4] and increased risk adult diseases such as T2DM and CVD.[5] An additional point to mention that may be more important to the child is a lower level of quality of life due to the obesity. Outlining these risks and using the statement that you are worried about the future health of their child emphasizes to the urgency of the situation to the family and establishes the need for dramatic lifestyle change.

Etiology

Another important point to emphasize to patients and their parents is the likely underlying genetic contributors to their obesity. Some of these genetic causes have been described, including single gene defects such as mutations in the melanocortin 4 receptor (at one point present in 5.8% of children in England with early-onset obesity[6]) or deletions in chromosome 16p11.2 (present in 1.7% of another British cohort with morbid obesity).[7] Other genetic causes include syndromes such as Prader Willi Syndrome. However, there are clearly a dozens of gene polymorphisms leading to less severe obesity phenotypes[8] that when present together contribute to increased appetite and/or slower metabolism—and are likely ubiquitous among children with morbid obesity. This likely genetic predisposition is important for the medical team to remember, since it appropriately distinguishes children with obesity from thin children in the current generation who seem to live a similar lifestyle without weight problems. Pointing out these genetic contributions helps explain to the child and his/her family that they are different and are likely to need a more significant amount of effort compared to those around them. In many cases this confirms their long-term suspicions, though data have not demonstrated that this helps motivate toward more significant changes.

Initial assessment

The initial assessment of a child with morbid obesity includes a focus on establishing rapport with the family and child, evaluating for potentially concerning etiologies, and assessing for current comorbidities. Etiologies beyond lifestyle/common underlying genetic issues include Prader Willi syndrome, Cushing's syndrome, and severe hypothyroidism, each of which result in a degree of growth suppression, necessitating acquisition of prior growth data. Potential current comorbidities include hypertension (via measurement with an appropriately-sized BP cuff), dyslipidemia (via fasting laboratory draw), obstructive sleep apnea (asking about snoring and pauses in breathing), polycystic ovary syndrome (PCOS—asking about menstrual regularity and virilizing features of acne and unwanted hair, and measuring free testosterone levels) and Blounts disease (asking about knee and leg pain). Each of these conditions may require additional treatment but also would be assisted by weight loss. Thus the presence of comorbidities may help in motivating a patient or family that otherwise seems skeptical regarding their need for change.

Clinical treatment of morbid obesity

Even if morbid obesity frequently has some degree of genetic underpinnings, its prevention and treatment still require strict lifestyle adjustments regarding reduced calorie intake and increased energy expenditure *(Table 1)*. The efficacy of these approaches in the short term as shown in in-patient controlled trials demonstrates the potential benefits.[9]

TABLE 1: Abbreviated list of considerations to guide out-patient assessment & treatment of obesity.

Assessment	
Medical:	• Timing of onset of weight gain, associated comorbidities • Family history of obesity, diabetes, early cardiovascular disease • ROS: snoring/obstructed breathing, leg/knee pain, polyuria, etc; adolescent females: menstrual pattern, virilizing features
Lifestyle/behavior	• Food assessment: food types, drinks, snacks, portion sizes • Exercise assessment: activity types, frequency, duration • Assess family dynamics: parental rule setting, obedience • Assess motivating factors, willingness to change
Physical exam	• Height, weight, BMI; past growth (height gain, timing of obesity) • Blood pressure for age and height • Acanthosis, straie, knee pain
Treatment	• Counsel regarding etiology of weight gain—genetic & lifestyle • Counsel family about co-morbidities and risks of obesity. • Form action plan with child each visit, document in chart: dietary changes and exercise goals • Address family dynamics: negotiating with adolescent, need to say "no" at times • Give printed information to hang on refrigerator • Consider alternate approaches including bariatric surgery if criteria met • Set follow-up time for 2-4 weeks initially, monthly for first several months

Unfortunately, it is difficult for patients and their families to maintain these types of changes, even in controlled out-patient trials. Dietary adjustments alone can lead to early improvements in weight loss that overall is sustained in only a subset of patients.[10] A more comprehensive approach including physical activity has had better success over time but involve intensive approaches such as weekly guidance sessions and phone follow-up that are difficult to replicate in most clinical settings.[11] Nevertheless, making a strong effort toward lifestyle changes is important because these efforts can be successful in some children and they underscore changes that at a minimum should help slow the worsening of obesity in these children.

The lack of success in lifestyle modification among individual patients can be due to a variety of reasons, some of which have to do with inertia of bad habits and potentially an accelerated appetite drive, but many of which are exacerbated by a lack of family support that is manifest in multiple ways. A significant part of the treatment plan is based on removing certain high-fat food items from the home, and a high degree of family commitment is needed to achieve this.[11] Family support is also needed in limiting screen time and encouraging additional physical activity. Because of this, an assessment of family dynamics is an important step in planning a change. Parents of obese children need to be counseled that limit setting and saying "no" is natural and an important part of providing for their children.[12] In a clinic setting this analysis and counseling can be time intensive and some of these issues may be developed over multiple visits.

Dietary changes are focused on decreasing calorie intake, with approaches that include elimination of unhealthy snacks and calorie-containing drinks (except milk), decreasing portion size (such as by using smaller plates and not allowing seconds), eating more slowly (to allow the satiety effect of food to initiate earlier), eating breakfast daily, and decreasing consumption of animal fats. Having printed material on these practices for the family to hang on their refrigerator is a good practice.

Exercise recommendations include gradually working up to daily physical activity that preferably "makes you sweat" for at least 30 minutes each day. The goal is for this activity to become part of the new norm for the child, so it is beneficial to choose activities that are a natural part of the schedule such as walking the dog, walking with an accountability partner, or stopping by a fitness center or YMCA that is on the way

to other usual activities. Some exercise options are more available to higher-income families such as walking on a treadmill while watching TV or joining a fitness center. Participating in athletics is not something most morbidly obese children do; if a patient is involved in sports, though, it is important to plan with them what they will do once the sports season is over. It is a good idea to get a sense for the safety of the child's neighborhood in assessing whether walking around the neighborhood is a good choice. Many children will cite PE at school or Wii as their regular exercise, and strongly advocating for additional activities is important.

Goal setting with the patient is key to producing quantifiable lifestyle adjustments that can be documented in the medical record, tracked and improved on over time. The optimal approach is to have the child himself or herself identify specific practices that he or she is willing to focus on. This provides ownership that is more powerful than having the clinician "preach" regarding these items. It may also give some sense of the child's willingness to change.

It is important to not lose faith in the process. Some patients may undergo several false starts before making durable lifestyle changes. There are some suggestions that insulin resistance will improve without appreciable change in BMI, potentially due to a gain in muscle mass during loss of fat mass. Simply preventing further worsening of BMI represents an improvement in many children who previously exhibited progressive worsening of BMI. This is particularly beneficial to children who still have linear growth ahead of them and for whom a stable BMI brings them closer to normal.

Medical treatments

Medical therapy for weight loss in adolescents and children is not recommended. The FDA has approved two drugs for use in weight loss treatment in adolescents: orlistat and sibutramine; however, sibutramine has been removed from the US market due to concerns of potential increased risk for cardiovascular side effects.[13] Orlistat inhibits fat absorption and when given three times a day can produce a drop in BMI of 2-3 kg/m2—weight which returns following discontinuation of the drug. Use of orlistat can lead to foul-smelling stools and soiling—not items associated with adherence in adolescents. At best lifelong treatment is unlikely and at worst it could have unforeseen dangers. Metformin can produce modest weight loss but this author recommends against its use except for cases of pre-diabetes (glucose-intolerance), PCOS or of course T2DM, for which it is the first line therapy. Regular metformin is associated with better weight loss, potentially because of its side effect of GI discomfort.

Special Considerations: Bariatric surgery

Because of the low success rate of lifestyle interventions at producing weight loss in the majority of obese patients and because of the high rate of severe comorbidities in the long-term, invasive measures have emerged as important considerations in the treatment of morbid obesity. Bariatric surgery in adolescents has progressed from being a rarity in 1997 (51 cases in the U.S. per year)[14] to an increasingly common option in the face of failed lifestyle interventions. Of utmost importance in considering bariatric surgery is short-term and long-term safety to the adolescent, which is weighed against risks of remaining or worsening obesity. In addition to the usual surgical risks (wound infections and other complications), risks of bariatric surgery in adolescents include potential effects on linear growth and effects related to malabsorption, such as vitamin deficiencies.[15] All of these considerations are taken into account in the recommended adolescent bariatric surgery criteria *(Table 2)* which address both the severity of obesity (BMI cut-offs), obesity related risks (number of comorbidities), potential growth suppression (Tanner stage and percent predicted final height) and ability to adhere to recommendations for after the surgery (such as nutrition adherence adequate to follow a diet with sufficient fluid, protein and vitamins).[16] Another important safety issue is the experience level of the surgeon, with a lower rate of surgical complications among surgeons who perform these procedures regularly.[14]

TABLE 2: Recommended criteria for consideration of bariatric surgery in adolescents.
Adapted from Hsai et al. *Arch Ped Adol Med* 2012;166(8):757-766 and Ibele et al *Surg Clin North Am* 91(6):1339-1351.

BMI >35 with severe comorbidities:	**BMI >40 with mild comorbidities:**
• T2DM • Moderate to severe obstructive sleep apnea (OSA) • Pseudotumor cerebri	• Hypertension • Dyslipidemia • Mild OSA • Venous stasis disease • Panniculitis • Urinary incontinence • Impairment in activities of daily living • Steatohepatitis • Gastroesophogeal reflux disease • Severe psychosocial distress • Weight-related arthropathies
Additional requirements for adolescents:	
• Have attained 95% of adult stature • Have failed to attain a healthy weight with prior organized attempts at weight loss • Demonstrate commitment to psychological evaluation in the peri-operative period • Avoid pregnancy for 1 year after surgery • Will adhere to postoperative nutritional guidelines • Have decisional capacity and will provide informed assent	

When these criteria are followed, bariatric surgeries among adolescents yield an impressive success rate among adolescents that varies according to the type of surgery pursued. The different procedures offered and their relative pro's and con's have been reviewed previously.[15] The Roux-en-Y gastric by-pass is the procedure with the most long-term data, revealing that on average adolescents have an excess body weight loss of 77.7% at 5-9 years after surgery.[17] The gastric sleeve method has been used with increasing frequency but has limited long-term data regarding efficacy and safety in adolescents.[15, 18] The lap-band method is not currently FDA-approved among adolescents and has had issues of poorer long-term weight loss (over 25% of adults failed to maintain 30% excess weight loss) and a higher re-operation rate (8-50%).[19]

Special Considerations: Removal from home
Success of both lifestyle modification and eligibility for surgery require significant treatment plan adherence by the child's family. However, clinical experience would suggest that some families fail to facilitate adjustments in their child's lifestyle practices despite warnings of the health consequences—resulting in continued weight gain. While controversial, one potential response that may be necessary is initiating involvement of social service agencies, with the ultimate potential of removing the child from the home.[20] The rationale behind this is that the parents' failure to adhere to the treatment regimen poses an imminent danger to the child's health. Potential improvements in treatment plan adherence by a foster family could be instrumental in reversing dangerous weight gain and start the process toward weight loss, reduced short-term and long-term risks. This process proceeds via contact of social services as part of mandated reporter laws regarding parental neglect. This weighty decision can be guided by criteria proposed by Varness et al.[21] It is important to note that taking these steps would typically not be performed in a family who could are eligible for bariatric surgery, who have to be able to adhere to a treatment plan to meet criteria.

MAIN CONCLUSIONS

Because of its strong associations with current and future comorbidities, morbid obesity in childhood represents an urgent condition requiring careful treatment. Unfortunately, patients and their families frequently do

not sense any immediacy to the issues, often limiting the success of attempts at lifestyle modification. While this is not a cause for clinical despair, it does mean that more intensive intervention such as bariatric surgery may be needed to help avoid some of the more dire long-term consequences for these children.

CASES WITH QUESTIONS AND DISCUSSION OF CASES AND ANSWERS

Case 1

TF is a 14 year old boy referred to his endocrinologist for evaluation and management of obesity. His BMI crossed the 95th percentile at age 5 and has risen steadily since then. In clinic he has a BMI of 39, a BP of 127/72 (just under the 95th percentile for height and weight) and Tanner 3 pubic hair. His mother reports that he snores loudly but she does not hear him obstruct his breathing. His referring doctor ordered an oral glucose tolerance test, revealing a 2-hour glucose of 145 mg/dL.

Points of consideration in response to questions *(Diagram 1)*:

1. Clearly he is at high risk for future complications, though at this point his only co-morbidities identified are glucose intolerance and possibly mild OSA. Based on his, BMI, lack of severe comorbidities and his early maturational status, he does not meet criteria for bariatric surgery. While off-label, it would be reasonable to consider treating his glucose intolerance with metformin, which may modestly assist his weight loss efforts.
2. Given his report of snoring, a sleep study would be helpful to assess whether he has obstructive events that are not witnessed.

Case 2

G.T. is a 15 year old girl referred to endocrinology for evaluation and treatment of extreme obesity. She has been obese since before 2 years old. Her BMI is currently 42 and she has a blood pressure of 142/88. The family reports that she is otherwise healthy besides having moderate knee pain and having irregular menstrual periods since menarche 4 years ago. She has been trying to walk their dog for 30 minutes on a daily basis and that she has cut soda and juice out of her diet. She has tried dieting in the past but has never seemed to be able to lose weight.

Points of consideration in response to questions *(Diagram 2)*:

DIAGRAM 1

Questions for discussion:

a. Should he fail to improve his weight during lifestyle modification therapy, is he a reasonable candidate for any other treatment approach?

b. What other treatments or laboratory studies would you like to pursue for him?

Laboratory findings	
HbA1c	5.7%
Fasting glucose	97 mg/dL
LDL cholesterol	100 mg/dL
HDL cholesterol	38 mg/dL
Triglycerides	120 mg/dL

DIAGRAM 2

Questions for discussion:

a. Should she fail to improve her weight during lifestyle modification therapy, is she a reasonable candidate for any other treatment approach?

b. What other treatments or laboratory studies would you like to pursue for her?

Laboratory findings	
HbA1c	6.1%
Fasting glucose	105 mg/dL
LDL cholesterol	120 mg/dL
HDL cholesterol	35 mg/dL
Triglycerides	160 mg/dL

1. This patient is quite obese and appears to have related hypertension. She is clearly at high risk for future co-morbidities. She meets criteria for consideration of bariatric surgery, including having a family that seems engaged in taking steps to try to lose weight but without success. Further attempts at weight loss are in order, including increased exercise and cutting back on portion sizes. It may be reasonable to treat with metformin either for PCOS or glucose intolerance. Nevertheless, evidence would suggest the step most likely to produce sustained, meaningful weight loss is bariatric surgery.
2. She should have knee x-rays to evaluate for potential Blount's disease and have free testosterone levels assessed for potential PCOS. Assessing an OGTT may also be helpful in determining glucose tolerance.

Case 3

H.B. is an 8 year old boy referred to endocrinology for evaluation and treatment of extreme obesity. He missed 2 previous appointments before coming this time. Review of his prior growth charts reveal that he became obese at 3 years of age and over the past two years has gained weight sharply. His height percentile has increased slowly and is not at the 90th percentile. His BMI is 28, which is approximately 6 standard deviations from the mean. He is pre-pubertal. His mother is not always coherent in the interview, which she attributes to poor sleep the night before. The mother is counseled regarding healthy lifestyle changes, both with a teaching session and written material. On follow-up (after missing two more appointments) his BMI has increased to 29.

Points of consideration in response to questions *(Diagram 3)*:

This boy is at high risk for future serious comorbidities related to his obesity. The family has not demonstrated engagement in the process toward improved lifestyle. He is clearly too young for bariatric surgery and does not appear to have the family support that would be required for this either. It will be important to work closely with the mother. Should future attempts at improved treatment adherence prove unsuccessful, it may be a consideration to contact social services because of neglect related to his obesity risks.

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DIAGRAM 3

Questions for discussion:

a. Should he fail to improve his weight during lifestyle modification therapy, is he a reasonable candidate for any other treatment approach?

b. What other treatments or laboratory studies would you like to pursue for him?

Laboratory findings	
HbA1c	5.8%
Fasting glucose	92 mg/dL
LDL cholesterol	115 mg/dL
HDL cholesterol	39 mg/dL
Triglycerides	129 mg/dL

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New Pharmacological Therapies for Obesity Management

M7
Saturday, June 15
3:00–3:45 PM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Overweight (BMI ≥25) and obesity (BMI ≥30) are global epidemics and, in the United States, affect approximately 70% and 35% of the population, respectively [1]. Because of associated co-morbidities, obesity adversely affects mortality, morbidity, and quality of life [2,3]. Regarding the public health burden, foremost among obesity-related complications is the exacerbation of cardiometabolic disease leading to increased prevalence of Type 2 Diabetes Mellitus (T2DM) and cardiovascular disease (CVD) [4–6]. Obesity is also associated with mechanical complications due to the increase in body mass including osteoarthritis, obstructive sleep apnea, and stress incontinence. In addition to patient suffering and the direct medical costs associated with treatment of these conditions, there is an indirect burden to society that includes decreased work productivity, absenteeism, disability, workplace injuries, and depression [7].

Current treatment options for overweight and obesity include lifestyle modifications, pharmacotherapy, and bariatric surgery. Lifestyle modifications include a reduced-calorie diet, physical activity, and behavior changes, and represent the initial approach and the cornerstone of weight-loss therapy, as recommended by National Heart, Lung, and Blood Institute (NHLBI) [3]. Bariatric surgery can be a highly effective weight-loss option [8]. However, indications for bariatric surgery are typically limited to morbidly obese patients (BMI ≥40 kg/m^2) or those with a BMI ≥35 kg/m^2 plus weight-related co-morbidities. Until recently, medication options were quite limited. There are four sympathomimetic medications, namely phentermine, benzphetamine, diethylpropion, phendimetrazine, which act by suppressing appetite and are approved only for short-term treatment of obesity (<3 months) [9]. These drugs have limited applicability to the long-term treatment of obesity which is a chronic and perhaps life-long disease. Orlistat (Xenical, Genentech, South San Francisco, CA, USA), a gastrointestinal lipase inhibitor that reduces the absorption of dietary fat, is approved for long-term treatment of obesity; however, in a 4-year, double-blind, prospective study of 3305 obese patients, only moderate weight loss over placebo was observed (5.8 kg vs 3.0 kg), together with variable improvements in cardiometabolic risk factors [10].

In the summer of 2012, two therapies were approved by the US Food and Drug Administration (FDA) as adjuncts to a reduced-calorie diet and increased physical activity. These medications, twice-daily lorcaserin (Belviq®, Arena Pharmaceuticals, Switzerland) and once-daily phentermine/topiramate ER (Qsymia®, VIVUS, Inc., Mountain View, CA, USA), have greatly enhanced medication treatment option for clinicians and patients. Both are indicated for chronic weight management in adult patients with an initial body mass index (BMI) of ≥30 kg/m^2 or BMI ≥27 kg/m^2 in the presence of at least one weight-related co-morbid condition (e.g., hypertension, dyslipidemia, T2DM) [11,12]. As demonstrated by several Phase II and Phase III clinical studies, these drugs can produce and maintain substantial weight loss and improvements in cardiometabolic disease risk factors when compared with placebo [13-20]. The drugs are well-tolerated

and can effectively prevent the progression to T2DM in patients with Prediabetes or Metabolic Syndrome; improve glycemia and blood pressure while at the same time allowing reductions in medications for T2DM and hypertension; and ameliorate functional indicators in patients with obstructive sleep apnea. Thus, the availability of these two new drugs enable effective medical options to complement lifestyle and surgical approaches, and a medical model for comprehensive obesity care that can be used to promote the health of individuals by ameliorating obesity complications.

BARRIERS TO OPTIMAL PRACTICE

- Lack of knowledge regarding new medical treatment options
- Inability to establish a team of health care professional needed to engineer lifestyle change
- Defeatist attitude towards treatment of obesity, and inattention to the potential for weight loss as a tool to treat cardiometabolic disease, due in part to historically inadequate treatment modalities

LEARNING OBJECTIVES

As a result of participating in this session learners should be able to:

- Understand efficacy and application of all treatment options for obesity management (lifestyle, medications, and bariatric surgery).
- Analyze the safety and efficacy profiles of current and emerging anti-obesity medications to better select agents that improve adherence while enhancing weight loss.
- Develop a rational approach to the use of medications in the management of overweight/obese patients.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

As demonstrated in Phase II and Phase III clinical studies, phentermine/topiramate ER and lorcaserin are well tolerated and can produce and maintain substantial weight loss and improvements in cardiometabolic disease risk factors when compared with placebo. While head-to-head studies have not been conducted, the clinical trials data support the contention that phentermine/topiramate ER is more efficacious than lorcaserin. For example, lorcaserin resulted in 3.6% placebo-subtracted weight loss after 1 year in the BLOOM Study (5.8% weight loss versus 2.2% for placebo), with some weight regain in treated patients over the second year of the study [13]. On the other hand, phentermine/topiramate ER produced 9.4% placebo-subtracted weight loss after 1 year in the EQUIP Study (11% versus 1.6% on placebo) [18], and the SEQUEL study demonstrated sustained weight loss over 2 years [20]. Even so, both drugs were able to improve cardiometabolic disease manifestations such as triglycerides, blood pressure, glucose intolerance, and insulin sensitivity; prevent progression to T2DM in high-risk patients with Prediabetes or Metabolic Syndrome; improve HbA1c and blood pressure in patients with T2DM or hypertension; and phentermine/topiramate ER markedly improve the apnea-hypopnea index in patients with obstructive sleep apnea [13-20]. The weight loss produced by these drugs is intermediate between that commonly achieved by lifestyle modifications or other less effective medications and the average weight loss following gastric bypass bariatric surgical procedures (~30%). By offering an effective medical option to complement lifestyle and surgical approaches, phentermine/topiramate ER and lorcaserin enable a medical model for comprehensive obesity care that can be used to promote the health of individuals by ameliorating obesity complications.

What is the appropriate medical model for obesity management? Any intervention entails risk, and treatment must be targeted to those patients who will derive the greatest benefits from the intervention according to considerations that optimally balance benefit and risk. The patients who will benefit most from the degree of weight loss achievable with the new drugs are not those seeking a cosmetic result, but rather patients with obesity-related complications that can be ameliorated by weight loss. These complications can be classified into 2

general categories, namely, those that relate to insulin resistance and cardiometabolic disease and those that relate to the mechanical consequences of excess body weight. Therefore, **Step 1** of the medical model is to evaluate and stage the patient for the presence and severity of obesity-related complications and the impact of these complications on the patient's well-being. **Step 2** for medical treatment of obesity is for the clinician and patient to set therapeutic targets and goals for improvements in complications, and identify the modality and intensity of therapy needed to achieve these goals. Following the initiation of the selected therapeutic option, **Step 3** involves reassessment of the patient for the impact of weight loss on complications after equilibrium weight loss is achieved. If the target for improvement in complications is not reached, then the weight-loss therapy should be intensified in order to achieve the desired goal. It is important to consider that many cardiometabolic disease and mechanical complications exist to a large degree independent of baseline BMI. From this perspective, baseline BMI is less important than the existence and severity of complications at baseline [21-24], and, by the same consideration, the degree of improvement in obesity-related complications is more important that the absolute amount of weight that is lost. Thus, this is a complications-centric model, rather than a BMI-centric model, for obesity management wherein weight loss is used as a tool to ameliorate the complications of obesity. This approach will optimize the benefit/risk ratio for the intervention, and achieve the best outcomes by aligning specific therapy with those patients who will derive the greatest benefit.

The clinical trial data raise three salient considerations. First, all enrollees in clinical trials engaged in a lifestyle intervention regardless of whether randomized to placebo or drug treatment arms. Therefore, the efficacies of phentermine/topiramate ER and lorcaserin reflect the combination of drug as an adjunct to lifestyle therapy. All patients being considered for weight loss drugs should also participate in a lifestyle intervention in order to achieve optimal outcomes [25]. The second point is that there is variability in the weight loss response, as is the case for any drug. Patients are not assured that the mean weight loss demonstrated in the clinical trials will be achieved, and some patients will represent primary drug failures. Therefore, it is important to follow the prescribing information that outlines scenarios for drug discontinuation when weight loss is not sufficient. The final point is that the duration of sustained weight loss on the new obesity drugs in unknown. Obesity is a life-long chronic disease, and will require prolonged therapy. Accumulating clinical experience together with protracted clinical trials will be needed to assess longer term efficacy and strategies that employ all treatment options to sustain weight loss over decades.

MAIN CONCLUSIONS

- Two new weight loss medications, phentermine-topiramate ER and lorcaserin, were approved by the FDA in the summer of 2012. In combination with lifestyle intervention programs, these drugs induce significantly greater weight loss than observed with placebo.
- The availability of these drugs represents a landmark development in the pharmacotherapy of obesity.
- By offering an effective medical option to complement lifestyle and surgical approaches, these drugs enable a comprehensive medical model for obesity care.
- The overall approach to the overweight and obese patient should be to identify individuals who will benefit most from therapy based on cardiometabolic or mechanical complications, establish therapeutic targets and goals for ameliorating these complications, and select the treatment modality and intensity for weight loss to achieve these goals. This complications-centric model emphasizes weight loss as a tool to ameliorate obesity-related complications, and optimizes benefit/risk, in achieving the best outcomes in overweight/obese patients.

CASES

Case 1

39 year old African American female, substitute grade school reading/English teacher, with a history of anxiety and depression, currently taking fluoxitine 40 mg once daily. She reports that she has gained over 50 pounds in the past ~10 years and wants to lose weight for a family reunion in 5 months. She has tried diet books and Weight Watchers which have led to some weight loss but quickly regained the weight. She tried Zumba classes but did not seem to "have the energy for it".

She is married and sexually active, nulligravida, and currently is not using any birth control. She reports irregular menses every 30-40 days. Her mother has type 2 diabetes and is on dialysis. She is worried that her continued weight gain will cause her to develop diabetes. Non-smoker and social alcohol ingestion. On review of systems she complains of low energy through the day and states that her husband complains of her snoring.

Case 2

52 year old European American male, bank executive, is referred to you for control of diabetes. He has had Type 2 Diabetes for 12 years, first treated "with diet" for 2 years and then with metformin 2,000 mg/day which he has been taking continuously since then for 10 years. 4 years ago he was also prescribed glyburide 15 mg/day which helped his sugars for only a while and was associated with accelerated weight gain. His "other doctor" wanted to put him on liraglutide but he did not want to do the injections. He is seeking another doctor for an alternative solution to diabetes control

He had gained weight steadily since the age of 30. He has received dietary advice from a dietitian and was put on a weight loss diet but it "didn't do much good". He complains of a decrease in libido. He has 2-3 drinks per day, eats at restaurants frequently, plays golf on one Sunday per month but no other exercise, is married, and has 2 children away at college

QUESTIONS FOR DISCUSSION OF CASES

Case 1

1. ***What is significance of African American ethnic identity?***
2. ***What is significance of acanthosis nigricans?***
3. ***Does patient have Metabolic Syndrome by ATPIII criteria?***
4. ***Does patient have Prediabetes?***
5. ***Do we know that the patient does not have Diabetes?***
6. ***Why might she be complaining of low energy through the day and too little energy for Zumba?***
7. ***Why might she have oligomenorrhea and history suggestive of infertility?***
8. ***What symptoms and laboratory parameters could be ameliorated through weight loss?***
9. ***What therapeutic options would you favor for weight loss?***
10. ***For weight loss pharmacotherapy, what would be the preferred drug and why?***

Case 2

1. ***What are the therapeutic options for glycemic control and which are preferred?***
2. ***What are the therapeutic options for hypertension control and which are preferred?***
3. ***What steps would you take in treating the dyslipidemia?***
4. ***Is there a role for medication-assisted weight loss?***
5. ***What is significance of low testosterone and decreased libido and how might this affect management?***
6. ***What is significance of elevated LFTs and how might this affect selection of therapy?***

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PEDIATRIC ENDOCRINOLOGY

Pediatric Bone Densitometry: Pearls and Pitfalls

M54
Tuesday, June 18
11:15 AM to 12:00 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

The demand for bone densitometry in pediatrics has grown with the increased concern for early bone fragility. Several genetic and acquired disorders have been linked to reduced bone quantity and quality during childhood leaving bones more vulnerable to fracture throughout life. Recurrent fractures even in otherwise healthy youth may be a sign of underlying bone fragility. Osteoporosis can be diagnosed definitively in a child once fragility fractures occur. The goal of clinical practice, however, is to predict and prevent fractures before they occur. This session will review pediatric guidelines for bone densitometry using clinical cases to highlight common conundrums in practice.

BARRIERS TO OPTIMAL PRACTICE

The surrogate measures of bone health (densitometry, bone markers) used to assess fracture risk in adults are far more challenging to interpret in children. In addition, treatment options for children are limited. The pharmacologic agents that have proven safe and effective to treat osteoporosis in adults have not been fully tested in children. As a result, there is no consensus about the optimal drug, dose or duration of therapy for pediatric patients. The limited therapeutic options make it all the more important to accurately identify those at greatest risk for fracture.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Identify the indications for bone densitometry in children and teens
- Recognize the challenges of interpreting results in patients with delayed growth or puberty
- Outline current criteria for diagnosing osteoporosis in younger patients
- Propose additional components of a comprehensive skeletal assessment

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

The complexities of evaluating skeletal health have left pediatricians in a quandary about how to best diagnose and manage skeletal fragility in young patients. The Pediatric Position Development Conference (PDC) held in 2007 developed recommendations for evaluating and managing skeletal health in children and teens. Guidelines developed by this panel of experts reflected the available scientific data and expert opinion where data were lacking. Many of the "pearls" identified below are drawn from the PDC guidelines. The pitfalls listed below underscore the need both for clinical judgment and more research to optimally evaluate the growing patient.

Densitometry Methods

Pearls

- DXA remains the preferred method for clinical bone densitometry in children because of its availability, speed, low radiation exposure and robust normative data
- Peripheral QCT (pQCT) measures volumetric bone mineral density (vBMD), identifies trabecular and cortical bone separately, and provides direct measures of bone geometry directly. However, pQCT

remains largely a research tool because of lack of standardized scanning protocols and reference data
- Quantitative ultrasound of bone has been limited by lack of precision and uncertainty about what aspect of skeletal integrity is captured by this technique.

Indications for Densitometry

Pearls
- The PDC identified the following disorders associated with altered bone mass and increased fracture risk for which DXA studies would be indicated:

Primary Bone Disorders
- Idiopathic juvenile osteoporosis
- Osteogenesis imperfecta

Disorders Secondary to

Inflammation
- Inflammatory bowel disease
- Juvenile idiopathic arthritis
- Cystic fibrosis

Immobilization
- Cerebral palsy
- Myopathies
- Epidermolysis bullosa

Endocrine disturbance
- Turner syndrome
- Anorexia nervosa

Cancer and therapies with adverse effects on bone
- Acute lymphoblastic leukemia
- After chemotherapy for childhood cancer
- Following transplantation

Hematologic disorders
- Thalassemia

When Should Initial and Repeat Scans be performed?
- For most conditions, first scan "at presentation" of disorder
- For thalassemia, DXA at the time of first fracture or at age 10 (whichever came first)
- For immobilization disorders, once a fracture had occurred
- For Turner syndrome, in adulthood.
- To monitor disease progression or therapy, scans should be repeated no more often than every six months

Which Skeletal Site(s) Should Be Studied by DXA?

Pearls:
- Lumbar spine and whole body less head (WBLH) are the most precise
- The cranium should be excluded if possible because the head contributes considerable mass to the WB and changes little with time which can mask subtler changes WB bone mass
- Distal radius is an alternative skeletal site which may the only one that will fit in the scanner in very obese subjects.
- Lateral distal femur is valuable for patients with immobilization disorders (CP, muscular dystrophy) or those with contractures that preclude proper positioning for spine or WB

Pitfalls
- Avoid metal (spine or femoral rods, umbilical rings) or contrast dye
- Exclude vertebrae with compression fractures which can result in increased aBMD

Reporting and Interpretation

Pearls:
- Bone mass is reported as mineral content (BMC) and density (aBMD)
- Z-scores (standard deviation by age) for these parameters should be used before age 20 since T-scores compare the patient with healthy young adults
- Choose reference data collected using similar DXA manufacturer and software as patient
- Bone mineral density (aBMD) is an areal not volumetric measure, resulting in lower values in smaller individuals. In children with delayed growth or maturity, height adjustment recommended
- "Gold standard" pediatric reference data from the Bone Mineral Density in Childhood Study (http://www.bmdcspublic.com)
  - Based on a representative sample of youth (ages 5 -23)
  - Black vs. non-Black norms for BMD and BMC for spine, WB, WB less head, distal 1/3 radius, total hip

- Statistical modeling accounts for non-linear gains and the increased variability in bone mass with age and puberty
- Provides height-corrected Z-score if you enter height
- Collected using current Hologic equipment and software; results converted to GE-Lunar equivalents (available in software version 13)
- Reporting Terms
  - Avoid using the terms "osteopenia" or "osteoporosis" based upon bone density only
  - If BMC or aBMD Z-score is <-2, refer to this as "low bone mass" for age

Pitfalls – Factors to consider before ordering a DXA

- Disease severity
- How much exposure to osteotoxic medications
- Feasibility
  - Can the patient lie still?
  - Are there contractures or hardware in the region of interest?
  - Are there vertebral fractures (diagnosed on lateral spine x-ray)?
  - Is the densitometry center experienced with pediatric patients?
  - How will DXA findings influence clinical management?
  - Therapeutic decisions should NOT be based on DXA findings alone
  - Risks not from radiation exposure but from errors of DXA interpretation!

Bone densitometry and fracture prediction

Pearls

- Low BMC and aBMD adjusted for bone area are linked to fracture risk in healthy youth
- Low spine aBMD Z-score linked to spine fractures in childhood leukemia
- Bone mass at lateral distal femur a better predictor than spine aBMD in immobilized youth
- Other clinical variables including nutrition, activity, medication exposure likely contribute to fracture risk
- Association between BMC and aBMD and fracture are NOT sufficiently robust to use densitometry to diagnosis osteoporosis
- Bone densitometry is only part of a comprehensive skeletal assessment. Genetic, inflammatory, nutritional, biomechanical, and endocrine risk factor s should be considered. The choice of specific tests is determined by history and physical exam.

Basic Laboratory Assessment for Skeletal Fragility

- CBC and ESR
- Serum calcium, phosphorus, intact PTH, total 25-hydroxyvitamin D, magnesium, alkaline phosphatase, BUN, creatinine
- Urine calcium/creatinine
- Free T4, TSH
- Celiac screen
- LH, FSH, estradiol or testosterone (if concern for hypogonadism)
- IGF-I (consider in those with growth failure or in males)
- Genetic screen for OI (indicated for those suspicious fracture history)
- Optional
  - Serum and urine biochemical bone markers may have a value in research or to monitor response to pharmacologic interventions.
  - A bone biopsy is helpful in distinguishing osteomalacia from osteoporosis and evaluating patients not diagnosed through routine evaluation.

Pitfalls

- "Osteoporosis" diagnosis in pediatrics requires both low bone mass (BMC or aBMD Z-score <-2) AND a significant fracture history (2 long bone fractures UE, 2 long fracture LE or vertebral fractures). Can osteoporosis be diagnosed by fracture alone?

MAIN CONCLUSIONS

The PDC guidelines provide expert opinion on indications for initial and repeat densitometry in children and teens. Appropriate interpretation of scans includes adjustments for delayed growth and puberty and use of age, sex and ethnic specific normative data. The diagnosis of osteoporosis in a child is

based on both low bone mass for age and a significant fracture history. Other components of a comprehensive skeletal assessment include screens for nutritional and hormone deficits as well a chronic acquired or genetic disorders affecting bone.

CASES WITH QUESTIONS

For each of the following clinical scenarios

- ***Would you order a DXA and why (or why not)?***
- ***Which skeletal site(s) would you examine?***
- ***What are the potential pitfalls in the evaluation of results?***
- ***What other tests might you order?***

Case 1

15 year old female runner with primary amenorrhea, height at the 3rd percentile, BMI of 15, and one stress fracture 6 months ago. Mother of patient (age 48) has "osteoporosis" by DXA but no fractures.

Case 2

10 year old wheel-chair bound boy with CP and seizures (on Dilantin). No h/o fractures.

Case 3

Apparently healthy 7 year old boy with his fourth fracture (age 3, right forearm; age 4, left radius; age 6, right radius; age 7, right tibia).

Case 4

9 year old boy with multisystem inflammatory disease involving heart, brain and muscles treated with high dose glucocorticoids for 2 years. Complaining of back pain. Height on 50%ile, weight on 80%, BMI on 90th%ile.

DISCUSSION OF CASES AND ANSWERS

Case 1

The patient likely has exercise-associated primary amenorrhea (with perhaps some occult disordered eating). She has no significant fragility fracture history. The family history of osteoporosis is limited to Mom's diagnosis of osteoporosis is based on DXA findings (rather than hip fracture, which is more reliable). If you order a DXA, you should do height corrected Z-score – but this will not correct for delayed maturity. An important question is how it will DXA findings change management? If bone density is low, will this motivate the patient to work on nutrition? If normal, will she be less likely to adhere to suggestions re: activity and diet? Other tests to consider in evaluating the delayed growth and menarche include FSH (r/o ovarian insufficiency), prolactin, karyotype (Turner syndrome), celiac screen, CBC, ESR, TFTs and pregnancy test.

Case 2

This child is at risk for bone fragility because of immobilization AND anticonvulsant therapy. In the absence of prior fracture, a DXA is not clearly indicated. Bone mass will be low. IF you do a DXA, most informative region of interest would be lateral distal femur. Other more useful work up: review of overall nutrition, calcium, vitamin D intake and levels, and physical therapy regimens (to optimize skeletal loading as tolerated).

Case 3

This otherwise "healthy" 7 year old child is concerning because he has had four fractures including some occurring before age 5. It will be important to review the nature of the trauma causing fracture but further work up is warranted. DXA of spine and WB if he will cooperate; lateral thoracolumbar spine x-rays should be done to rule out vertebral fracture. To determine WHY bone quantity and quality is low requires additional testing. Consider measuring serum 25 OHD, celiac screen, CBC, ESR, IGF-I, TFTs, urine calcium/creatinine ratio and possibly test for osteogenesis imperfecta. This can be performed commercially with 3-5 ml of EDTA blood in children (Matrix DNA Diagnostics – Tulane).

Case 4

Back pain in this setting is worrisome and may indicate vertebral fractures. He warrants a lateral plain film of thoracolumbar spine. The report cites several vertebral compression fractures and "washed out" bones throughout. DXA adds little to the diagnosis but might be done as baseline before starting treatment. Care must be taken to exclude vertebrae with

fractures. The causes for fractures in this patient are myriad including inflammatory cytokines, periods of reduced mobility, long term high dose glucocorticoid therapy, and potential nutritional deficits. It would be worthwhile to check a 25 OHD vitamin D but searching for additional occult risk factors may not be high yield. Bisphosphonate therapy should be offered to the family.

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Controversies in the Management of Congenital Hypothyroidism

CMF3
Tuesday, June 18
12:15 – 1:00 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM:
Congenital hypothyroidism (CH) is one of the most frequent congenital endocrine disorders and occurs in about 1 of 3000 live births. It is the most common preventable causes of mental retardation and neonatal screening programmes which have been run over the last 30 years in most industrialized countries, with early institution of thyroid hormone replacement therapy have largely eliminated the severe neurodevelopmental deficit of untreated CH. Results from neonatal screening programmes have also helped to identify a wide spectrum of thyroid dysfunctions. The most common form of CH is primary hypothyroidism with elevated thyroid-stimulating hormone (TSH) levels related to various types of abnormal thyroid gland development or dyshormonogenesis. Secondary (central) hypothyroidism is much less frequent with either isolated TSH deficiency due to mutations inactivating the TSH β subunit, the TRH receptor, or IGSF1 or, more commonly, TSH deficiency associated with other pituitary hormone deficiencies.

Impaired thyroid hormone production may also be temporary or permanent and requiring lifelong treatment, and thyroid dysfunction may change in a given individual with growth and development stages. Transient primary CH can be defined as an increase in TSH levels during the neonatal period, with or without low total or free thyroxine levels, with normal thyroid function test results obtained off treatment at a later stage. Isolated hyperthyrotropinaemia refers to a mild increase in TSH concentration (e.g. 6–20 mU/L) with normal thyroid hormone concentrations. It may also be transient or permanent.

Recent reports have indicated that the incidence of primary CH may be increasing in some countries, particularly for cases with a normally located (eutopic) thyroid gland and milder dysfunction. The reasons for this remain unclear, but may relate to changes in screening thresholds.

BARRIERS TO OPTIMAL PRACTICE:
Some barriers to optimal practice remain:
- Implementation of screening in countries without screening programmes.
- Clarifying elements of screening procedures which remain controversial: TSH cut off levels, retesting in some conditions, raised TSH in preterm infants.
- Treatment of patients with mild isolated hypertropinaemia and determining the outcome of these cases.
- Improving long-term adherence to treatment and the management of the transition from pediatric to adult care.
- Treatment monitoring in pregnant women with CH.
- A greater understanding when aetiology is unknown.
- How to manage fetal treatment in utero

LEARNING OBJECTIVES:
As a result of participating in this session, the learners should be able to:

- recognize the values of current screening programs
- understand the key tests to perform to establish the diagnosis and recognize the causes of CH
- monitor therapy to achieve maximal benefits
- identify the key issues involved in the management
- understand when to consider genetic testing.

SUCCINCT REVIEW- STRATEGIES FOR DIAGNOSIS, THERAPY AND MANAGEMENT:

In 2011, The European Society for Paediatric Endocrinology (ESPE) decided to examine current best practice for the screening, diagnosis and management of patients with CH and to formulate evidence-based recommendations. The principal conclusions are as below. We will review the specific evidence-base of the recommendations following each case example.

The benefits of CH screening

Early detection and treatment of congenital hypothyroidism (CH) through neonatal screening prevent neurodevelopmental disability and optimize developmental outcomes.

Analytical methodology, effectiveness and efficacy of CH screening strategies

Screening for primary CH should be introduced worldwide. The initial priority of neonatal screening for CH should be the detection of severe and mild forms of primary CH. The most sensitive test for detecting primary CH is thyroid-stimulating hormone (TSH) determination.

Screening in special categories of neonates at risk of CH

A special screening strategy involving multiple sampling collection should be considered for the following conditions: preterm neonates; low-birthweight (LBW) and very low-birthweight (VLBW) Neonates; Ill and preterm newborns admitted to neonatal intensive care units (NICU); early specimens collected within the first 24 hours of life from neonates from multiple births.

CASES WITH QUESTIONS:

The cases below illustrate some of the dilemmas as a result of screening for CH for discussion during the session.

Case 1

A term newborn was detected by the neonatal screening with raised whole blood TSH (175 mU/L). At 10 days of life, the child was seen in the paediatric endocrinology clinic. The infant was the second child of non-consanguineous healthy parents. The mother reported an uncomplicated pregnancy and delivery. Clinical evaluation showed moderate hypotonia and jaundice. Both the anterior and posterior fontanelles were present and large.

What form of CH does this infant have?
What investigations are needed?
What treatment is indicated?
How should the infant be followed up on thyroid hormone supplementation?
Should further evaluation be done?
What is the risk of associated morbidity?
What are the significant clinical consequences of inadequate treatment?
How would you advise the parents about genetic counselling?

Case 2

A term newborn 4.13kg had tachypnoea and sepsis. In the neonatal unit on day 3 venous TSH was 98.8mU/L and Free T4 18.6 pmol/L, but the screening whole dried blood TSH taken on day 5 was only 20mU/L. The family revealed consanguinity and an older sibling with CH.

How do you explain the result of DB TSH?
What would you do for the treament and management of this patient?
What is the place of imaging in this situation?
What should you do if genetic counselling is desired?

Case 3

A well term baby 3.49kg was screened on day 5. Whole blood TSH was 7mU/L. On recall at 20 days venous TSH was 15.8mU/L and

Free T4 19pmol/L. TPO antibodies were not detected and a Technetium isotope scan was normal.

Does this infant have CH?
What treatment should be given and how should it be administered and monitored?

Case 4
A 24 week gestation infant had a day 6 screening TSH of 0.6mU/L. He had necrotizing enterocolitis, intestinal perforation with ileostomy sepsis, chronic lung disease and cholestatic jaundice possibly related to total parenteral nutrition. Venous TSH on day 52 was 29.6mU/L and Free T4 6.3 pmol/L. Ultrasound scan showed a structurally normal, normally sited thyroid gland.

What treatment is indicated?
What follow up programme should happen?

Case 5
A baby was delivered at 37 weeks by Caesarean section due to IUGR birth weight 1.73kg. He was dysmorphic with congenital heart disease and poor self-ventilation. Parents were first cousins. Screening whole blood TSH on day 7 was 40 mU/L, repeat venous sample on day 14 gave TSH >100 mU/L and Free T4 4.0pmol/L.

Should further evaluation be considered?
What genetic counselling should you give the parents?

DISCUSSION OF CASES WITH ANSWERS:

Case 1
This is a case of unambiguous classic CH with clinical signs present too.

ESPE consensus recommendations are as follows:

Biochemical criteria used in the decision to initiate treatment

- Capillary TSH concentration obtained in neonatal screening
- If capillary TSH concentration ≥ 40 mU/l of whole blood, we recommend starting treatment as soon as a good venous sample can be obtained, without waiting for the venous blood test result, unless venous thyroid function test (TFT) results are available on the same day
- If capillary TSH concentration < 40 mU/l of whole blood, the clinician is may wait for the results of venous TFT, provided that these results are available on the following day.

Decision to start treatment on the basis of venous TFTs

- If venous free T4 concentration is below norms for age, treatment should be started immediately.
- If venous TSH concentration > 20 mU/l, treatment should be started, even if fT4 concentration is normal
- If venous TSH concentration ≥ 6 to 20 mU/l beyond 21 days in a well baby with a FT4 concentration within the limits for age, we suggest:
  - Investigation, which should include diagnostic imaging, to try to obtain a definitive diagnosis
  - Consideration, in discussion with the family, of the immediate initiation of thyroxine supplementation
  - Retesting, off treatment, several months later or retesting 2 weeks later in the absence of treatment.

Treatment and monitoring of CH

- L-T4 alone is recommended as the medication of choice for treating CH.
- L-T4 treatment should be initiated as soon as possible and no later than two weeks after birth or immediately after confirmatory serum test results in infants in whom CH is detected by a second routine screening test.
- An initial L-T4 dose of 10-15 μg/kg per day should be given.
- Infants with severe disease, as defined by a very low pre-treatment T4 or FT4 concentration, should be treated with the highest initial dose.
- L-T4 should be administered orally or i.v, if required (no more than 80% of the oral dose).

- The dose should then be adjusted according to TSH and FT4 determinations.
- L-T4 tablets should be used, crushed and administered via a small spoon, in a few ml of water or breast milk.
- L-T4 liquid can be used only if pharmaceutically produced

Monitoring of dose

- Serum or plasma free T4 (or total T4) and TSH concentrations determined at least 4 hours after the last L-T4 administration.
- TSH concentration should be maintained in the age-specific reference range and T4 or FT4 concentration should be maintained in the upper half of the age-specific reference range.
- The reduction of LT4 dose should not be based on a single increase in FT4 concentration during treatment
- The first follow-up examination should take place 1-2 weeks after the start of L-T4 treatment and subsequent evaluations should take place every 2 weeks until a complete normalisation of TSH concentration is reached and then every 1 to 3 months thereafter until the age of 12 months.
- Between the ages of one and three years, children should undergo frequent clinical and laboratory evaluations (every 2 to 4 months)
- Thereafter, evaluations should be carried out every 3 to 12 months until growth is completed.

More frequent evaluations should be carried out if compliance is questioned or abnormal values are obtained and additional evaluations should be carried out 6 weeks after any change in L- T4 dose or formulation.

Case 2

This infant is likely to have dyshormonogenesis on account of the family history. Biochemistry suggests moderately severe CH but this can be confirmed by imaging.

ESPE consensus recommendations are as follows:

Radiological features indicating severity of CH

- X ray of the knee may be carried out to assess the presence or absence of femoral and tibial epiphyses
  - The absence of one or both epiphyses indicates severe intrauterine hypothyroidism
  - The presence of both epiphyses indicates moderate, mild or no hypothyroidism
- Imaging of the thyroid gland should be performed by ultrasound, radioisotope scanning, or both.
  - The absence or severe hypoplasia of the thyroid gland indicates severe primary congenital hypothyroidism due to dysgenesis
  - A complete organification defect on radioisotope scans with perchlorate indicates severe dyshormonogenesis.

Case 3

This is an uncertain or borderline case identified due to a lower threshold screening TSH level. Repeat evaluation has shown a mildly raised TSH but with normal Free T4. It is prudent that this infant receives thyroxine supplementation but that re-evaluation should take place in the future.

ESPE consensus recommendations are as follows:

Thyroid re-evaluation method

- For a precise diagnosis, L- T4 treatment should be phased out over a six-week period and a full re-evaluation should be carried out, with both biochemical testing and thyroid imaging if hypothyroidism confirmed.
- If the presence or absence of primary CH is being assessed, rather than an exact diagnosis being sought, re-evaluation may be carried out by decreasing the does of L-T4 by 30% for 2-3 weeks and then rechecking thyroid function.
- If an increase in TSH concentration to ≥ 10 mU/l is demonstrated, CH can be assumed, but if thyroid function remains normal , the dose should be reduced still further and retesting repeated.

Case 4

This sick preterm infant may have a delayed

diagnosis of CH. Follow up is essential for both neonatal and CH reasons. Cognitive, intellectual, visual and hearing impairment may be seen resulting from CH so should be routinely looked for during follow up.
ESPE consensus recommendations are as follows:

Evaluating the outcome of CH in long-term follow up of children with CH

- A personalized educational plan is required if school progression is affected
- Concerns about behaviour should be addressed from the time of diagnosis until the child reaches school age.
- Educators and teachers should not be informed about the child having CH to avoid stigmatisation due to 'labelling'.
- Adequate treatment throughout childhood is essential and overtreatment should be avoided.
- Memory deficits may be remedied by enrichment programs
- Repeated (not just neonatal) hearing tests should be carried out, as required
- The assessment of patients for evidence of visual processing problems (not just visual acuity) is suggested
- Specialized stimulation of motor development is required
- There is a risk of low HrQOL, particularly if treatment is suboptimal.

Developmental assessment

- Formal developmental testing should be considered:
  - Severe CH: absent knee epiphyses at term, very low T4 and very high TSH concentrations at diagnosis
  - Athyreosis
  - Delayed normalisation of TSH concentration
  - Poor endocrine control during the first year
  - Delayed milestones or learning difficulties
- Hearing and visual impairment should be regularly assessed and speech delay screened.

Case 5

There is likely to be a genetic cause for the severe CH in this infant in combination with dysmorphic features and other organ system defects. This will require further evaluation and the family should have access to genetic counselling.

ESPE consensus recommendations are as follows:

Criteria for genetic counselling

- Genetic counselling should explain the risk of recurrence of CH in a family with CH, based on family history and thyroid morphology.
- Each family with an affected child should have access to information about the two major forms of CH (dyshormonogenesis and dysgenesis) and should receive an explanation of inheritance and recurrence rate.
- Targeted rather than a general genetic counselling

Molecular biology in the diagnosis and management of CH

- Careful phenotypic description of CH patients (including morphology of the thyroid gland)
- Any syndromic association should be studied genetically, to identify new CH genes and to make it possible to provide appropriate genetic counselling.
- The presence of familial cases of dysgenesis should lead to a search for TSH receptor and *Pax8* gene mutations.

Potential indications for antenatal diagnosis

- Fortuitous discovery of a goiter during an ultrasound scan of the fetus
- Familial recurrence of CH due to dyshormonogenesis (25% recurrence rate)
- Known defects of genes encoding proteins involved in thyroid function or development, with potential germline transmission
- Syndromic cases with potential mortality and possible germline mosaicism (as for *NKX2-1* gene mutation/deletion and severe pulmonary dysfunction)
- The treatment of affected fetuses should comply with the laws in force in the country concerned

Further research is required into the familial recurrence of CH due to dysgenesis, including true athyreosis (2% of familial occurrences).

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Phosphate Disorders in Children

M31
Sunday, June 16
1:00–1:45 PM & 3:00–3:45 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Abnormalities of phosphate metabolism are frequently overlooked in infants, children, and adolescents leading to delayed diagnosis and, at times, progression of medically preventable skeletal disease. The differential diagnosis for phosphate disorders is broad, ranging from rare genetic disorders to common iatrogenic circumstances. Despite this, the initial approach to the diagnostic evaluation is similar. Understanding the fundamentals of phosphate, vitamin D, and fibroblast growth factor 23 (FGF23) physiology and the interrelationships with the kidney, gut, and skeleton are critical for making the diagnosis and initiating the correct therapy.

BARRIERS TO OPTIMAL PRACTICE

- Phosphate levels are frequently not included in routine chemistry panels and must be specifically ordered as an individual test. As a result, practitioners may not realize that a patient has an abnormal serum phosphate level.
- The normal range for serum phosphate is age specific, with normal levels being much higher in children than adult. Thus, hypophosphatemic states often go unrecognized when laboratories report results using adult normal ranges.
- Available therapies for several conditions are suboptimal and often associated with co-morbidities.

LEARNING OBJECTIVES

As a result of participating in this session, learners should:

- Recognize the signs and symptoms of pediatric phosphate disorders, formulate an approach for evaluation, and order the necessary diagnostic tests.
- Be aware of the most common causes of pediatric phosphate disorders and understand the underlying pathophysiology.
- Be able to develop a treatment and monitoring plan, keeping in mind the potential co-morbidities that may be associated with the underlying disease and/or its therapy.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Phosphate Homeostasis

Approximately 85% of the body's phosphorus is contained within the skeleton, complexing with calcium to form hydroxyapatite. The remaining 10-20% is found within the soft tissues, extracellular fluid and red blood cells. Intracellular phosphate plays a critical role in cellular signaling and metabolic pathways, as well as being an essential component of nucleotides and cell membranes. In the plasma, phosphorus circulates predominantly as inorganic phosphate (Pi) or bound to lipids and esters. Under normal conditions, Pi is maintained within an age-specific normal range starting at approximately 4.6-8 mg/dL (1.48 – 2.58 mmol/L) in the neonate, gradually decreasing to 3.5-6 mg/dL (1.13 – 1.94 mmol/L) during childhood and adolescence, ultimately declining to the normal adult range of 2.5-4.5 mg/dL (0.8 – 1.45 mmol/L) by late adolescence.

Circulating levels of Pi are tightly regulated by the PTH-Vitamin D-Fibroblast Growth Factor (FGF23) system, which controls gastrointestinal absorption, skeletal accretion

and renal reabsorption. An estimated 70% of dietary phosphorus is readily absorbed in the jejunem, typically in excess of what the body requires, through both paracellular processes, as well as transcellular transport mediated by sodium-phosphate IIb co-transporters. In response to rising circulating phosphate concentrations, FGF23, a 251 amino acid peptide produced by osteocytes and osteoblasts, plays a critical role in phosphate metabolism. Through receptor binding in association with the co-receptor KLOTHO, FGF23 acts as a phosphatonin by suppressing 1-α-hydroxylase activity and the sodium phosphate IIa and IIc co-transportors (NaPi-IIa and II-c) in the proximal tubule of the kidney. This, in turn, results in decreased intestinal absorption and increase renal excretion of phosphorus. Frank hyperphosphatemia can lead to calcium-phosphate precipitation resulting in hypocalcemia with a compensatory increase in PTH secretion, further inhibiting NaPi-IIa and promoting phosphaturia. Conversely, under normal circumstances, hypophosphatemia suppresses FGF23 secretion and stimulates 1-α-hydroxylase, thus increasing production of 1,25-OH_2-Vitamin D which enhances gastrointestinal absorption of calcium and phosphorus and also promotes osteoclastic bone resorption acting through RANK ligand.

Hypophosphatemia

Phosphate is critical for both the normal mineralization of the skeleton, as well as numerous cellular processes. Symptoms of cellular phosphate depletion, such as muscle weakness, typically only occur when the phosphate levels are extremely low. In growing children, the most common sign of chronic hypophosphatemia is rickets, as demonstrated by poor growth, bowing of the extremities, widening of the growth plates, frontal bossing, and skeletal fragility.

Hypophosphatemia can be due to a variety of etiologies including decreased intestinal absorption, cellular redistribution, or increased renal excretion. The recommended daily allowance (RDA) for phosphate varies with age ranging from 100 mg/day in infants peaking at approximately 1200 mg/day in adolescents. The RDA in adults is approximately 700 mg/day. As phosphorus is ubiquitous in foods, inadequate dietary phosphate intake is extremely rare. Common phosphate-rich foods include dairy products, beans, nuts, meats, potatoes, and dark sodas. In children, inadequate phosphorus intake is most frequently seen in pre-term neonates, as human milk and regular formulas do not provide adequate phosphate to meet the skeletal need of a premature infant. Thus it is important to use human milk fortifiers and preterm formulas. In cases of ill neonates requiring parental nutrition, maximal calcium and phosphate content may be limited by solubility; thus, wherever possible, oral supplements should be provided to avoid rickets and osteopenia of prematurity. Intestinal malabsorption can occur in children treated with medications that bind phosphate, such as aluminum, magnesium, and calcium. In addition, chronic diarrhea is associated with poor phosphate and calcium absorption, with the latter resulting in secondary hyperparathyroidism and PTH-mediated renal phosphate wasting.

As phosphate is essential for many intracellular functions, stimulation of processes that increase phosphorylation may result in hypophosphatemia as phosphorus is transported from the extracellular into the intracellular compartments. This is classically seen as part of the refeeding syndrome. During starvation, intracellular phosphate is depleted while circulating levels are maintained. When the individual is fed the rise in insulin results in a rapid reclamation of phosphate by the cells with a drop in serum phosphate. This phenomenon is also seen during the treatment of diabetic ketoacidosis; total body phosphate depletion caused by osmotic diuresis occurs while the child is hyperglycemic. With the initiation of insulin, hypophosphatemia can ensue if phosphate is not administered concurrently. Transcellular phosphate shifts are also seen in acute respiratory alkalosis, most commonly due to hyperventilation. In addition, rapid re-mineralization of the skeleton in a child being treated for rickets or after parathyroidectomy for hyperparathyroidism, called the "hungry bone

syndrome", can result in hypophosphatemia.

The kidney is the principal gatekeeper regulating phosphate balance, thus excessive urinary phosphate excretion is an important cause of hypophosphatemia. The majority of renal phosphate reabsorption occurs in the proximal tubule under the direction of the sodium-phosphate co-transporters regulated by circulating PTH and FGF23, both of which stimulate phosphate excretion. In children, primary hyperparathyroidism is relatively rare with most increases in PTH due secondary hyperparathyroidism associated with calcium or vitamin D deficiency. There are several genetic and acquired conditions of FGF23 excess *(see Table 1)*, all of which lead to hypophosphatemia, hyperphosphaturia, normal or slightly elevated PTH, low or "inappropriately normal" 1,25-OH_2-Vitamin D, and rickets/osteomalacia. The most common of these conditions is X-linked hypophosphatemic rickets (XLH), an X-linked dominant condition caused by mutations in the PHEX gene. Individuals with genetic forms of FGF23 excess often also experience sterile dental abscesses, short stature, and enthesopathies, in addition to skeletal disease. FGF23 excess has also been seen in children with epidermal nevus syndrome of unclear etiology. Homozygous mutations in the renal sodium-phosphate co-transporters cause two rare FGF23-independent phosphate wasting conditions: autosomal recessive Fanconi syndrome, (NaPi-IIa mutation) and Hereditary Hypophosphatemic Rickets with Hypercalciuria (HHRH, NaPi-IIc mutation), both of which are associated with appropriately elevated 1,25-OH_2-Vitamin D and hypercalciuria at presentation. Renal phosphate wasting is seen acquired types of Fanconi syndrome, where generalized proximal tubular dysfunction is associated

TABLE 1

	Gene	Location	Inheritance	Phenotype
FGF23-mediated hypophosphatemic disorders				
X-linked Hypophosphatemic Rickets (XLH)	PHEX	Xp22.11	X-linked dominant	Dental disease and enthesopathies particularly common
Autosomal Dominant Hypophosphatemic Rickets (ADHR)	FGF23	12p13.32	Autosomal dominant	May present older; association with iron deficiency
Autosomal Recessive Hypophosphatemic Rickets 1 (ARHR1)	DMP1	4q22.1	Autosomal recessive	Clinically similar to XLH
Autosomal Recessive Hypophosphatemic Rickets 2 (ARHR2)	ENPP1	6q23.2	Autosomal recessive	May initially present with generalized arterial calcification of infancy
Hypophosphatemic Rickets with Hyperparathyroidism(HRHPT)	KLOTHO	13q13.1	Translocation	Very elevated PTH prior to therapy
Tumor-induced Osteomalacia (TIO)	N/A	N/A	Acquired	Acquired; rare in children
McCune-Albright Syndrome (MAS)	GNAS	20q13.32	Sporadic	Severity correlated with burden of FD
Osteoglophonic dysplasia (OGD)	FGFR1	8p11.23-p11.22	Autosomal dominant	Craniosynostosis, rhizomelia, non-ossifying bone lesions
FGF23-associated hyperphosphatemic disorders				
Hyperphosphatemic Familial Tumoral Calcinosis/ Hyperphosphatemic Hyperostosis Syndrome (HFTC/ HHS)	GALNT3 FGF23 KLOTHO	2q24.3 12p13.32 13q13.1	Autosomal recessive	Peri-articular, subcutaneous, soft-tissue calcifications; gingivitis and vasculitis also seen

with conditions such as cystinosis or Wilson's syndrome. Renal tubular acidosis (RTA) and medications that induce an RTA (e.g. acetazolamide) are associated with renal phosphate wasting.

Diagnostic Evaluation

As always, a careful history and physical with special attention to family history, co-morbidities, and rachitic deformities, are important. Laboratory investigations include concurrent blood levels of intact PTH, calcium, phosphorus, alkaline phosphatase, magnesium, creatinine, 25-OH-Vitamin D, and 1,25-OH_2- Vitamin D along with urine calcium, phosphorus, creatinine, and urinalysis. These labs should ideally be obtained in the fasting state as dietary phosphate may transiently elevate serum levels. Age-appropriate normal ranges should be used for interpretation of labs, especially serum phosphorus which is significantly higher in neonates and gradually decreases during childhood and adolescents until finally reaching the adult normal range. To determine if the hypophosphatemia is due to renal phosphate wasting, one must calculate the tubular reabsorption of phosphate (TRP = (1- [UPhos x SCr] /[SPhos x UCr])x100) or the Tubular maximum reabsorption of phosphate/GFR (TMP/GFR = TRP x SPhos). A normal TRP is approximately 85-95%; however, it is important to remember that during hypophopshatemia, the TRP should be closer to 100% as the kidney attempts to compensate. Thus a TRP of 87% would be considered low in a patient with hypophosphatemia. Similar to serum phosphate levels, TMP/GFR is higher in infants and declines with age. If a generalized renal tubular defect is suspected, 24-hr urine collections should also be performed for calcium, creatinine, amino acids, glucose, uric acid and bicarbonate. Measurement of the FGF23 level is useful in confirming if one is dealing with an FGF23-mediated form of hypophophosphatemia, which would be suggested by low or inappropriately normal 1,25- OH_2-Vitamin D along with a normal or slightly elevated PTH. As with all mineral disorders, it is crucial to ensure that the patient is vitamin D sufficient when performing the diagnostic evaluation, as Vitamin D deficiency can lead to secondary hyperparathyroidism and renal phosphate wasting, which could confound the diagnosis. Skeletal radiographs are useful for characterizing rickets and fibrous dysplasia. Genetic testing is currently available for several of the genes associated with FGF23-mediated hypophosphatemia; where not available, one might consult with a research lab to confirm the diagnosis. While rare in children, tumor-induced osteomalacia should be considered in acquired forms of FGF23-mediated hypophosphatemia and thorough imaging starting with octreotide scanning is warranted in an attempt to locate the FGF23-producing tumor.

Management

Unless the patient is severely hypophosphatemic or is IV dependent because of gastrointestinal issues, hypophosphatemia can be treated with oral phosphate. Children recovering from DKA can adequately replete their phosphate through regular diet, once IV therapy has been discontinued. In conditions with ongoing renal losses, oral phosphate supplements must be given in regular intervals, often 4-5 times per day, to maximize skeletal mineralization. In HHRH, patients experience a normal compensatory response to hypophosphatemia with elevated 1,25-OH_2-Vitamin D and an absorptive hypercalciuria; thus these patients are treated only with phosphate supplements. In FGF23-mediated conditions, 1-α-hydroylase activity is suppressed; therefore, calcitriol supplementation is also necessary to increase gastrointestinal absorption of calcium and phosphorus and prevent secondary hyperparathyroidism which could worsen bone disease and magnify renal phosphate wasting. In renal phosphate wasting, serum phosphate remains low despite therapy, as renal losses are ongoing. Thus, the goals of therapy are to reduce alkaline phosphatase, heal rachitic changes, improve linear growth and reduce skeletal deformities, while avoiding iatrogenic comorbidities such as secondary/tertiary hyperparathyroidism, hypercalcemia/hypercalciuria, and nephrocalcinosis. Periodic monitoring of therapy includes physical

examination, blood and urine tests, and renal ultrasound.

Hyperphosphatemia

As discussed above, serum phosphate levels are tightly regulated by the kidney. Hyperphosphatemia can ensue when the kidney loses the ability to excrete sufficient phosphate to maintain serum levels within the normal range. This can occur with an endogenous phosphate overload, as seen in the tumor lysis syndrome or rhabdomyolysis, or an exogenous phosphate load, classically in response to overuse of phosphate containing enemas/laxatives or large blood transfusions. In both cases, the renal capacity for phosphate excretion is exceeded and the patients can become severely hyperphosphatemic, often associated with dangerous hypocalcemia. Hyperphosphatemia is also seen in renal failure, as the kidney loses its ability to filter and excrete phosphate.

Several conditions are associated with inappropriate excessive phosphate reabsorption by the kidneys. The classic endocrine examples are hypoparathyroidism or pseudohypoparathyroidism, where the lack of PTH effect on the proximal tubule results in increased renal phosphate reabsorption. Rarely, severe Vitamin D deficiency can mimic pseudohypoparathyroidism, causing hypocalcemia and hypophosphatemia with increased PTH (pseudohypoparathyroidism Type II). Vitamin D toxicity can cause not only hypercalcemia but also hyperphosphatemia due to increased intestinal absorption and renal reabsorption (due to suppressed PTH). Increased TRP is also sometimes seen in growth hormone excess. A rare but important cause of hyperphosphatemia is Hyperphosphatemic Familial Tumoral Calcinosis (HFTC), an autosomal recessive disorder cause by mutations in FGF23, its co-receptor KLOTHO, or GALNT3, a glycosyl transferase that protects FGF23 from inactivation by proteolytic cleavage. In all three mutations, FGF23 is essentially inactive resulting in a biochemical "mirror image" of the FGF23 excess conditions described above. As a result of their functional FGF23 deficiency, renal tubular reabsorption of phosphate is increased and 1,25-OH_2-Vitamin D is normal or inappropriately elevated, further enhancing gastrointestinal absorption of phosphate and calcium. This leads to an increased circulating calcium-phosphate product such that patients experience increased extraskeletal calcification, ranging from cortical hyperostosis to large calcific tumors next to joints, under the skin, or in areas of trauma. Inflammatory reactions may also be seen.

Diagnostic Evaluation

Initial evaluation for hyperphosphatemia is the same as for hypophosphatemia. Renal function should be assessed as well as enzymes of muscle breakdown. The hallmark of hypoparathyroidism and pseudohypoparathyroidism is hypocalcemia, in addition to hyperphosphatemia. It is important to calculate the TRP and TMP/GFR to assess phosphate reabsorption. In cases of phosphate overload, urinary phosphate excretion should be maximal and the TRP will be appropriately low. Conversely, TRP will be inappropriately elevated in hypoparathyroidism, tumoral calcinosis, and other disorders of increased phosphate reabsorption. In HFTC due to FGF23 and GALNT3 mutations, FGF23 measured by commercially available assays is elevated because these assays measure C-terminal FGF23 which includes both intact FGF23 and inactive cleavage products. Despite this very elevated C-terminal FGF23, the biologically active intact FGF23 (only available in research laboratories) is typically very low. When HFTC is suspected, a skeletal series should be performed to look for cortical hyperostosis. Additional imaging may be warranted to evaluate calcific tumors. Genetic testing for mutations in FGF23 is commercially available.

Management

In acute, severe hyperphosphatemia, intravenous saline can promote phosphate excretion in patients with functioning kidneys; hemodialysis may also be indicated. Concurrent hypocalcemia should be treated. An increased calcium-phosphate product can promote soft tissue calcifications;

recommendations based on patients with renal insufficiency suggest that one should attempt to maintain a calcium-phosphate product < 55 mg2/dL2 in adults and < 70 mg2/dL2 in children. In hypoparathyroidism, simply increasing the serum calcium to the lower end of the normal range will often reduce the serum phosphate to just above the upper limit of normal. Dietary phosphate should be restricted in patients with hyperphosphatemia, a difficult task given its ubiquity in common foods. In patients with HFTC, treatments are limited to phosphate binders (sevelamer, aluminum hydroxide) and medications that promote renal excretion of phosphate (acetazolamide, probenecid). Side effects of these treatments include gastrointestinal obstruction (sevelamer), aluminum toxicity (thus, aluminum hydroxide should only be given to children with intact renal function), and metabolic acidosis (acetazolamide). Unfortunately, these treatments are of limited efficacy and patients can develop disabling tumors. De-bulking surgery may be performed to decrease disability, keeping in mind that these tumors often recur. Anti-inflammatory medications may be needed if there is associated inflammation.

MAIN CONCLUSIONS

While the differential diagnosis of pediatric phosphate disorders is broad, most are due to altered renal handling. A careful history and physical examination combined with focused studies evaluating the major players in phosphate homeostasis can rapidly elucidate the etiology. Therapy should be tailored to the underlying disease, recognizing the potential complications and co-morbidities.

CASES WITH QUESTIONS AND DISCUSSION OF CASES AND ANSWERS

Case 1

An otherwise healthy 5-year-old girl presents to the clinic for evaluation of bowed legs. Radiographs at 15 months old revealed rickets; however, laboratory test results were reported to be normal at 15 months and again at 3 years of age. The family was told that she had a metaphyseal dysplasia. Family history is unremarkable. On exam, height is 5th percentile, weight is 25th percentile, head circumference > +2 SD, and upper to lower segment ratio is 1.5. She has frontal bossing, dolichocephaly, genu varum with widening at the wrists and ankles. Radiographs reveal irregular metaphyses.

Laboratory test results:

Calcium = 9.2 mg/dL (8.2-10 mg/dL)
Magnesium = 2.23 mg/dL (1.8-2.4 mg/dL)
Phosphorus = 2.7 mg/dL (3.1-5.5 mg/dL)
Bicarbonate = 27 mEq/L (21-31 mEq/L)
Alkaline phosphatase = 547 U/L (96-297 U/L)
25-Hydroxyvitamin D = 30 ng/mL (25-80 ng/mL)
1,25-Dihydroxyvitamin D = 56 pg/mL (24-86 pg/mL)
Intact PTH = 73 pg/mL (16-87 pg/mL)

1. ***What is the most likely cause of her rickets? Why do you think that the family was told that her lab results were normal?***
2. ***What other tests could you do to help make the diagnosis?***
3. ***What is the preferred treatment for this patient?***

Answers

1. This patient has hypophosphatemic rickets, most likely due to FGF23 excess given her normal 1,25-OH_2-Vitamin D level, which should be elevated in the face of hypophosphatemia. The top-normal PTH level is also suggestive of this diagnosis in untreated patients. The family was previously told that her labs were normal because her serum phosphate level of 2.7 mg/dL, while quite low for a 5-year-old girl, is in the normal range for adults. Many labs continue to print adult normal ranges on their lab reports, thus phosphate levels that are low for children are often not flagged as abnormal. In addition, many "comprehensive chemistry panels" do not include phosphate and practitioners do not even realize that they have failed to order a phosphate level when evaluating a child for rickets.
2. It is important to confirm that this child is experiencing renal phosphate wasting by calculating the TRP and TMP/GFR

which would be inappropriately low in this scenario. Measurement of FGF23 and genetic testing for common causes of hypophosphatemic rickets would help to confirm the diagnosis.

3. This patient should be treated with oral phosphate, given 3-4 times per day and calcitriol. Care should be taken to avoid secondary hyperparathyroidism and hypercalciuria. Even with healing of the rickets, deformity may persist requiring surgical intervention later in life. These patients tend to have disproportionate short stature, even with optimized therapy.

Case 2

An 11-month-old infant experiences a tonic-clonic seizure. In the emergency department, his parents report that he had been previously healthy except for constipation, which they have been treating with over the counter therapies.

1. ***What additional history would you like to know?***
2. ***What would you expect his calcium, phosphate, sodium, and PTH levels to be?***
3. ***How would you treat this patient?***

Answers

1. In any child with a reported history of constipation, parents should be questioned about the use of over the counter sodium-phosphate enemas. While they are readily available in the drugstore and can even be purchased in "pediatric" sizes, they must be used with extreme caution as they can cause severe hyperphosphatemia in very young children or older children with renal insufficiency or decreased gut motility (causing prolonged intestinal retention of the enema). Hyperphosphatemia induces hypocalcemia primarily by complexing with calcium in the blood. In addition, hyperphosphatemia inhibits the production of 1,25-dihydroxyvitamin D, leading to decreased intestinal calcium absorption.
2. Administration of saline phosphate enemas in infants can result in hyperphosphatemia, hypernatremia, hypocalcemia and elevated PTH.
3. Treatment of hypocalcemia due to an excessive phosphate load may require intravenous calcium to ameliorate tetany and seizure. In addition, gastrointestinal lavage and oral phosphate binders such as sevelamer can be used to decrease intestinal absorption of phosphate. Alkalinization of the urine with acetazolamide may be tried to promote urinary phosphate excretion. In some cases, therapy with intravenous insulin and glucose may be considered to promote intracellular translocation of phosphate. In extreme cases, dialysis may be necessary. Correction of the hypertonic dehydration is also critical to restore electrolyte and mineral balance.

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Androgen Insensitivity: Diagnosis and Management

M60
Tuesday, June 18
12:15–1:00 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Amongst the "Disorders of Sex Development" (DSD), androgen insensitivity syndromes (AIS) are a common cause of underandrogenisation in 46,XY individuals. They are diagnosed clinically, because at the time of assessment, apparently the capability of the testes to synthesize adequate amounts of testosterone is perceived as within the male reference interval for age, however, the responsiveness to these androgens in diminished. The unresponsiveness to androgens can be quite variable; therefore the range of phenotype is broad. Three categories have been crudely described in 46,XY children: a complete AIS with a completely female appearance of the external genitalia; a partial AIS with a variable degree of genital ambiguity ranging from hypospadias in a child reared male to a slight virilisation in a child reared female; and a minimal AIS in children with isolated micropenis without any urethral abnormality. At the time of puberty, the phenotype is more distinct, as patients with complete AIS may sometimes develop some degree of sexual hair, while others remain "hairless women". In partial AIS, at puberty a degree of virilisation in combination with feminization is seen, also the patients assigned male mostly develop striking gynecomastia. Minimal AIS is also usually associated with gynecomastia as well as a variable degree of spermatogenic failure. Therefore Quigley et al. (1995) and Sinnecker et al. (1997) describe up to 7 different clinical categories in AIS. This knowledge is important for the understanding of AIS, especially for counseling of affected individuals. The management of AIS includes adequate disclosure, assessment of the need of hormone therapy, especially in males with partial and minimal AIS as well as in females whose gonads have been removed; the evaluation of the possibility of benign and malignant tumors of the gonads, the need for genital operations, and of utmost importance, the psychological counseling of the affected and their families.

BARRIERS TO OPTIMAL PRACTICE

- The diagnosis of AIS in infants and children is difficult and depends both on clinical findings in conjunction with molecular genetic investigations
- Therapeutic management is case-based and lacks long-term evidence based data both for males and females with PAIS with regard to surgical and hormonal treatment. In CAIS, long-term preservation of gonadal function needs to be investigated, as well as hormone replacement in the cases of gonadectomy.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to

- Make a clinical diagnosis of AIS in childhood, adolescence, and adulthood.
- Provide patients with adequate diagnosis and management strategies.
- Understand the provision of care for AIS during childhood, adolescence, and adulthood, which should be formalized in known centers of expertise.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Diagnosis

In infants and children the initial diagnosis of AIS is difficult. Laboratory values are mostly inconclusive and usually show a "normal" testicular function according to age-related reference intervals. In patients with complete AIS, there may be even low values for LH and testosterone during the so-called mini-puberty, and only after LHRH stimulation there is a strong rise in gonadotrophins and also in testosterone. In some cases of partial AIS, testosterone levels may even be elevated. During puberty, the diagnosis often becomes clearer, because normal to elevated LH levels are found in conjunction with rising and even above the male reference interval lying testosterone levels despite a lack of androgenisation as seen in the clinical investigation of the patient. So after puberty, AIS is a clinical diagnosis depending on the typical phenotype with underandrogenisation and feminization. Only after structured clinical assessment and appropriate laboratory and imaging investigations (including laparoscopy), detailed molecular genetic studies should be ordered.

Genetics in AIS

With the identification and characterization of the AR gene, mutations within the coding region have been identified associated with all forms of AIS. More than 800 different mutations have been recorded in the international AR gene mutation database (www.mcgill/androgendb/), with most of them point mutations leading to amino acid substitutions in the protein structure. However, splice-site mutations, and also complete deletions, as well as small insertion and deletions, and substitution mutations leading to premature termination of the protein are reported. While the latter are nearly always associated with complete AIS, the amino acid substitutions can be associated with complete, partial or minimal AIS, depending on the site of the mutation and the residue exchange. Due to the hemizygous inheritance pattern, de novo mutations are as frequent as in autosomal-dominant disorders and may comprise up to 30% of the cases. This is of importance for genetic counseling, but in the case of somatic de novo mutations may also affect the phenotype of the patient and, hence, influences therapeutic decision making.

For many mutations, the deleterious effects have been proved through detailed in-vitro studies. For novel mutations, this should be performed by re-creating the mutation in an appropriate expression vector and study the impact on transactivation employing co-transfection of an androgen responsive reporter gene in an AR-negative mammalian cell line. Usually, the analysis includes hormone binding of the mutant, as well as protein stability, nuclear transport, as well as in some cases DNA-binding. Also the effects of different androgens and different promoters of the AR responsive genes can give novel insights into the pathogeneity of any mutant. At this time, however, these studies do not explain the highly variable phenotypes seen with the same mutation in many reported cases of partial AIS. Mutations leading to these phenotypes often affect ligand-binding, but also chaperone interactions, and may alter posttranslational modifications of the receptor. With a partial residual function of the mutant, cell-dependent expression of co-activators and co-repressors of the AR is particular important and might be modulated very differently. Therefore, in the cases of these mutants, the use of different reporter genes and cell lines may be necessary to investigate the pathogenicity of such a variation.

Management of AIS

The diagnosis of a DSD is often seen as very disturbing for a patient and the family. It has been agreed upon that the disclosure of any DSD diagnosis, as well as the discussion of the diagnostic steps and the counseling of further management requires an expert multidisciplinary team, consisting of a pediatric endocrinologist, a pediatric surgeon or urologist, a psychologist, a geneticist and several other subspecialities, depending on the need for this individual. These include specialists in gonadal pathology, laboratory medicine, gynecology or neonatology, depending on the age of the patient, urology and internal medicine. The multidisciplinary team may be completed with an ethicist and

a socio-religious counsel for the family, as patients and their families may come from different cultural backgrounds.

The German Ethical Council of the German Parliament recently published recommendations for dealing with patients with DSD and favored the implementation of competence centers, which act as tertiary care centers for both patients and also physicians requiring additional help (www.ethikrat.org/intersexualitaet). The competence centers are then urged to act professionally in defining structured diagnostic pathways, but also to inform both patients and caring physicians about their management possibilities in full disclosure. Furthermore, the centers are the hubs for linking appropriate research with clinical care and should provide structured teaching to health care professionals, namely physicians, nurses and midwifes, who may be confronted in dealing with DSD patients and their families.

With respect to AIS, current management strategies opt for as little interventions as possible with as much as absolutely necessary. In the cases of partial AIS with female sex assignment, this should include the options for genital surgery. The current statements point towards deferring genital operations to a time when the patient can give informed consent and the gender identity is stabile. Therefore, in contrast to current management in congenital adrenal hyperplasia, genital surgery in partial AIS females may be performed late. Controversial is the management of patients with partial AIS, who have been assigned to a male sex. As in other cases of hypospadias, the repair is usually favored in the first year of life. In complete AIS, often genital surgery is not necessary. Some patients may require elongation of the vagina, but this should be decided on the basis of informed consent after the patient has reached adulthood and wants to be sexually active.

In recent years, dramatic changes have occurred regarding the management of the gonads in AIS. In patients with a female or almost female phenotype, corresponding to complete AIS or partial AIS, the gonads are left in situ until the patient can give consent to the management procedures. In cases with partial AIS and female sex assignment at birth, decision making should be discussed at the onset of puberty. In case of a stable female gender identity of the patient, gonads may still be removed to prevent unwanted virilisation. If there is still uncertainty about gender in the patient, puberty may be postponed with the use of GnRH-analogues.

In patients with complete AIS, the gonads should be left in situ throughout puberty and maybe also beyond. The overall prevalence of testicular malignancies may be below 1%. However, as there are no regular registries available to record the development of benign or malignant tumors, a structured regular assessment of the gonads should be offered, e.g. with regular ultrasound every six months with the start of puberty.

If the gonads are removed in patients with complete AIS, usually a mono-therapy with continuous estrogens is used for hormone replacement to maintain secondary sexual characteristics and to promote physical and social well-being. However, this has been challenged by some patients with complete AIS, who reported that this would not correspond to their typical hormone profiles and that they felt diminished in their health-related quality of life. Some women with complete AIS have started with a high dose testosterone therapy, but this practice remains anecdotal until a recently started double-blind clinical trial employing testosterone versus estradiol therapy in complete AIS has been evaluated (www.cais-studie.de). The management of hormone therapy in partial AIS and other forms of DSD may also change in the near future depending on the outcome of this trial.

To gain better understanding and knowledge on the diagnosis of all forms of DSD including AIS, international collaborations have been established including both clinical and research-based networks. This collaboration includes an international DSD database which allows the anonymized registration of all cases of DSD with clinical descriptions and possible diagnosis to allow the exchange of data and biomaterials between centers according to the specified consent of the patients. This database termed I-DSD

arose from a recent European collaborative study funded by the 7thEU framework programme and should provide the basis for successful future research and hopefully also for respective clinical trials.

MAIN CONCLUSIONS

1. The diagnosis of AIS is challenging in childhood and requires a structured assessment of clinical phenotype, Leydig- and Sertoli-cell function, as well as molecular genetic studies of the androgen receptor gene.
2. The management should be performed under the supervision of a tertiary center offering care with a multidisciplinary team. These centers of expertise should counsel patients, families, but also health care professionals appropriately and sustain the long term care of the individuals with AIS
3. Modern treatment options include physiological hormone replacement, adequate surgery with informed consent with preservation of the gonads, as well as adequate psychological counseling.

CASES WITH QUESTIONS

1. A case of intrauterine detected DSD.
2. An adolescent with CAIS and an abnormal gonad on ultrasound
3. An adolescent with PAIS and male phenotype

DISCUSSION OF CASES AND ANSWERS

Will be provided in the lecture.

REFERENCES

This text was adapted from the recent publication: Hiort O (2013). Clinical and molecular aspects of androgen insensitivity. Endocr Dev. 24:33-40, where further references can be found.

Premature Adrenarche: Evaluation and Management

M11
Saturday, June 15
3:00–3:45 PM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Adrenarche is the gradual rise in adrenal androgen secretion after about age 6 years in girls and 7 years in boys. Although adrenarche is a normal developmental process, recent evidence suggests that premature adrenarche in childhood may be associated with the development of insulin resistance, with or without functional ovarian hyperandrogenism, polycystic ovary syndrome (PCOS) or features of the metabolic syndrome (MS).

Adrenarche is the normal maturation of the zona reticularis (ZR), resulting in the development of pubic hair, axillary hair, and adult apocrine body odor. These physical changes are preceded by biochemical adrenarche, which has been described to begin physiologically as early as age 5-6 years, and consists of increased ZR production of Δ5 steroids, principally dehydroepiandrosterone (DHEA) and dehydroepiandrosterone (DHEAS).

Premature adrenarche (PA) occurs when signs of adrenarche begin before the age of 8 years in girls or 9 in boys. The majority of children with PA have idiopathic premature adrenal androgen secretion. Idiopathic PA occurs more frequently in girls than boys by a ratio of about 9:1.

While PA was formerly thought to be a variant of normally timed adrenarche, studies support an association between PA and a history of small for gestational age (SGA) and low birth weight (LBW), as well as an association with obesity. PA is also associated with a risk of PCOS and metabolic syndrome (MeS). Metabolic abnormalities reported in prepubertal children with PA include IR, hyperinsulinism, increased free IGF-1 and plasminogen activator inhibitor 1 (PAI-1), and lower IGFBP-1. It has been suggested that in prepubertal girls with PA, PAI-1 levels can predict progression to PCOS.

BARRIERS TO OPTIMAL PRACTICE

Despite these preliminary data, it is not known which children with PA are most at risk of developing MeS or PCOS. Thus, while PA is frequently a benign process, the diagnosis carries a heightened suspicion for future metabolic and endocrine abnormalities. Further, management issues are still controversial regarding treatment modalities.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- understand the terms pubarche, premature pubarche, adrenarche, and premature adrenarche
- recognize the common manifestations of premature adrenarche and its relationship to PCOS and metabolic syndrome in adolescents
- understand the current evolving areas of potential intervention and treatment for this condition

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY AND/OR MANAGEMENT

1. Definitions

Pubarche

- The term applied to the onset of sexual hair growth.

- In girls, sexual hair usually appears first on the labia majora and the hair gradually spreads upwards onto the mons; in some girls it begins in the axillae.
- In boys, sexual hair may begin on the scrotum.

Premature Pubarche

- Refers to the isolated appearance of sexual hair before the age of 8 years in girls and 9 in boys.
- It is often accompanied by an increase in axillary apocrine odor and a minor degree of microcomedonal acne.
- It is NOT accompanied by any other signs of gonadarche, frank virilization, or an abnormal advance in bone age.
- The sexual hair development increases slowly, and the bone age increases in proportion to linear growth.

Adrenarche

- The term for maturational increase in adrenal androgen production that begins at about 6 years of age in girls and 7 in boys.
- Represents a change in the pattern of adrenal secretory response to corticotropin (ACTH), characterized by a disproportionate rise of 17-hydroxypregnenolone and dehydroepiandrosterone (DHEA) relative to cortisol. This response occurs primarily in the zona reticularis of the adrenal cortex, possibly due to phosphorylation of P450c17 enzyme resulting in 17, 20 lyase activity of the enzyme. Associated with increased cytochrome P450 oxidoreductase (POR), increased SULT2A1 (DHEA-sulfotransferase) and increased cytochrome b5 in the reticularis.
  - Recently has been suggested to be due to a rise in intra-adrenal cortisol, which may lead to inhibition of 3βHSD2 activity.

Premature Adrenarche

- The most common cause of premature pubarche.
- It is the term applied when the androgen profile in a child with premature pubarche is in the adrenarchal range.

Hormone Levels in Premature Adrenarche

  - The serum concentration of DHEAS is the best marker for the presence of adrenarche. The serum DHEAS concentration is typically appropriate for the stage of sexual hair development.
  - Serum testosterone and androstenedione concentrations are near the upper limit of the normal range.
  - Occasionally, all circulating adrenal hormone values are in the prepubertal range, but the serum DHEA and 17-hydroxypregnenolone responses to ACTH are in the adrenarchal range.

Bone Age in Premature Adrenarche

  - Usually not significantly advanced. However if at diagnosis, BA – CA > 1, generally taller than peers
  - . Most children attained adult height in line with mid-parental target height range.
  - Weight, estradiol and DHEAS are the strongest predictors of BA/CA

2. Evaluation of Premature Pubarche

A definitive algorithm for the evaluation of PA cannot be recommended; however, in our practice, all patients with PA receive blood tests for androgens (testosterone, Δ4, DHEAS), gonadotropins (LH and FSH), and 17OHP. Thyroid studies (TSH and free T4) are ordered if hypothyroidism is suspected. If early morning 17OHP is above 200 ng/dl, an ACTH-stimulation test to evaluate for NC-CAH is indicated.

The decision to order imaging studies is based on clinical impression and results of initial laboratory evaluation. Rapid virilization or physical signs of precocious puberty are indications to obtain an x-ray of the left hand to determine bone age if not already obtained. If initial studies show very elevated DHEAS, abdominal ultrasound may be indicated as an initial screen to evaluate for adrenal neoplasm. Abdominal CT or MRI is indicated if a mass is noted, although controversy still exists regarding which of these is preferred. Similarly, ultrasonographic evaluation of the ovaries or testes may be indicated if significantly elevated testosterone or Δ4-A are found, if a testicular mass is palpated, or if there is significant testicular asymmetry.

Elevated β-hCG in boys should prompt a search for a tumor of the testis, liver, or brain. Finally, brain MRI with contrast may be indicated in precocious puberty (especially in boys), or if there is any suspicion of CNS pathology.

3. Differential Diagnosis of Premature Adrenarche *(Table 1)*
(adapted from Oberfield et al., Approach to the Girl with Early Onset of Pubic Hair. J Clin Endocrinol Metab 96: 1610–1622, 2011)

4. Points of Interest
- There is mounting evidence to suggest that PA is a risk factor for development of ovarian hyperandrogenism, PCOS, and metabolic syndrome in adulthood.

Ethnicity:
- PA has been studied extensively in Hispanic and African-American populations in the US and in Northern Spanish populations
- Race/ethnicity are independent risk factors for development of IR in women in PCOS

Metabolic issues:
- Insulin/IGF Issues
  - Hyperinsulinemia, insulin resistance, decreased IGFBP-1 and elevated total

TABLE 1

	Pubic Hair	Breast Development, Testicular Enlargement, Other Physical Findings	Androgens	LH and FSH	Bone Age	Growth Velocity	Additional Notes
Isolated Premature Pubarche	Present	Absent	Prepubertal, DHEAS not elevated	Prepubertal	↔	↔↑	Possibly related to increased androgen receptor sensitivity
Premature Adrenarche (PA)	Present	Absent	↑ but appropriate for Tanner II-III	Prepubertal	Slight ↑ correlated with height age	Slight ↑	Most common cause of premature pubarche
Precocious puberty	Present	+ Breast development + Testicular enlargement	↑↑ for males Can be ↔ for females	Early prepubertal	↑	↑↑	More common in girls; more often pathologic in boys
Non-classical congenital adrenal hyperplasia (NC-CAH)	Present	+/- Penile/ clitoral enlargement Absent breast development or testicular enlargement	↑↑ May be elevated for Tanner stage, with adrenal androgen precursors	Prepubertal	↑	↑	↑ 17OHP in 21-hydroxylase deficiency (most common form)
Virilizing Tumors	Present	+/- Breast development + Penile/clitoral enlargement Infantile testes	Usually ↑ but variable, depending on tumor expression	Prepubertal or ↓	↑	↑	May have ↑ DHEA, DHEAS, T, Δ4-A, or βhCG
Exogenous Hormone Exposure	Present	Variable; may have breast development, small testes, and/ or penile/clitoral enlargement	Variable, depends on specific exposure	Prepubertal	↑	↑↑	Take careful medication history from all caretakers

IGF-1 have been observed in PA.
- ◊ PA may be associated with low birth weight
- ◊ Recent genetic studies suggest an association with a variant in the insulin like growth factor receptor-1 (IGF1R) in PA populations
- ◊ In PA boys, elevated IGF-1, fasting insulin, ISI (composite), and SHBG were found in PA boys with a trend toward higher triglyceride levels. In another study, IGF-1, IGFBP-1, SHBG, and measures of glucose and insulin responsiveness to oral glucose load were comparable in PA boys and controls

º PA & PCOS: Interrelationship of Insulin/Androgens/IGF System
- ◊ Summary: Common findings include acanthosis nigricans, hirsutism, menstrual irregularities, obesity, risk for type 2 diabetes or insulin resistance, low birth weight, increased levels of DHEAS, Δ5 steroid response to ACTH, insulin, IGF1. PAI-1, triglycerides, intramyocellular lipids

Obesity:
- ◊ The exact relationship between obesity and PA is not fully known. The adipose tissue expandability hypothesis may help explain the development of PCOS in a subtype of girls who are born SGA

º Bone mineral density/body composition
- ◊ Although data is limited, we have previously described that girls with PA have higher bone mineral content and density than controls
- ◊ Additionally, preliminary data from Ibanez group suggest that girls with PA have a greater total and trunk fat mass in prepubertal and pubertal states and that fat mass has an independent and significant relationship with fasting insulin and free androgen index.
- ◊ We have found increased IMCL in PA girls (6) compared to controls (8), but no difference in visceral adipose tissue (VAT), abdominal subcutaneous adipose tissue (SAT), or VAT:SAT ratio.
- ◊ Ibanez's group recently demonstrated that girls with PA who were treated with metformin for 4 years (starting at the age of ~8 years) had sustained decreases in total, abdominal, and visceral fat, as well as intrahepatic lipid, 2 years after cessation of treatment, when compared with similar untreated controls.

º Other
- ◊ Psychosocial functioning

º Monogenic Genetic Defects in Steroidogenesis (rare)
- ◊ PAPSS2 (31-phosphoadenosine-51-phosphosulfate (PAPS) synthase type 2 deficiency)
- ◊ ACRD (Apparent Cortisone Reductase Deficiency), H6PDH aturday June 15, 2013A. Premature Adrenarche. Arch Dis Child, 97:250-254, 2012. centrations in premature adrenarche. JCEM, 98 (1(hexose-6 phosphate deficiency)

5. Management:

General

º Once the diagnosis of PA is made, follow-up is usually indicated at no less than every 6 months. Careful assessment of growth velocity, weight gain, and progression of signs of androgen excess are indicated. Yearly fasting measures of insulin resistance (such as FGIR) and lipid levels are often recommended. Some clinicians follow adrenal androgen levels.

º Most children do not demonstrate rapid pubertal progress or bone age advancement and do well with lifestyle interventions. However, should the rate of pubertal changes accelerate, a bone age should be repeated to help determine adult height potential. If not previously performed, an ACTH stimulation test should be conducted to exclude defects of adrenal steroidogenesis.

6. Treatment and pharmacotherapy

º We continue to follow girls with a history of PA at least yearly after menarche. We encourage continued adherence to a low-fat, low-glycemic index diet

and regular exercise. If menstrual regularity has not been established two years post-menarche, additional evaluation including a pelvic sonogram is obtained. At that point, we may recommend metformin, particularly if there is evidence of IR, and/or an oral contraceptive pill.

MAIN CONCLUSIONS

- In the past, the early development of pubic hair (pubarche) related to modestly elevated levels of adrenal androgens (adrenarche) before the onset of puberty had been considered to be a normal variant and benign
- However, recent studies demonstrate that in girls premature adrenarche may herald the development of ovarian hyperandrogenism post-menarche (virilization, menstrual irregularities and infertility with associated lipid abnormalities and IR).
- The risk may be increased in girls with a history of low birth weight and postnatal catch-up weight gain and/or non-Caucasian ethnicity.
- Similar abnormalities, particularly in lipids and alteration of cardiovascular risk factors, may occur in boys with premature adrenarche.
- Issues regarding early intervention tactics and preventative measures for development of metabolic syndrome are currently under review.

CASES WITH QUESTIONS

Case 1

Age 5 years

A 5 -year-old Caucasian girl is referred for evaluation of apocrine body odor. She was born full-term and weighed 7 lb. at birth. There were no complications during pregnancy, including gestational diabetes, and the 17-hydroxyprogesterone (17OHP) newborn screen for congenital adrenal hyperplasia (CAH) was normal. She has grown consistently along the 75th percentile for height, but her growth velocity has recently increased to 3.2 cm in the past 4 months. She has always plotted in the 50th -75th percentile for weight, but she now plots in the 75th -90th percentile.

Her parents are both of Ashkenazi Jewish heritage; mother is 5 feet, 7 inches tall, father is 6 feet tall. Her mother had menarche at age 12 years. The patient's father was treated for severe acne at age 14, had his growth spurt at 15, and developed frontal balding at 30. There is a family history of type 2 diabetes.

On examination, her height is 116cm (~90th percentile), weight is 22.5kg (90th percentile), and BMI is 16.7 kg/m^2 (83rd percentile). Her blood pressure is 106/70 mmHg. She has no glandular breast tissue (Tanner I), faint pubic down on the mons pubis, and sparse curly hairs along the labia majora (Tanner II) and peri-rectal hairs. Her clitoris is 0.5cm by 0.3cm, her posterior labia minora are not fused, and her vaginal mucosa is shiny, pink-red, and non-estrogenized. She has no axillary hair, but does have adult-like apocrine odor.

Evaluation includes a bone age of 5 to 6 years, consistent with her height age. Blood work drawn at 7:30AM reveals 17OHP of 90 ng/dl, Δ4-A of 66 ng/dl, DHEA of 120 ng/dl, DHEAS of 80 µg/dl, testosterone of 8 ng/dl, FSH of 1 mIU/ml, and LH of 0.12 mIU/ml. Fasting serum lipids demonstrate elevated triglycerides for age, a fasting glucose-to-insulin ratio (FGIR) of 6.5, fasting glucose in the upper range of normal at 98 mg/dl, and fasting insulin of 15 IU/ml.

Questions: Diagnosis? Intervention? Follow-up?

Age 10years

The patient continued to grow along the 75th -90th percentile for height and 90th percentile for weight. By age 9 years, she had Tanner III-IV pubic hair and Tanner stage II breast tissue was noted at age 9 years. Menarche had just occurred at age 10 years.

Her height is 150cm (~90th percentile), weight is 48kg (~90th percentile), BMI is 21.3 kg/m^2 (~90th percentile), and blood pressure is 110/70 mmHg. She has a fine moustache, greasy facial skin with comedones, and two pustules on her chin. She has Tanner IV breasts and pubic hair, with mild periareolar, periumbilical, and perirectal hair.

Her height age is 11 years, her bone age is 12 years, and her estimated adult height is 64½±2 inches. She has triglyceride levels of 162mg/dl, HDL of 36mg/dl and LDL of 130mg/dl. Her

FGIR has decreased to 4.5, and her oGTT reflects hyperinsulinemia. Her testosterone is 28ng/dl, Δ4-A is 200ng/dl, DS 237μg/dl, LH 4.4mIu/ml and FSH 2.1mIu/ml.
Questions: Diagnosis? Intervention? Follow-up?

Age 16 Years
She had menarche at 10 years. After two years of persistently irregular cycles and increasing hyperinsulinemia, she was started on metformin. She has followed a Mediterranean diet (low glycemic index, low carbohydrate, high grain and fiber content). She does aerobic and resistance exercises three times per week. She reports continued acne and the presence of increased body and facial hair, and regularly undergoes laser hair removal.

Her height is 165.2cm (50^{th}-75^{th} percentile), weight is 77.5kg (95^{th} percentile), BMI is 28.4 kg/m^2 (>90^{th} percentile), waist circumference is 82cm (75^{th} percentile), and blood pressure is 118/76 mmHg. She has significant facial hair, periumbilical and perirectal hairs, and mild acne. Her Ferriman-Gallwey score is elevated at 16. She has Tanner IV breasts and Tanner V pubic hair and faint acanthosis nigricans of the neck and periaxillary areas. Laboratory tests show elevated Δ4-A at 310ng/dl, DHEAS at 282g/dl, and LH at 18mIu/ml, and borderline-high fasting lipids (LDL 120mg/dl, HDL 35mg/dl, triglycerides 190mg/dl). oGTT shows an FGIR of 5.2. She now has 40% body fat on DeXA.
Questions: Diagnosis? Intervention? Treatment?

Case 2
7-year-old female. She has consistent growth along the 75th percentile since age 3 years, 90th percentile for weight. She has intermittent nasal comedones. Her mother has a history of menarche at age 11 and irregular cycles. Physical examination is positive for early Tanner III pubic hair, axillary hair and odor, and Tanner II breast tissue. Bone age is 10 years.
Questions: Diagnosis? Further evaluation?

Case 3
8-year-old male. He had onset of pubic hair at age 6 years. He has Tanner III pubic hair, 3 ml testes, and a bone age of 11 years. He has been growing along the 75^{th} percentile for height and weight. He has a 6 month history of "rapid" growth and now plots at the 90^{th} percentile channel for both. Physical examination was positive for axillary hair. Lab data reveals an 8AM 17-hydroxyprogesterone of 350 ng/dl, DHEAS of 100 μg/dl, D4-A of 250 ng/dl, and a testosterone of 30 ng/dl.
Questions: Further evaluation? Management?

Case 4
A 6-year-old girl is seen because of recent onset of pubic hair. She has prepubertal breast tissue. Her growth rate is normal. Bone age is 7 years. Her serum testosterone level is 30 ng/dl, 17-OHP 20 ng/dl, DHEAS 30 μg/dl and D4-A of 20 ng/dl. Her father is receiving an androgen-containing gel.
Question: Etiology?

DISCUSSION OF CASES AND ANSWERS

Case 1

Diagnosis: Adrenarche; minimal elevation of androgens; prepubertal gonadotropins. Bone Age = Height Age. Slight elevation of lipid levels and fasting glucose upper range of normal.
Intervention: None other than counsel on prudent dietary intake re lipids and carbohydrates and no "concentrated sweets."
Follow-Up: Somewhat controversial. Suggest 6 month visit for height, weight, pubertal assessment and counseling.
Diagnosis: Progression of adrenarche to early normal menarche. Mild hirsutism and early lipid elevations with hyperinsulinemia.
Intervention: Prudent diet (? Mediterranean diet), chart menstrual cycles, controversial regarding pharmacologic interventions.
Follow-Up: 3-6 month intervals because of progressive rise in BMI.
Diagnosis: Hirsutism. Early signs of metabolic syndrome and possible evolution to PCOS.
Intervention: Obtain testosterone and free testosterone levels. Continue diet.
Treatment: Controversial; consider addition of OCP to metformin.

Case 2

Discussion: Having Tanner II Breasts at age 7 is still considered somewhat precocious pubertal development. Obtain LH, 17OHP and, for general health measures, fasting lipid levels, glucose/insulin. Evaluation is somewhat physician dependent. If bone age advanced at age 7, should consider initiation of evaluation for precocious puberty.

Case 3

Discussion: Early pubarche, prepubertal testes, BA advancement with elevated early AM 17OHP level. Increased androgen levels for age.

Further Evaluation: Should include ACTH stimulation testing to confirm diagnosis of defect in adrenal steroidogenesis, likely steroid 21 OH deficiency.

Management: Will need to prospectively determine if observation is sufficient re progression of "disorder." Consider bone age advancement and height prediction when making decision re treatment, likely with glucocorticoid therapy.

Case 4

Question: Was written to raise awareness of exogenous exposure to androgen (and estrogen) containing compounds. Reminder to ask for commercial product usage in history.

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Delayed Puberty: Diagnosis, Evaluation, and Management

M46
Monday, June 17
1:00–1:45 PM & 3:00–3:45 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Delayed puberty is among the most common problems seen in pediatric endocrinology clinics. Its causes, diagnostic testing, and treatment have recently been reviewed [1, 2], and those reviews form the basis of this syllabus.

Delayed puberty is defined as the absence of testicular enlargement in boys or breast development in girls 2–2.5 standard deviations later than the population mean (traditionally age 14 years in boys and 13 in girls). However, because of a downward trend in pubertal timing [3-7] and because of differences in pubertal timing among ethnic groups, some advocate for updated definitions, especially for girls, perhaps with younger age cutoffs for the general population and/or in particular countries or among specific population groups. Data regarding secular changes in the onset of puberty in boys is more controversial, and it is less clear the age definitions for delayed puberty in boys need to be adjusted [7-9]. Given the current lack of clear data/guidelines, I continue to use the traditional definitions of 14 years for boys and 13 years for girls in my practice. Unlike for sexual precocity, development of pubic hair is usually not considered in the definition of delayed puberty because pubarche may result from maturation of the adrenal glands (adrenarche) and onset of pubic hair can be independent of hypothalamic-pituitary-gonadal (HPG) axis activation.

Delayed puberty can have profound effects on an adolescent's psychosocial well-being and can be a cause of bullying, difficult peer relationships, and poor self-esteem. Patients, families, and practitioners are also often concerned that delayed puberty may affect adult stature. Adult height can be affected, but on average is only slightly below the genetic target [10]; however, many adolescents present with delayed puberty combined with relative familial short stature, compounding these concerns and leading to more subspecialty referrals than either condition alone.

BARRIERS TO OPTIMAL PRACTICE

Challenges in clinical practice include:

- Lack of data regarding utility and cost-effectiveness of components of routine diagnostic evaluations and lack of tests that can reliable distinguish constitutional delay of growth and puberty (CDGP) from isolated hypogonadotropic hypogonadism (IHH).
- Inadequate data regarding pros/cons of different sex steroid replacement regimens, particularly for young women with delayed puberty.
- Inadequate data regarding utility of and safety of using height-promoting therapies, such as aromatase inhibitors, in treatment of CDGP.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be familiar with:

- The diagnostic evaluation and etiologies of delayed puberty.
- The use of sex steroids to treat delayed puberty and induce secondary sexual characteristics.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY,

AND/OR MANAGEMENT

Etiologies of Delayed Puberty

The single most common cause of pubertal delay in boys and girls is constitutional delay of growth and puberty (CDGP). CDGP represents the extreme end of the distribution of normal timing, rather than overt pathology. CDGP is a diagnosis of exclusion, and other etiologies must be considered, especially in girls in whom CDGP is less common. CDGP accounted for approximately 65% of cases among boys and 30% among girls in one tertiary center, but it is likely an even more common diagnosis in primary care settings [11]. Other causes of delayed puberty can be divided into 3 main categories[11] -- hypergonadotropic hypogonadism (characterized by elevated luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels due to lack of negative feedback from the gonads); permanent hypogonadotropic hypogonadism (characterized by low LH and FSH levels due to hypothalamic or pituitary disorders); and transient hypogonadotropic hypogonadism (functional hypogonadotropic hypogonadism) where pubertal delay is due to delayed maturation of the HPG axis secondary to underlying conditions. Hypergonadotropic

TABLE 1: Listing of Causes of Delayed Puberty other than Constitutional Delay of Growth and Puberty.

Hypergonadotropic Hypogonadism (5-10% of boys; 25% of girls)	**Permanent Hypogonadotropic Hypogonadism (10% of boys; 20% of girls)**	**Functional Hypogonadotropic Hypogonadism (20% of boys and girls)**
Genetic Syndromes • Turner Syndrome • Noonan Syndrome and related disorders Fragile X premutation Cryptorchidism Gonadal Dysgenesis Vanishing Testes Syndrome Trauma/Testicular Torsion Chemotherapy/Radiation Therapy Gonadal Infection • Mumps, Coxsackie Galactosemia Autoimmune Oophiritis Autoimmune Orchitis Defects in Steroidogenesis • 5-alpha reductase deficiency • 17, 20 lyase deficiency • Congenital Lipoid Adrenal • Hyperplasia Androgen Insensitivity Sertoli Cell only Syndrome • (Del CastilloSyndrome)	CNS Tumors/Infiltrative Diseases • Astrocytoma • Germinoma • Glioma • Craniopharyngioma • Prolactinoma • Langerhans Cell Histiocytosis Rathke Pouch Cyst Genetic Defects* • Kallmann syndrome (KAL1, FGFR1, PROK2, PROKR2, FGF8, HS6ST1 and CHD7) • Isolated hypogonadotropic hypogonadism (KAL1, GNRHR, GNRH1, GPR54, FGFR1, FGF8, PROK2, PROKR2, TAC3, TACR3. HS6ST1, NELF and CHD7) • HPG Axis Development (DAX1, SF-1, HESX-1, LHX3, and PROP-1) • Obesity and hypogonadotropic hypogonadism (LEP, LEPR, and PC1) Syndromes • Prader-Willi • Bardet-Biedl • CHARGE Gaucher Disease Post Central Nervous System Infection Midline Defects • Septo-Optic Dysplasia • Congenital Hypopituitarism Chemotherapy/Radiation Therapy Trauma	Systemic Illness/Conditions • Cystic Fibrosis • Asthma • Inflammatory Bowel Disease • Celiac Disease • Juvenile Rheumatoid Arthritis • Anorexia Nervosa/Bulimia • Sickle Cell Disease • Hemosiderosis • Thalassemia • Chronic Renal Disease • AIDS Endocrinopathies • Diabetes Mellitus • Hypothyroidism • Hyperprolactinemia • Growth Hormone Deficiency • Cushing Syndrome Excessive Exercise Malnutrition

**Some genes have been identified as causes of both Kallmann syndrome and isolated hypogonadotropic hypogonadism (IHH). Reprinted with permission from [NEJM, Palmert MR and Dunkel L, Delayed Puberty, 366:443-53. Copyright © (2012) Massachusetts Medical Society] [2].*

hypogonadism represents approximately 5-10% of cases of delayed puberty among boys and 25% of cases among girls; permanent hypogonadotropic hypogonadism represents approximately 10% of cases among boys and 20% among girls; and functional hypogonadotropic hypogonadism comprises approximately 20% of cases among both boys and girls

The etiology of CDGP is unknown. CDGP does have a strong genetic basis. Fifty to 80% of variation of the timing of puberty in humans is due to genetic factors [12], and 50 to 75% of individuals with CDGP have a family history of delayed puberty [13, 14]. The inheritance patterns observed among pedigrees with CDGP are variable but most often consistent with an autosomal dominant pattern, with or without complete penetrance.

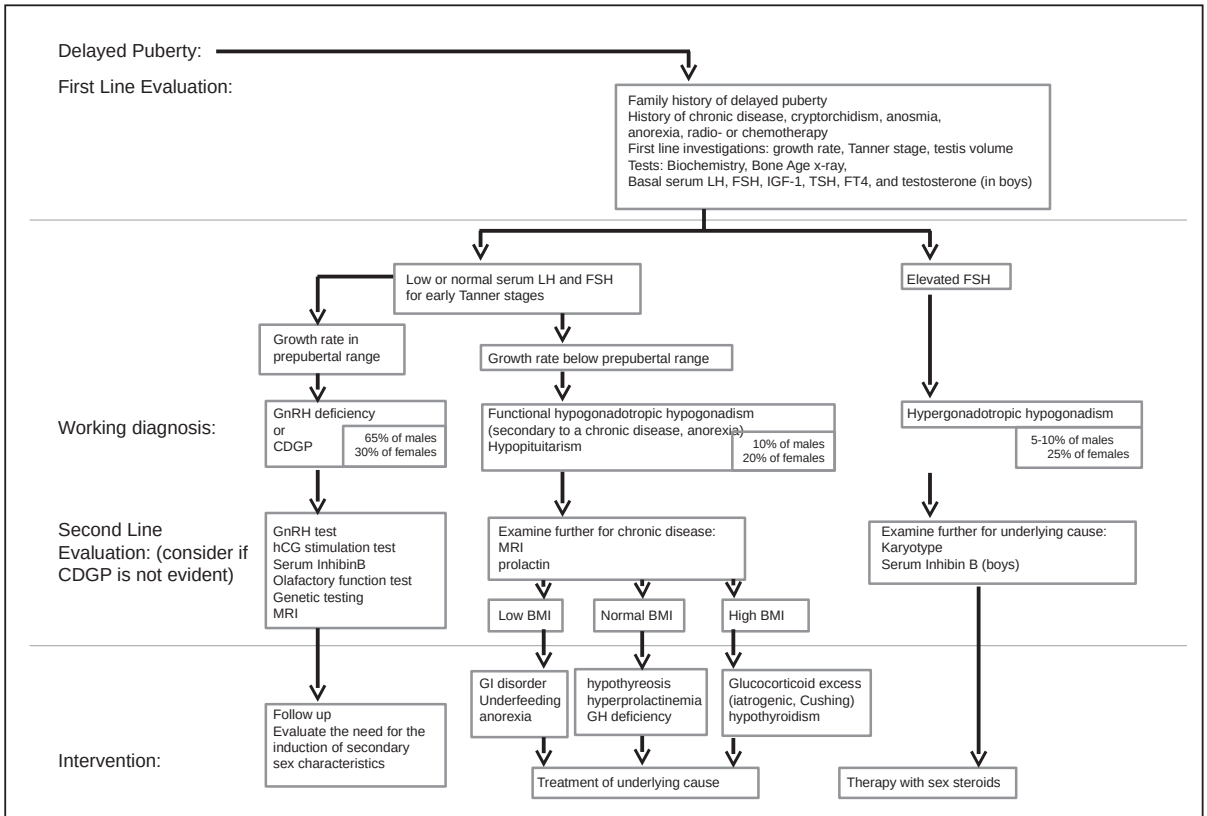
Evaluation of Delayed Puberty

The aim of the initial evaluation is to rule out causes of delayed puberty other than CDGP.

A family history, including childhood growth patterns and age at pubertal onset of the parents should be obtained. Delayed puberty in a parent or sibling followed by spontaneous onset of puberty suggests CDGP. Patients and their parents should be questioned about a history or symptoms of chronic disease, with emphasis on disorders (e.g. celiac disease, thyroid disease, anorexia), that may cause temporary delay of puberty (functional hypogonadotropic hypogonadism), as well as medication use, nutritional status, and psychosocial functioning. Bilateral cryptorchidism and/or small penis at birth, hyposmia, or anosmia may suggest permanent hypogonadotropic hypogonadism.

Previous height and weight measurements should be obtained and plotted so that longitudinal growth can be carefully assessed. Individuals who are underweight for height have a higher likelihood of an underlying condition delaying HPG axis activation. Tanner Staging should be performed and

FIGURE 1. Schematic of diagnostic evaluation.



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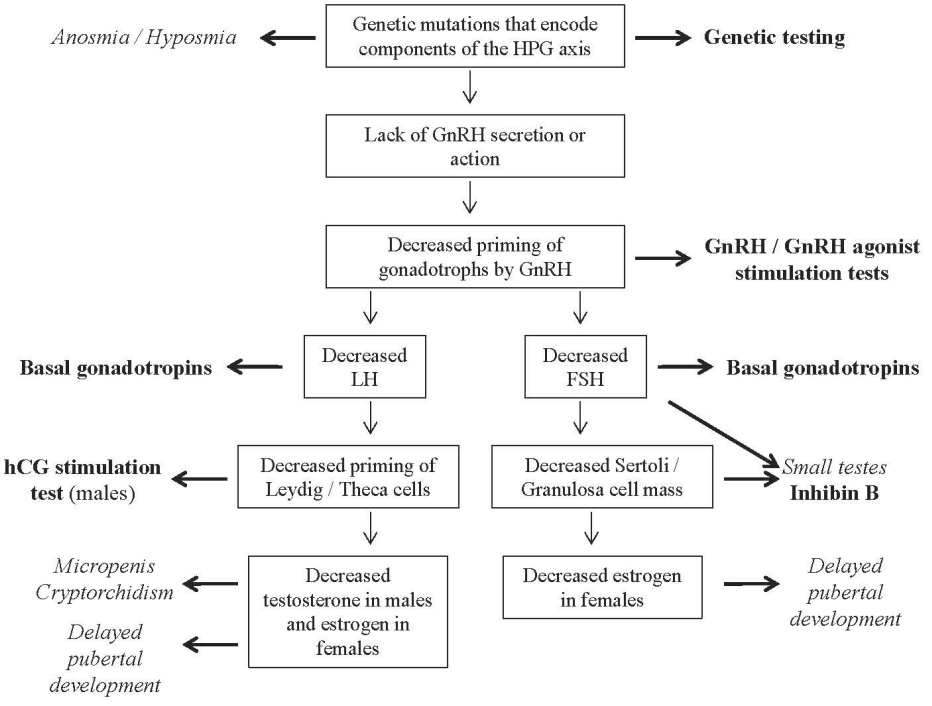
testicular size should be measured in boys; a volume ≥ 4 cc indicates initiation of central puberty. In patients with CDGP, both adrenarche and hormonal activation of the gonads often occur later than average, but in isolated hypogonadotropic hypogonadism, adrenarche usually occurs at a normal age [11, 15].

A bone age should be obtained and reviewed by an individual who is experienced in interpreting these x-rays. A delay in bone age is characteristic but not diagnostic of CDGP, and also may occur in individuals with chronic illness, hypogonadotropic hypogonadism, or gonadal failure. Adult height prediction is an important part of counseling if short stature is a component of the presentation, and practitioners should be aware that the Bayley Pinneau tables may overestimate adult height in patients with CDGP if bone age is delayed by more than two years.

To rule out underlying disorders, screening laboratories are often obtained. Testing should be directed by the history and physical examination so that a parsimonious, cost-effective evaluation is performed; certainly not all tests should be performed in all patients. Commonly obtained tests include complete blood count, erythrocyte sedimentation rate, creatinine, electrolytes, bicarbonate, thyrotropin, and free thyroxine. LH, FSH, and sex steroid levels (estradiol or testosterone) are obtained to assess for central vs. peripheral causes of hypogonadism. IGF1 levels can be obtained to screen for growth hormone deficiency, but results must be interpreted carefully because levels are often low for chronologic age but within normal range for bone age. If provocative growth hormone

FIGURE 2



In a subset of adolescents with IHH (and Kallmann's syndrome) mutations in genes that encode critical components of the hypothalamic-pituitary-gonadal (HPG) axis lead to either a lack of gonadotropin releasing hormone (GnRH) secretion or action. The etiologies in the remaining cases are undetermined. The lack of GnRH action leads to a deficiency of both priming and hormonal secretion of the gonadotrophs in the pituitary and of the Leydig / Theca cells in the gonads. These characteristics of the HPG axis form the physiologic basis for the diagnostic tests and typical clinical characteristics (anosmia / hyposmia, small testes, micropenis, cryptorchidism) used to identify patients with a higher likelihood of IHH than CDGP.

testing is performed, I believe it should only be done with sex steroid priming.

Brain MRI is indicated when there are signs or symptoms to suggest a CNS lesion; otherwise, a reasonable strategy is to defer this until age 15, at which point many patients with CDGP will have spontaneously begun puberty and will require no further evaluation.

Distinguishing CDGP From IHH

If these initial studies are not suggestive of an underlying disorder, the diagnosis of CDGP is most likely. However, no test can reliably distinguish CDGP from IHH, so the diagnosis of CDGP cannot be made with certitude [1, 16]. Observation is required; IHH is diagnosed if endogenous puberty has not begun by age 18 years. Several tests, including genetic analyses, have been proposed to distinguish CDGP from IHH, but none has yet demonstrated robust clinical utility and none is recommended for routine clinical practice. The bases for these tests are outlined in *Figure 2*.

Stimulated LH levels in the pubertal range indicate reactivation of the HPG axis, and suggest that secondary sexual development is likely to occur within one year. However, the GnRH test alone often cannot differentiate CDGP from HH because prepubertal values may be observed in HH or in individuals with CDGP who have not yet activated the HPG axis. Recent data suggest that baseline inhibin B levels may facilitate discrimination between these conditions [17, 18], but replication is needed before this or other tests can be adopted routinely [1, 16].

Treatment of Delayed Puberty

The options for management of CDGP include expectant observation or therapy with low dose testosterone (in boys) or estrogen (in girls). If puberty has started, clinically or biochemically, and stature is not a major concern, reassurance with realistic adult height prediction is frequently all that is needed. If therapy is initiated, it is usually to assuage psychosocial difficulties that may derive from negative interactions with peers, decreased self-esteem, and anxiety about growth rate and/or body habitus. Therapy is usually not initiated solely for medical reasons, such as accrual of bone mass, but additional data are needed to determine definitively whether medical reasons to initiate therapy should be given more consideration [19].

For a subset of patients with CDGP, short stature can be more concerning than delayed puberty, and indeed CDGP is considered by some to be a subgroup of idiopathic short stature (ISS). Although GH is approved for the treatment of ISS and height SDS < 2.25 for age, it has at best a modest effect on adult height in adolescents with CDGP, and I believe its routine use in CDGP is not warranted. In boys with CDGP and short stature, another potential therapeutic approach is aromatase inhibition, but this treatment requires further study before it is incorporated into routine practice [20, 21]. Aromatase inhibitors (AIs) inhibit conversion of androgens to estrogens. Because estrogen is the predominant hormone needed for epiphyseal closure, AIs could prolong linear growth and potentially increase adult height. However, the amount of height gained as well as the optimal timing, dose, and duration of AI treatment remain uncertain [22]. Moreover, potential adverse effects, especially impaired trabecular bone development and vertebral body deformities observed in boys with ISS treated with letrozole[23] must be considered along with theoretical risks related to spermatogenesis and development of non-alcoholic hepatic steatosis.

For boys, testosterone esters, such as testosterone cypionate and enanthate, are often used, and common protocols involve an initial dose of 50-100 mg IM each month (I use 50 mg) for 3-6 months (I usually treat for 3 months initially). After the initial course, if no secondary sexual characteristics have developed and/or spontaneous puberty has not ensued, then the regimen can be repeated for another 3-6 months, perhaps with a dose escalation of 25-50 mg but with the new dose typically remaining £ 100 mg per month. If, after one year of therapy, spontaneous puberty has not occurred, then other diagnoses, such as permanent hypogonadotropic hypogonadism, should be considered and further evaluation with an MRI of the brain may be warranted. Alternative forms of testosterone treatment

include transdermal patches and a gel formulation, but their use during initiation of secondary sexual characteristics has been limited by the requirement for low doses that can be delivered reproducibly.

In cases of permanent hypogonadism, initial dosing is the same as indicated for CDGP, but the doses are gradually increased to full adult replacement over a period of two to three years. Typically, doses are increased 50 mg every 6 months depending on bone age advancement, height prognosis, and development of secondary sexual characteristics. During the last year of dose escalation, the interval is decreased from once each month to once every two weeks, with a typical regimen for adult replacement being 200 mg every two weeks. Transdermal preparations can be initiated during the final stages of dose escalation, if preferred. In hypogonadotropic hypogonadism, exogenous testosterone does not induce testicular growth or spermatogenesis. Thus, if male patients with permanent hypogonadotropic hypogonadism wish to father a child or achieve increased testicular volume, gonadotropin therapy can be utilized, or, in hypothalamic disorders, pulsatile GnRH, can be also be considered.

TABLE 2. Induction of secondary sexual characteristics in girls.

Drug and Formulation	**Treatment of Girls Recommended Dose**		**Side Effects and Cautions**
	CDGP	**Hypogonadism**	
Estrogen			
Ethinyl estradiol (EE). Component of contraceptive pills. Lower dose EE PO preparations are available in Europe.	Initial dose 2 µg daily. Increase after 6-12 months to 5 µg daily.	Initial dose 2 µg daily. Increase every 6 to 12 months to 5 µg, 10 µg and 20 µg daily (adult dose).	Liver toxicity, increased levels of some plasma binding proteins. Potentially greater risk of thromboembolism and arterial hypertension than natural estrogens.
17β-estradiol. Oral tablets	Initial dose 5 µg/kg daily perorally, increase after 6-12 months to 10 µg/kg daily	Initial dose 5 µg/kg daily perorally, increase every 6-12 months to10 µg/kg daily, then to 15 µg/kg and to 20µg/kg daily. Adult dose 1-2 mg daily.	Natural estrogen, may be preferable to synthetic estrogens. Transdermal route may have advantages over oral administration.
17β-estradiol. Transdermal patch or gel. Patches overnight daily, Topical gel applied daily.	Patch: initial 3.1-6.2 µg/24h (1/8-1/4 of 25 µg/24h patch). Increase by 3.1-6.2 µg/24h every 6 months.	Overnight patch: initial 3.1-6.2 µg/24h (one-eighth to one-fourth of 25 µg/24h patch). Increase by 3.1-6.2 µg/24h every 6 months. Adult dose 50 (to 100) µg/24h.	No dosage equivalent data between patches and gel available in younger patients.
Conjugated equine estrogens (CEE) Oral tablets.	Initial dose 0.1625 mg daily for 6-12 months, and then titrating to 0.325 mg daily. Dosing depends on formulation.	Initial dose 0.1625 mg for 6-12 months, increase every 6-12 months to 0.325, 0.45, and 0.625 mg daily. Common adult dose 0.625 mg.	CEE are not estradiol precursors. Use questioned by some as not physiological and because of reported increased cardiovascular risks in postmenopausal women.
Progestogens/Progestins Various options, usually perorally	Usually necessary only if treatment continues longer than 12 months.	5-10 mg of medroxyprogesterone acetate (MPA) daily during the last 7 days of menstrual cycle. Alternative: micronized progesterone, dose 100-200 µg daily.	Progesterone added to induce endometrial cycling after 12-18 months of estrogen therapy (later if estrogen dose increased slowly; sooner if break-through bleeding).
Modified from [NEJM, Palmert MR and Dunkel L, Delayed Puberty, 366:443-53. Copyright © (2012) Massachusetts Medical Society] [2]			

Regimens used for sex steroid replacement in females are more varied and more controversial than those used for males. The basic principles are similar: short-term treatment in CDGP with interruption of therapy to allow for assessment of endogenous pubertal development, and gradual escalation of doses toward full adult replacement in cases of permanent hypogonadism. However, the regimens employed are much more varied. Timing of therapy and initial doses have also been points of controversy with tendency to delay therapy in cases of permanent hypogonadism in an attempt to maximize final height giving way to earlier initiation of therapy with lower doses and more gradual dose escalation [24].

Agents used for treatment of delayed puberty in females, including examples of dosing regimens, are displayed in *Table 2*.

Regardless of formulation used, several issues should be considered. These include cautioning patients against smoking and screening for family histories of thromboembolism, premature cardiovascular disease, and lipid abnormalities because these factors may alter choice of therapeutic agents. For example, despite their many benefits, transdermal formulations do not have the beneficial effects on lipid profiles seen with oral agents, and this might favor oral formulations in particular cases. Alternatively, concern regarding thromboembolism may favor transdermal preparations in other cases. Once adult height has been achieved, estrogen and progestin combinations (oral contraceptive pills or OCPs) are often used in the treatment of female sex steroid deficiency. Although these regimens do not necessarily mimic physiologic replacement, OCPs are very convenient for patients, offering low-dose estrogen (20-30 μg of ethinyl estradiol) in combination with progestins in a single pill taken daily. The estrogen and progestin combination allows for regular endometrial cycling and can help prevent unwanted pregnancy.

MAIN CONCLUSIONS

Diagnostic testing in cases of delayed puberty can be extensive and expensive, and not all tests have high discriminatory value. Evaluations should, therefore, be thoughtful and judicious. In CDGP, where pubertal delay is transient, the decision regarding whether to treat should be made by the patient; the goal of therapy, when used, is to induce secondary sexual characteristics and/or growth acceleration and to mitigate psychosocial difficulties. When therapy is initiated in CDGP in boys, it should be with testosterone alone, even if stature is a prominent concern. I do not advocate use of growth hormone or anabolic steroids for treatment of delayed puberty, nor do I recommend aromatase inhibitors for CDGP, pending availability of more data regarding outcomes, optimal regimens, and safety.

Areas for further investigation include development of transdermal regimens (and perhaps formulations) that can be used routinely for pubertal induction in males. For females, it will be important to obtain additional data directly comparing oral vs.transdermal formulations and determining whether differences in subclinical cardiovascular outcomes are observed in youth (who are being provided physiologic as opposed to post menopausal therapy and who are being treated for relatively short periods of time). Dose equivalencies among the various estrogen replacement regimens are often quoted, but these need to be more rigorously defined.

Finally, studies are needed that carefully assess the psychosocial distress experienced by individuals with delayed puberty, whether this distress has long-term sequelae, and what impact sex steroid supplementation has on these outcomes.

CASES WITH QUESTIONS

1. A 14 year old boy presents because of lack of pubertal development.

What are key questions to ask about his past medical history? His family history?

What are key findings on physical examination?

What testing would you recommend? Are there specific tests you do in specific situations? What if he is 16 and still has not entered puberty?

Assuming no underlying disorder is identified, what therapy would you initiate?

He is currently slightly below the 3rd percentile for height. How do your responses differ if his target (genetic) height is at the 5% vs. at the 25% vs. at the 50%? How do your responses differ if his predicted adult height is at the 3rd percentile vs. at the 1st percentile? What if his current height were at the 1st percentile?

2. A 13 year old girl presents due to lack of breast development and slowed growth compared to peers.

Related to the questions above, how does your approach change because the patient is female? Or does it?

DISCUSSION OF CASES AND ANSWERS

The syllabus provides the needed core information, but interactive discussion, with input from session attendees, will be used to arrive at "answers" to the questions posed in the specific cases.

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Pediatric Perspective on Insulin Pumps and Artificial Pancreas

M10
Saturday, June 15
3:00–3:45 PM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Since the publication of the DCCT (1) we are all aware of the importance of intensive diabetes therapy and the lowering of the HbA1c levels. Diabetes treatment has been intensified in pediatric patients by the use of multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII), the use of new short and long-acting insulin analogues, and increased frequency of daily self-monitoring of blood glucose (SMBG). Despite these changes in diabetes therapy, the anticipated improvement in metabolic control in children & adolescents with type 1diabetes (T1D) has not been achieved in most diabetes centers surveyed in the world.

Data from 21 centers of the Hvidoere Study Group reported that most patients with T1D aged 11-18 years, did not achieve the target HbA1c with a mean level of 8.2% (2). HbA1c data in the T1D Exchange group (centers of excellence in the USA) showed that patients younger than 26 years had HbA1c ~8.3%. A large registry of 30,708 children and adolescent patients with T1D documented from 305 diabetes centers in Germany and Austria between 1995 and 2009 demonstrated a significant improvement in metabolic control with a decrease in mean HbA1c from 8.7±1.8% to 8.1±1.5% during the past decade with a simultaneous decrease in hypoglycemic events (3). However, the mean HbA1c in these studies was above the targets defined by ISPAD and ADA (4,5).

BARRIERS TO OPTIMAL PRACTICE

CSII is the most physiologic method of insulin delivery currently available. It is able to closely mimic the normal pattern of insulin secretion; namely, continuous 24-hour adjustable "basal" delivery of insulin upon which are superimposed prandial "boluses". In addition, it offers the possibility of more flexibility and more accurate insulin delivery than MDI. However, there are still problems with achieving the desired glycemic targets due to multiple reasons including: skipping insulin boluses with high blood glucose levels, the need to estimate carb intake, the need for intensive monitoring in order to prevent DKA events secondary to mechanical problems, the occurrence of hypoglycemia and the fear of hypoglycemia, especially during the night, and the dependency on "the human factor" (patient/caregiver) making decisions about treatment.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Know the advantage of CSII
- Know the barriers of CSII in achieving target glycemic levels
- Know the use of continuous glucose monitoring (CGM) augmented CSII therapy to improve diabetes treatment
- Know the need of using a closed-loop system simulating the artificial pancreas and progression in human studies done in this area.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Advantage of CSII

Young patients with diabetes and their

care providers continue to be faced with the challenge to maintain blood glucose levels in the near-normal range and to achieve the target HbA1c levels (4,5) in order to prevent the short-term complications of recurrent episodes of hypoglycemia and DKA and the long-term microvascular and macrovascular complications.

Patients treated with MDI can have erratic absorption and action of insulin with unpredicted swings in blood glucose. The long acting insulin analogues cannot be modulated after injections with increased risk of recurrent severe hypoglycemia, and in patients with needle phobia the regimen of MDI can be associated with non-compliance.

Over the past decade, CSII has become a standard treatment option for patients with T1D.

CSII is the most particular way to mimic normal insulin secretion because basal rates can be programmed to deliver insulin in short-time segments throughout a 24-hour period.

Patients can accommodate metabolic changes related to eating, exercise, illness, or varying work load and schedule by modifying insulin availability on an hour-to-hour basis.

Basal rates can be adjusted to match lower insulin demands at night and higher requirements between 3 to 8 AM.

Different basal rates may be used on weekends vs. weekdays, or while on vacation.

Given these benefits, numerous observational studies in pediatric patients with T1D have reported a decrease in HbA1c with CSII (6-11).

Inadequate glucose control can lead to wide glycemic excursions or frequent hypoglycemia. Recurrent episodes of hypoglycemia at a very young age have been associated with neurocognitive dysfunction. Fear of hypoglycemia is prevalent in adolescents and the families of children with T1D, and may pose a barrier to improved glycemic control. Pediatric observational studies, but not randomized controlled trials (RCTs), have demonstrated that CSII decreases the frequency of severe hypoglycemia (8,11,12). In children, CSII monitored with CGM, has shown also a decrease in glucose variability in some trials (13, 14).

Children and adolescents with T1D are encouraged to exercise regularly. However, plasma glucose concentrations are often difficult to manage during prolonged periods of physical activity. With CSII insulin delivery can be temporarily suspended during prolonged physical activity, and this feature decreases the risk of exercise-related hypoglycemia in patients using CSII (15).

Most current pumps can track the "insulin-on-board" for safer use of correction doses. A major advantage of new CSII is the option of "temporary basal rates", i.e., an insulin dose increase (such as during intercurrent illness) or an insulin dose decrease (such as during or after exercise) for a specific period of time. Pumps can be programmed for individual boluses to be administered over an extended period of time ("extended" or "square wave" bolus).

This feature may be particularly helpful for very high-fat meals, or those patients with delayed gastric emptying. The new pumps generation has a bolus calculator incorporated into the insulin pump, making calculation easier and more precise (16). The calculator estimates the dose of insulin to be administered at the meal on the basis of the following parameters: current blood glucose level, grams of carbohydrate in the meal, carbohydrate-to-insulin ratio, insulin sensitivity factors, target blood glucose, quantity of insulin previously administered, and duration of insulin action ("insulin on board").

The ability to review insulin boluses, carbohydrate intake used in bolus calculations and blood glucose levels from pump memory may be useful for counseling patients on their diabetes management, particularly for adolescents, who often omit boluses and have difficulty with manual record keeping

In spite of the intensive nature of CSII, quality of life with CSII therapy is similar to or higher than that reported in youth treated with MDI. Clinical experience has shown that instances of patient/family choice to discontinue CSII and return to MDI are not common in any of the pediatric age groups, suggesting that CSII is a preferred modality of treatment (17).

Barriers of CSII in achieving the target glycemic levels

Imperfect adherence with diabetes management has been recognized as an obstacle to successful intensive treatment, specifically in the adolescent age group. A large study from 17 countries included 1041 patients, age 11.8±4.2 years with a mean HbA1c level of 8.0±1.3% that were treated with CSII, demonstrated a significant negative correlation between HbA1c levels and the number of the daily boluses (18). Skipping boluses, incorrect carbohydrate counting and decreased monitoring of blood glucose levels can cause the occurrence of hypo or hyperglycemia events. In addition, individuals using CSII are at increased risk of developing DKA if there is a mechanical interruption of insulin infusion due to the solitary use of short acting insulin analogues.

The use of CGM augmented CSII therapy to improve diabetes treatment

Previous data reported the association between lower HbA1c levels and a higher frequency of daily SBGM. The use of a device such as real-time CGM that provides 24-hour continuous glucose measurements may have the potential to increase the proportion of patients who are able to maintain target HbA1c values, to decrease glucose excursions, and to decrease the risk of severe hypoglycemia. The CGM use can improved daytime bolus dosing according to trend arrows and hyper- and hypoglycemia alarms, to improve overnight control by hypoglycemia alarms and retrospective data to optimize overnight basal insulin, and enhance understanding of diabetes management teaching.

The Guardian study evaluated the effect of a new real-time CGM on glycemic control in patients with poorly controlled T1D. This RCT demonstrated a clinically meaningful reduction in HbA1c using real-time CGM (19). In the last years, several studies evaluated the implications and advantages of using CGM alone or as a part of sensor-augmented pump (SAP) therapy in pediatric patients. The Juvenile Diabetes Research Foundation (JDRF)-CGM Study Group (20) demonstrated the effectiveness of SAP therapy over MDI after 12 months, and that frequent usage (> 6 days/week) of continuous monitoring in patients with T1D results in lower HbA1c levels and avoidance of biochemical hypoglycemia. Consistent usage of CGM has been difficult to achieve, especially among children and adolescents. In the STAR3 study (21) SAP therapy was shown to allow both children and adolescents with marginally or inadequately controlled T1D to reduce HbA1c values, hyperglycemic excursions, and glycemic variability in a rapid, sustainable, and safe manner. In the percentage of youth meeting age-specific HbA1c goals was significantly greater for the SAP group. Both CSII and CGM in combination was tolerable and effective.

A multicenter crossover RCT study that included children and adults randomized to a Sensor On or Sensor Off arm for 6 months determined the efficacy of adding CGM to CSII in T1D (22) demonstrated that the use of CGM was associated with decreased HbA1c levels and time spent in hypoglycemia in individuals with T1D using CSII. A meta-analysis of RCTs (23) showed that CGM use was associated with a significant reduction in HbA1c level, which is greatest in those with highest baseline HbA1c values and in those who use the sensor most often.

Another study demonstrated that the use of CGM was associated with significant reduction of time spent in hypoglycemia (24). However, when the use of CGM was evaluated in toddlers with T1D (25), a group in which parents are responsible for diabetes management and parental fear of hypoglycemia often prevents better glycemic control, no benefit was found in using a CGM on glycemic control, despite high parental satisfaction with CGM.

The first step towards a closed loop artificial pancreas was already approved in many countries for routine clinical use. It is the low glucose suspend (LGS) function to turn off an insulin pump when a low glucose level (<70mg/dL) is reached on a CGM. This could potentially reduce the time spent in hypoglycemia and reduce the severity hypoglycemic episodes at night, when 75%

of episodes occur in the youth. A recent study using the LGS (26) clearly showed its effectiveness in reducing time spent in hypoglycemia in children with T1D.

Using a closed-loop system simulating the artificial pancreas

It was reported that the CGM alarming for decreasing blood glucose level are not successful in significantly reducing nocturnal hypoglycemic events (71% of children with diabetes do not respond to the alarms during the night). Therefore, an artificial pancreas that automatically regulates blood glucose can help to overcome this problem, and would greatly improve the quality of lives of individuals with diabetes. Such a device would prevent hypo- and hyperglycemia as well as will ease some of the day-to-day burden of frequent blood glucose measurements and insulin administration. A feedback closed-loop system for controlling glucose levels throughout the night has the potential to decrease hypoglycemic events, maintain good glycemic control, and liberates the patients/caregivers from the anxiety. An example of such a system is the MD-Logic artificial pancreas system that has a wireless automatic communication with the insulin pump and glucose sensor. This communication method has safety measures included to account for the technical difficulties that can arise in this kind of system, and it also gives alert massages (for example : basal to bolus ratio is high, missing boluses etc.). Few recent studies evaluated the MD-logic system, and demonstrated that the mean percentage of time spent in the near normal glucose range increased for the overnight closed-loop sessions compared with the homecare open-loop setting, without hypoglycemic events occurring during the closed-loop sessions (27). Recently a successful use of the system for nocturnal metabolic control during a diabetes camp, a challenging environment, was described in the literature (28).

MAIN CONCLUSIONS

The never-ceasing challenge faced by patients and their care-givers has inspired continuing efforts to find ways and means for achieving better glycemic control. With the help of modern technology, young patients with T1D can live a normal life since they have better options, such as methods of glucose testing and insulin administration.

However, despite advancement in diabetes technologies, a large percent of patients with T1D do not achieve the target glycemic levels. The artificial pancreas systems may offer a potential major impact on the normalization of metabolic control and preventing hypoglycemic events, with "bypass" of the "human factor" that has a major impact on metabolic control

CASES WITH QUESTIONS

Case 1

Amy is a 16.5 year old girl with type 1 diabetes since the age of 10 years. She is treated with MDI basal- bolus regimen with lantus+novorapid injections in the last 3 years. She performs 4-5 daily self-blood glucose measurements (SMBG), and her mean glucose values are 215 mg/dL. Her last HbA1c was 7.2%.

What can be the reason for the discrepancy between her mean glucose values and her HbA1c level?

Case 2

Dan is a 21 year old man with type 1 diabetes since the age of 5 years. He is treated with CSII in the last 4 years. He has a history of 2 episodes of severe hypoglycemia. However, he has difficulties in performing frequent SMBG due to his busy job. His HbA1c levels during the last year ranged between 8-8.3%.

How can you help him improve his diabetes therapy?

Case 3

Sara is a 14 years old girl with type 1 diabetes. She is treated with CSII in the last year. Her HbA1c level is 8.4%, and she is very frustrated, because she thinks that she does "everything that is needed for good metabolic control".

What can be the reason for her moderate glycemic control? What can be done to

improve her glycemic control?

Case 4

Bred is a 22 year old college student with type 1 diabetes in the last 18 years. He is treated with an MDI regimen - lantus at bedtime and novorapid before meals. He usually measures his blood glucose levels only 3 times daily. His SMBGs levels are between 150-300 mg/dL, with elevated levels usually appearing during the morning and late afternoon hours. His HBA1C level is 6.7% (within the target range for his age).

What can be the reason for his high BGMs during the morning? What can be done to help him?

DISCUSSION OF CASES AND ANSWERS

Case 1

Patients with type 1 diabetes have to perform frequent SMBG in order to achieve good metabolic control. The adolescence period is particularly problematic due to the increased rate of non- compliance that can be reflected as decreased frequency of SMBG and skipping insulin injections or insulin boluses with the pumps. The current available glucometers allow the download of the glucose measurements and supervising the compliance of the patient. However, in our case, most of the measurements are above the target range, while the HbA1c level is within the target for pediatric patients. It may be possible therefore that there are periods of time when the blood glucose levels are low but are not recorded.

The additional value of CGM is in detecting recurrent nocturnal hypoglycemic episodes that are not seen with the regular mode of therapy. *(Figure 1)*

Case 2

Dan was connected to a real time-CGM with alarms for hypo and hyperglycemia, and initiated treatment with sensor augmented pump therapy. When the sensor measured high blood glucose levels it activated the alarm, and Dan could give insulin correction boluses. When the sensor measured low blood glucose levels it activated the hypo-alarm and made Dan react to them. When the glucose values went too low, it activated the low glucose suspension and

FIGURE 1

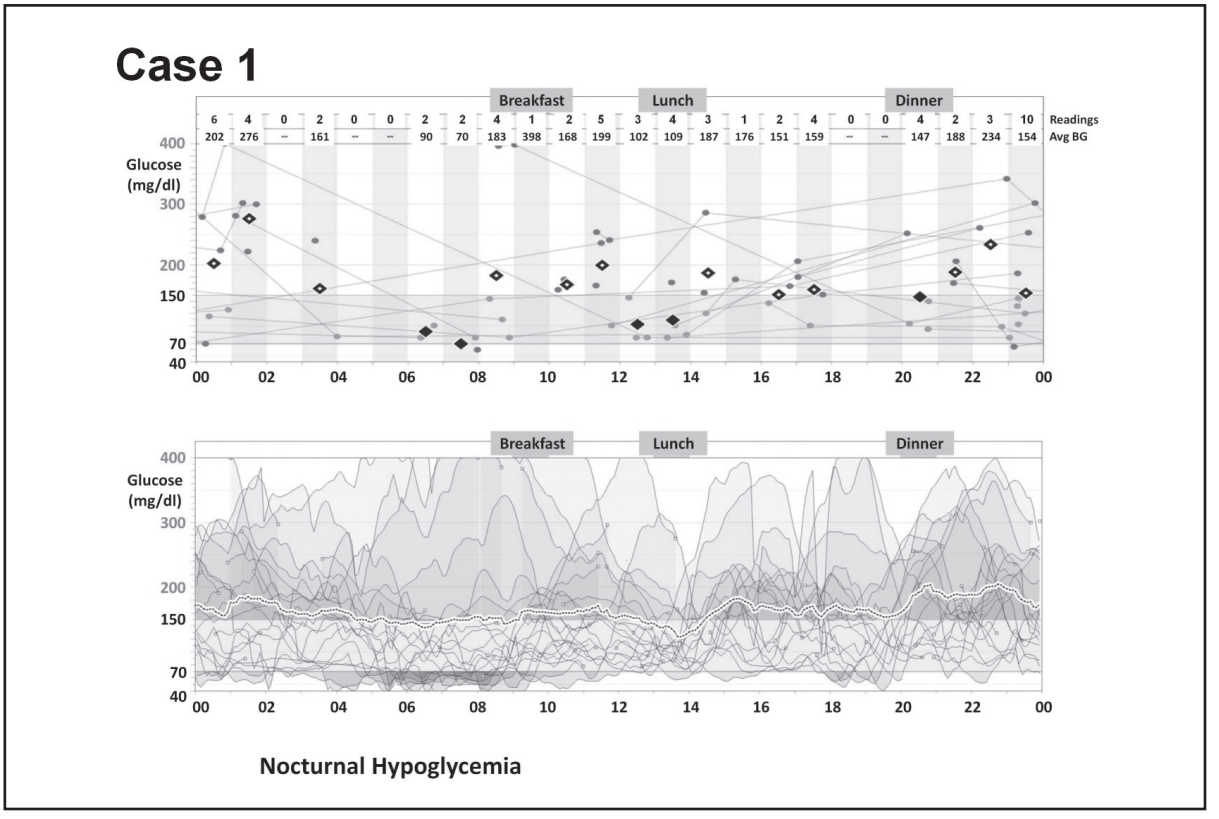


FIGURE 2

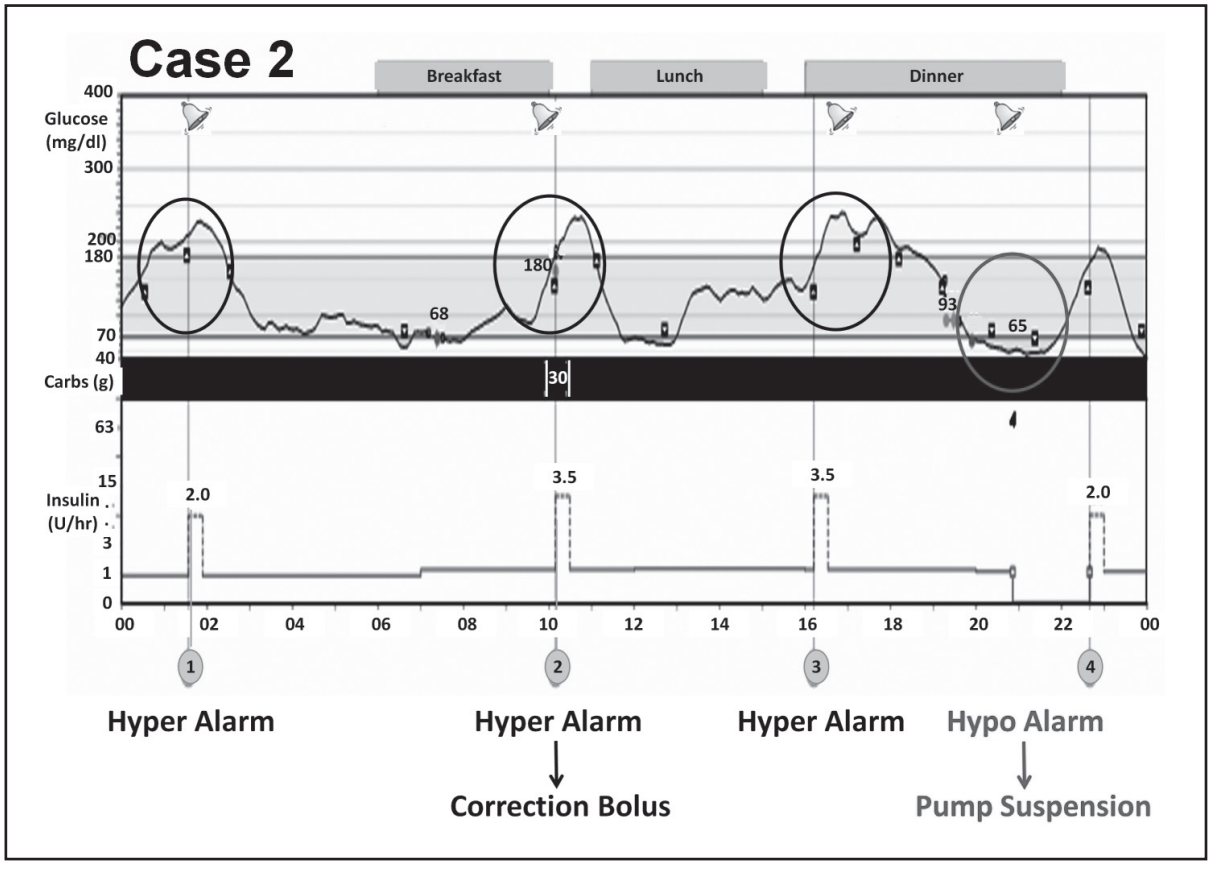
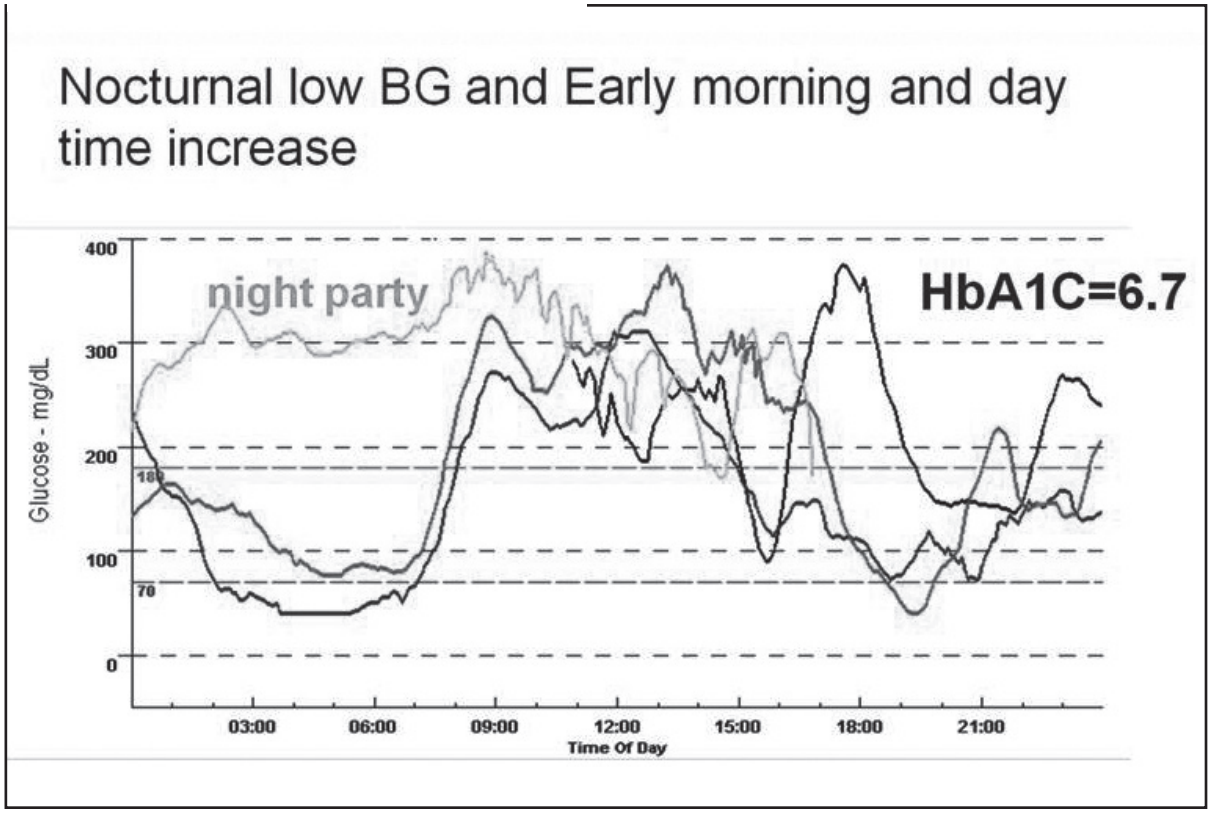


FIGURE 3



insulin infusion was stopped for 2 hours.

After 4 months with this treatment his current HBA1C is 7.1%. Several studies have shown that continuous use of CGM can significantly improve HbA1c levels. *(Figure 2)*

Case 3

Sara is a teenager with fear of hypoglycemia. She uses the pump to give the meal boluses, but she usually does not use the carbohydrate counting, and she omits insulin than is needed for "correction" of elevated blood glucose levels.

Using the CGM enabled us to share with Sara the printout and discuss with her the postprandial hyperglycemia and the huge glucose variability and to convince her to start using the "bolus wizard" in order to give the correct insulin doses. After 3 months her HBA1C improved (6.9%) with decreased post prandial glucose excursions and decreased diurnal glucose fluctuations.

Case 4

There are a few reasons that can cause morning hyperglycemia in patients with type 1 diabetes: Insufficient insulin administration during the night, eating carbohydrate snacks at bedtime, Dawn phenomenon (an early-morning, usually between 2 a.m. and 8 a.m. increase in blood glucose) or Somogyi phenomenon (post-hypoglycemic hyperglycemia, a rebound high blood glucose level in response to low blood glucose).

Bred usually increase the long-acting insulin dose based on his high blood glucose levels in the mornings. Using the CGM we determined early morning hypoglycemia followed by hyperglycemia, and therefore decrease the dose of the daily Lantus accordingly. *(Figure 3)*

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Idiopathic Short Stature (ISS): Whom Should We Be Treating?

M35
Monday, June 17
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

From the public health point of view there is very little clinical significance to short stature, per se. The issue is mainly considered in the psychosocial context and that will be considered below. The data are a bit different whether one is evaluating a clinical sample (referred to a growth clinic) or a population sample (for example, a school class). In either case the short stature is not a major public health problem that must be "fixed", although there are individual subjects who may benefit from growth-promoting therapy.

Short stature is variably defined as those children whose height falls below the third percentile (-1.88 SD) or the 2.3 percentile (-2.0 SD). For our purposes we shall use –2.0 SD, but consider the two values to be indistinguishable [1-4]. Short stature comes in many forms, physiological as well as pathological and it is virtually axiomatic that the closer one is to the cut-off value noted above, the less likely that there is a remediable cause for the present height of the child. Perhaps we are facing the issue at hand (short stature) but ignoring the more important "physiology", that is growth (height velocity), since the latter is a strong sign of the general overall good health of the child/adolescent. To the contrary, ill children with any one of a host of conditions [5, 6]] may grow slowly. That, in fact, is the rationale for growth monitoring of all children by a primary care practitioner or specialist.

Children whose stature falls below 2 SD of the mean for age and whose predicted adult height is <63 inches (160 cm) for males and <59 inches (149 cm) for girls, and for whom no endocrine, metabolic or other diagnosis can be made are considered to have idiopathic short stature. This is a heterogeneous group of children/adolescents. A more stringent definition is used when considering therapy with growth hormone [FDA-approved indication is height below -2.25 SD of the mean (US)]. They have normal (often at the lower limit) growth velocity, no biochemical or other evidence for a specific growth-retarding condition, normal serum concentrations of insulin-like growth factor-I (IGF-I) and IGF-binding protein-3, and normal serum growth hormone responses to drugs that stimulate growth hormone release.

BARRIERS TO OPTIMAL PRACTICE

- Measuring (and weighing) each patient at each encounter
- Measuring each patient accurately
- Plotting the data accurately on an appropriate growth chart
- Interpretation of the trajectory of growth (height velocity)
- Understanding the error in measurements of height and the added error in measurements of growth

LEARNING OBJECTIVES

As a result of participation in this session learners should be able to:

- Know proper measurement techniques for infants and children/adolescents
- Understand the primacy of growth (height velocity)
- Interpret growth trajectories
- Order and interpret generalized laboratory testing (and when to use such testing) for short children

- Define idiopathic short stature
- Understand the psychosocial context of idiopathic short stature
- Understand the use (and non-use) of growth promoting therapies
- Counsel children and parents of children with idiopathic short stature about the use (or not) of growth promoting therapies

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

How does one accomplish growth monitoring?[4] Immediately one must focus on the height measurement process, plotting those points on an appropriate growth chart, and then interpreting the entire pattern, because we are discussing trajectories: what happened in the past and what might happen in the future if we do "nothing". Please note that we are not yet considering the subspecialist (e.g., endocrinologist) point of view, because if we consider that, then all short or slowly growing children (2 to 3 per 100) should be evaluated by pediatric endocrinologists. If we did that, then we would not have time for any other patients.

Let's begin with height measurements. A proper apparatus must be used, but these do not have to be either fancy or expensive ("stadiometer"), but can be useful if placed on a hard, flat surface (uncarpeted) against a vertical, bare wall, or firmly hung from that wall. Periodically the accuracy of the device should be checked with a calibrated rule (e.g., a carpenter's steel tape). The technique is critical because there are a number of sources of error, given that the body is not a rigid device with an "absolute height". It is relatively straight forward with practice and following a single standard operating procedure with periodic quality control among all who measure (and weigh) children at that site. Since children shrink during the day, it would be prudent to measure early in the morning; however, that is not always possible. If height and height velocity is the issue in a particular child, then serial measurements over time should be done at approximately the same time of day, and plotted.

Measurement technique [2]

- Check calibration periodically
- Remove shoes, bulky clothing (for weight)
- Take down upswept hair or ornaments in the hair
- Feet together—heels, buttocks, shoulders against the wall or back of a free standing device
- Head with ears perpendicular to the floor—Frankfurt plane
- Lower head board to just touch the top of the head
- Note the height to the nearest millimeter, record height, and plot on growth curve

For infants (children below age 2 years, the usual charts are for length) one uses an infant stadiometer with a flat head board and a moveable foot board. The technique is similar (although at 90° different from the standing child). One significant difference is that for infant measurements one requires two persons. One is at the head board to be sure that the top of the head is in contact with the fixed board and the nose points straight up. The second person makes sure that the legs are flat (no flexing at the knee or ankle) and the foot piece is at the bottom of the foot, which is 90°to the lower leg. Similar to the standing child, the length is noted to the nearest millimeter, recorded and plotted on the appropriate infant length chart.

There is an error attached to each measurement, even with a well-standardized technique and periodic quality control. For a single measurement it should not be more than 4 mm, but for a height velocity in which two measurements are required it is likely double that. Given these issues, it is important to take into account all of the data to interpret the "preponderance" of them. One does not have the ability to return to a previous visit to re-measure a child at a point in time when, in retrospect, that height point appears to be in error. One can re-measure a child at the present time if after plotting that point; it is the one that appears out of register.

It is the interpretation of the trajectory of those measurements that determines the next steps:

(1) Do no further tests (but reassure the child

and parents) if growth is physiologic. This is especially important if the parents are short (measured, not by "history") and the child within the mid-parental target height range (percentile)
(2) Do some screening tests (see below)
(3) Refer to an appropriate subspecialist (not necessarily an endocrinologist)

Please note that (2) and (3) are not mutually exclusive and one may wait for a few more measurements if the growth data are ambiguous. Additional issues include referral patterns and gender bias [8, 9]

What tests should be done to be more certain that the short stature measured is really "idiopathic"? This is a philosophic impossibility and a quagmire for one could take the clearly absurd stance that short stature cannot be idiopathic unless "all" tests are done. Here is where judgment becomes of great import. Consider a short child of short parent with a normal height velocity. It can easily be argued that no testing is required and that the general pediatrician (or endocrinologist, if the patient has already been referred) can discuss physiologic growth and that this child is following such a trajectory. That is not always easily done, especially if the patient and parents have pushed the pediatrician to refer to an endocrinologist or self-referred for "something" to be done about the child's stature, because it is a severe psychosocial burden (see below for the data concerning clinical and population samples).

If "screening" tests are considered, some or all of the following have been recommended [2]:

1. Complete blood count with sedimentation rate (or C-reactive protein)
2. Comprehensive metabolic panel
3. Tissue transglutaminase, Immunoglobulin A (with total IgA)
4. Thyroxine (or free thyroxine) and TSH
5. Insulin-like growth factor 1 (IGF-I) and IGF Binding protein-3
6. Karyotype

The yield from these tests is quite low, even when some "signals" (signs and symptoms) are elicited, for example, fatigue, abdominal discomfort or pain, or headache, but in the truly asymptomatic short child growing with the normal range, the yield of a diagnosis that leads to remediable therapy is likely under 1-2 percent. The very few children with a specific diagnosis, for example Crohn's disease, celiac disease, hypothyroidism, growth hormone deficiency or Turner syndrome would much more likely be picked up by specific signs and symptoms and then referred to the appropriate subspecialist. Most would likely have an abnormal height velocity (irrespective of where they plot on the height chart) except at the onset of the disease.

My personal thoughts on the screening tests are the following: the blood count and sedimentation rate are quite non-specific, but may be clues to underlying pathology, or just an inter-current illness. Follow-up of the child is important. The comprehensive metabolic panel may be most helpful in the youngest children, especially if indicative of acidosis. The tissue transglutaminase IgA is quite specific for celiac disease and children may be quite asymptomatic early on. Appropriate referral to a gastroenterologist may permit early intervention if indicated. Hypothyroidism and GH deficiency are uncommon conditions; however, the thyroid tests are quite specific and relatively inexpensive. An indication of hypothyroidism can lead to appropriate referral and specific treatment. I am less enamored with the measurements of IGF-I and its major binding protein for two reasons: one is that not all labs measure it accurately and the values (especially for IGF-I) quite non-specific for GH deficiency. The karyotype is quite important for the diagnosis of Turner syndrome, although there are now molecular probes available [10]. The issue is almost always mosaicism in those without the obvious stigmata. It is recommended that at least 30 cells be counted in an appropriate lab. Most commercial labs (and insurances of the patients) count 2 cells, often with unknown quality control. Thus, I believe that if GH deficiency or Turner syndrome is seriously considered more specific testing by an endocrinologist (or geneticist for suspected Turner syndrome), is a more effective course to

take than just generalized screening.

The psychosocial burden of short stature has generated some controversial discussions and increased interest in the benefits of rhGH. Some studies have found evidence of adverse psychosocial effects associated with short stature, [12-14] although others suggest that confounding variables in the analysis of psychosocial effects of short stature are too great and that definitive conclusions cannot be made. [15-19]. It has been suggested that part of the reason that conflicts arise among researchers in psychological studies may be attributed to the specific setting in which the study is conducted and how well the trial is controlled [16, 17]. The potential adverse psychosocial effects of short stature not observed in community-based studies may be revealed in clinical studies. In an analysis of results from clinical trials versus community-based studies, some preconceptions about the psychosocial stress of being short have been challenged. Among those preconceptions is the suggestion that children and adults of short stature are not treated fairly by the general population and that they have a lower education level and decreased intelligence. When analyzed in community-based studies, no differences were observed among those of short stature versus those of average or tall stature. A contributing factor for finding evidence of psychosocial effects in the clinical setting may be that the focus is on short stature, and psychosocial issues present in the general population (i.e., including those without short stature) are not considered

MAIN CONCLUSIONS

Idiopathic short stature is not a disease and is fundamentally a physiological process

- Growth monitoring with evaluation of the growth trajectory is fundamental
  - To accomplish this, one must measure accurately and plot the data on an appropriate growth chart
  - The psychosocial impact of children with short stature is not significantly different from children in the general population
  - Treatment with growth-promoting drugs will likely be in a minority of children with ISS

CASES WITH QUESTIONS

M.M. is a 14 0/12 year old male who presents for a well-child visit. He has no specific medical complaints, but states that he is the shortest in his class and wants to grow, NOW.

DISCUSSION OF CASES AND ANSWERS

Past medical history includes a normal birth weight at term with no significant illnesses, hospitalizations, or surgical procedures. He reached all of the developmental milestones within the usual time frame. Review of systems notes that he is healthy without significant medical complaints and has noted early stages of pubertal development. He is a good student and has many friends.

Family history notes no significant illnesses:

- Mother 152 cm, menarche at 12 6/12 years
- Father 165 cm, on time pubertal development
- Sister 9 years old and short-for-age
- Grandparents on both sides 147 to 158 cm

Physical examination

- Height 145 cm, weight 35 kg (both below 1st centile
- General physical examination—within normal limits
- Genitalia: pubic hair III; Phallus III, testes 10 mL, bilaterally

Screening laboratory evaluation

- Complete blood count, comprehensive metabolic panel and sedimentation rate—within normal limits
- T4, TSH-within normal limits
- Celiac screen—within normal limits
- Bone age—14 3/12

Assessment (at this time)

- Constitutional delay of growth and puberty (CDGP)
- Familial short stature (idiopathic short stature)
- Chronic gastrointestinal disease
- Noonan syndrome
- Growth hormone deficiency

THERAPIES FOR THE CHILD/ ADOLESCENT WITH SHORT STATURE

- Diagnosis dependent
- May include
  - º Nutrition
  - º Dietary supplements
  - º Antibiotics
  - º Anti-inflammatory medications
  - º counseling
  - º Endocrine agents
    - ◊ Thyroid
    - ◊ Sex-steroids
    - ◊ Growth hormone [20-24]
    - ◊ "None of the above"

It should be noted that I have not specifically answered the question in the title, "whom should we be treating"? This is done purposefully because no firm specific guidelines that reach all of our patients can be made. The issues of fairness, justice, "real" psychosocial suffering (that can be "fixed" by growth-promoting therapy) cannot be summed in a simple formula. Please note references [25 and 26] for a debate on this issue and a thoughtful commentary concerning some of the ethical aspects of treatment of children with ISS with rhGH.

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Girl? Boy? What to Do When the Answer to the Parents' First Question is Not Obvious in the Delivery Room?

M23
Sunday, June 16th
8:00 AM-8:45 AM & 5:45 PM-6:30 PM

Guy Van Vliet, MD
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SIGNIFICANCE OF THE CLINICAL PROBLEM

It is estimated that, in approximately one in 10,000 newborns, the appearance of the external genitalia does not allow for a clear answer to what is often the parents' first question in the delivery room: is it a girl or a boy?

BARRIERS TO OPTIMAL PRACTICE

Given its rarity, most health professionals are uncomfortable with this clinical situation because they feel they have insufficient knowledge (both of the complex biological basis of the problem and of its psychological repercussions on the parents and on the child) to adequately deal with it.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to

- Have a basic knowledge of the developmental steps of the gonads, of the internal genital ducts and of the external genitalia and how they are influenced by genes and hormones
- Apply this knowledge to the clinical approach to a newborn with ambiguous genitalia
- Understand the importance of interdisciplinary management of these children, including psychosocial support

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

An essential concept to understand disorders of sex development (DSD) is that the human embryo is bipotential until 40 days gestation: regardless of whether the embryo is 46,XX or 46,XY, its gonads and internal (Müllerian and Wolffian ducts) and external genitalia (genital tubercle and urethral and genital folds) have a similar appearance. After 40 days, the gonads differentiate into either testes, which start producing anti-Müllerian hormone (AMH) and then testosterone, or into ovaries. Recent studies have shown that the differentiation of both the ovaries and the testes require activation of specific gene cascades, thus challenging the long-held concept of "female development by default". However, this concept still applies to the differentiation of the internal and external genitalia and of the urogenital sinus.

Gonads

With few exceptions, the presence of a Y chromosome containing a normal SRY (sex determining region of the Y chromosome) gene will result in the differentiation of the bipotential gonad into a testis. However, a number of other genes, acting up- or downstream of SRY, are required for normal testicular development. Ovarian differentiation also requires activation of specific gene pathways, notably the WNT-4 (Wingless Type, member 4) pathway (1).

Internal genitalia

From 6-8 weeks, in the presence of a testis, the Müllerian ducts involute under the influence of the AMH secreted by the Sertoli cells, while the Wolffian ducts are stabilized by testosterone secreted by the Leydig cells, which are stimulated by placental hCG. The Wolffian ducts form the epididymis, vas deferens,

seminal vesicles and ejaculatory ducts. AMH exerts its effect in a paracrine fashion (i.e. a local effect near its site of production), while testosterone acts both locally (to stabilize the Wolffian ducts) and in a classical endocrine way (to masculinize the urogenital sinus and the external genitalia) after being transported through the bloodstream. In the absence of testes, the Wolffian ducts involute and the Müllerian ducts develop into the Fallopian tubes, uterus and upper third of the vagina. Under the influence of testosterone, the urogenital sinus narrows to form the male urethra and the prostate. In the absence of testosterone, the sinus separates to form the female urethra and the lower two-thirds of the vagina.

External genitalia

From 8 weeks onwards in the male, under the influence of dihydrotestosterone (DHT, converted from testosterone in genital skin by 5-alpha reductase type 2), the genital tubercle will grow to form the penis, the urethral folds will develop into the corpus spongiosum surrounding the urethra and the genital folds will fuse in the midline to form the scrotum and ventral part of the penis. In the female, the same structures will form the clitoris, the labia minora and the labia majora.

DSD classification and etiologies

The currently proposed nomenclature (2) is predominantly based on the sex chromosome constitution of the individual. In 46,XX newborns, the commonest cause of ambiguous genitalia is congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. 11-beta-hydroxylase and aromatase deficiencies are much less common and maternal causes (luteoma of pregnancy, treatment with progestins having an androgenic effect) are exceedingly rare. In 46,XY newborns, incomplete masculinization may result from abnormal testicular development (testicular dysgenesis), defects in testosterone or DHT biosynthesis or partial androgen resistance. Mixed gonadal dysgenesis, a relatively common form of DSD, results from 45,X/46,XY mosaicism associated with ambiguous genitalia, a streak gonad on one side and a dysgenetic testis on the other. The external and internal anatomy will depend on the degree of testicular dysgenesis. With severe androgen and AMH deficiency, the external genitalia will be undermasculinized and both vagina and uterus will be present. Regression of the uterine horn and of the Fallopian tube on the side where testicular differentiation occurred may be seen, illustrating the paracrine action of AMH. The exceedingly rare ovotesticular DSD (formerly called true hermaphroditism) may result from the formation of a 46,XX/46,XY chimeric zygote.

Initial diagnosis

Ambiguous genitalia are usually identified at birth, in which case they raise the dilemma of sex assignment. Both parents should be seen as soon as possible. The initial approach by attending staff should be backed up as quickly as possible by a pediatric endocrinologist. The following wording is suggested: “there is something the matter with the way that the baby’s genitals have formed, so that we cannot at present say whether the child should be brought up as a boy or a girl”. The infant should be referred to as “the baby” or “the child” not as he, she or it. There is no medical reason to separate mother and baby. Choice and registration of first name should be postponed and urgent investigations initiated, aiming for definite gender assignment within 2 weeks. On history, it is relevant to enquire about consanguinity and blood relatives born with ambiguous genitalia or with infertility and about maternal virilization or use of medications during pregnancy. Examination should include a general assessment focusing on dysmorphisms and congenital anomalies. The critical importance of palpating the inguinal regions for gonads cannot be over-emphasized. A meticulous description of the external genitalia should use neutral words such as labioscrotal folds and genital tubercle; the urethral meatus should be identified where possible. A medical photograph with legs spread apart and a ruler next to the genital tubercle should be taken. The degree of masculinization can be expressed as a Prader stage (3). In premature girls, with apparent

clitoral hypertrophy because of the lack of subcutaneous fat, it is useful to estimate the ratio of the distance between the anus and the posterior labial fourchette to the distance between the anus and the base of the clitoris: a ratio less than 0.5, regardless of gestational age, reasonably excludes androgenization during the first trimester (4).The pediatric endocrinologist is probably best placed to coordinate DSD care, in collaboration with a radiologist, a surgeon and a mental health professional with expertise in disorders of sex development. A medical geneticist should also be consulted urgently, especially when there are dysmorphic signs. Typically, only tertiary care centers can provide this combination of health care professionals.

Blood for a karyotype analysis should be drawn urgently but results can only be obtained after a minimum of 3 days. If available, DNA amplification by polymerase chain reaction to determine the presence of SRY sequences or Fluorescent in situ hybridization to determine the presence of a Y chromosome gives a "provisional karyotype" within hours. An abdominal ultrasound should be performed, principally to establish whether a uterus is present; the adrenal and inguinal areas should also be explored. At 3 days of age, plasma 17-hydroxyprogesterone (17OHP) should be measured, with results requested stat. Androstenedione, testosterone and DHEAS should be measured at the same time. A genitography is usually only necessary prior to surgery to define the point of confluence of the vagina and urethra.

Management

In CAH due to 21-hydroxylase deficiency (diagnosed on the basis of plasma 17OHP, androstenedione, testosterone and DHEAS), there is a high risk of salt wasting and plasma electrolytes are often measured early after birth in newborns with genital ambiguity. This may give a false sense of reassurance, because plasma electrolytes are usually normal at that time and the initial salt-wasting episode typically occurs only in the second or third week of life, so that the infant's weight should be carefully monitored even if the plasma electrolytes were normal in the first few days. If there is significant weight loss (up to 10% weight loss is within normal limits in newborns but babies should regain their birth weight by 14 days of age) or if weight does not increase satisfactorily subsequently, plasma electrolytes should be measured again and, if hyponatremia develops, urine sodium should be measured to document inappropriate natriuresis. Based on their normal female internal genitalia and potential fertility, sex assignment is considered to be straightforward in newborn girls with CAH. Likewise, newborns with ambiguous genitalia due to mixed gonadal dysgenesis are usually assigned a female sex. The presence of a uterus in this condition makes assisted fertility possible. However, the gonads should be removed as soon as the diagnosis is made because of the risk of gonadoblastoma. Whether in CAH or in mixed gonadal dysgenesis, the psychosexual consequences of clitoral/vulvar surgery in infancy are controversial and one line of thought is that genital surgery should be deferred until the patient is old enough to consent.

From the point of view of diagnosis and of sex assignment, the most difficult cases are 46,XY infants with partial androgen resistance, in whom the growth potential of the phallus at puberty is unpredictable. In contrast, 46,XY infants with defects in testosterone or DHT synthesis have normal sensitivity to androgens and can therefore be assigned a male sex if diagnosed early enough. The diagnosis in this group of patients has classically been based on the measurement of precursor/product ratios of various plasma steroids before and after stimulation with hCG. However, this approach is fraught with difficulties and detecting a mutation in a candidate gene is often required to establish a diagnosis. An exome wide approach has recently been proposed (5).

Ultimately, criteria for sex assignment include the specific diagnosis, presence of female internal genitalia (i.e. vagina, uterus), size and androgen sensitivity of the genital tubercle, parental wishes and cultural aspects. The advice given as to sex assignment should ideally result from a consensus between physicians, surgeons and mental health

professionals of both sexes. Subsequently, age-appropriate counseling of the child is essential, with the goal of full disclosure (including karyotype) before transition to adult care.

MAIN CONCLUSIONS

In spite of the rarity of the situation and of the complexity of the differential diagnosis and management, the unavoidable psychological trauma experienced by the parents of a an infant born with ambiguous genitalia can be greatly alleviated by their prompt transfer to an interdisciplinary team of competent and caring health professionals.

CASES WITH QUESTIONS

Case 1

A 3.5 kg term newborn is of indeterminate sex, with a genital tubercle measuring 3X1 cm, labioscrotal folds, a single urogenital orifice and no gonad palpable. Pelvic ultrasound shows a uterus.

Question: What is the most likely diagnosis and what immediate investigations should be performed?

Case 2

A 2.5 kg term newborn has abnormal genitalia with a gonad palpable in one labioscrotal fold and no gonad palpable on the other side. Pelvic ultrasound and genitography show a vagina and uterus. Karyotype is 45,X/46,XY. 17-OHP levels are normal.

Question: What is the diagnosis and how should the child be assigned?

Case 3

A 3.0 kg term newborn has a small genital tubercle (1.5X0.8 cm) and gonads palpable in partially fused labioscrotal folds. Pelvic ultrasound shows no uterus and genitogram shows a blind vaginal pouch. Karyotype is 46,XY. 17-OHP levels are normal.

Question: What is the most likely diagnosis and how should the child be managed?

DISCUSSION OF CASES AND ANSWERS

Case 1 Answer

The most likely diagnosis is congenital adrenal hyperplasia in a genetic female. Essential investigations are the karyotype, which was 46,XX, and the 17-OHP level, which was 300 nmol/L [10,000 ng/dL] on day 3.

Case 2 Answer

The diagnosis is mixed gonadal dysgenesis with a dysgenetic testis on one side and probably a streak gonad on the other. The presence of Müllerian structures suggests that it is probably appropriate to raise this child as a female. The gonads should be removed.

Case 3 Answer

The absence of female internal genitalia indicates that the gonads are testes which have produced AMH normally. The differential diagnosis is between a biosynthetic defect in testosterone or DHT production and partial androgen resistance. A family history suggestive of autosomal recessive or X-linked inheritance orients to the former and latter possibility, respectively. If a biosynthetic defect is found, a male sex assignment is appropriate. If the diagnosis is partial androgen resistance, a female sex assignment could be considered.

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THYROID

Presentation and Management of Thyroid Nodules and Cancer in Children

M55
Tuesday, June 18
11:15 AM to 12:00 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

There are an increasing number of children and adolescents being diagnosed with thyroid nodules and differentiated thyroid cancer (DTC). With rare exception, the majority of patients are asymptomatic at the time of diagnosis, with the thyroid nodule most frequently discovered during routine physical exam or unrelated head and neck imaging. While the risk of malignancy is 5-6 fold higher when a nodule is discovered in a patient < 18 years, the majority of nodules are benign. An understanding of the risk factors for malignancy, the ultrasound findings associated with benign and malignant lesions, and an understanding of the cytology classification system is essential to stratify which patients should be referred for surgery. For patients ultimately diagnosed with DTC, the endocrinologist is the gatekeeper for care managing a plan that balances the risks and benefits of therapy for the individual patient.

In this session we will review cases that highlight a multi-disciplinary approach to evaluation and management of thyroid nodules and DTC in children and adolescents highlighting recent data and challenging aspects of care.

BARRIERS TO OPTIMAL PRACTICE

- The low-incidence of disease poses significant challenges to optimizing and individualizing care. This is associated with a wide-variability in approach to diagnosis, treatment and an increased risk of complications.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Describe the differences in clinical behavior between adult and pediatric differentiated thyroid cancer
- List the current treatment strategies in the management of pediatric thyroid cancer
- Recognize and translate into practice the risks and benefits of current treatment strategies
- Apply the current strategies into the development of individual treatment plans for pediatric patients with thyroid cancer

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Multiple risk factors are associated with the development of a thyroid nodule and/or thyroid cancer including; iodine insufficiency, a personal history of autoimmune thyroid disease, genetic syndromes (i.e. PTEN Hamartoma syndrome), a previous history of exposure to ionizing radiation, and a family history of thyroid nodules or thyroid cancer.

The majority of pediatric patients are asymptomatic at the time of diagnosis, with the thyroid mass discovered during routine physical exam or as an incidental discovery during unrelated head, neck or chest imaging. While a significant number of these referrals are often for lower-risk lesions (cystic or mixed solid-cystic lesions), there is no evidence to suggest that an incidentally discovered thyroid nodule is associated with a lower likelihood of a clinically significant malignancy. No matter the method of discovery a thyroid ultrasound (US) is an appropriate starting point for the

evaluation, with additional testing dictated by the sonographic features.

Increased Risk of Malignancy

When a nodule is discovered in a patient ≤ 18 years of age, there is a 5-6 fold increased risk of malignancy, 5-10% for adults compared to 25-30% for children and adolescents. Similar to adults, over the last decade the annual incidence of pediatric thyroid carcinoma has steadily increased. TC is now the 8th most common cancer diagnosed in 15-19 year olds and the 2nd most common cancer diagnosed in adolescent girls [1]. Papillary thyroid carcinoma (PTC) comprises the majority of cases (85-90%), with follicular thyroid carcinoma (FTC) accounting for the rest.

In addition to an increased risk of malignancy, children also have an increased burden of disease at the time of diagnosis and a higher rate of recurrence. At the time of presentation, up to 80% of children will have cervical lymph node metastasis, up to 20% will have lung metastasis, and up to 30% of patients will experience recurrence of disease, occasionally decades after diagnosis [2].

Diagnosis

Ultrasound

Ultrasound can detect lesions as small as 2-3mm and provides information on the size, location, echogenicity, blood flow, multiplicity and potential involvement of regional lymph nodes.

- As a matter of practice, if a thyroid ultrasound is being conducted to evaluate for the potential of a thyroid malignancy, a 'thyroid and neck' ultrasound should be ordered.
- The size of the nodule should be interpreted in context to the age of the patient, particularly important for pre-pubertal children, as well as predisposing risk factors (previous history of exposure to ionizing radiation, history of familial thyroid cancer, or a history of a tumor syndrome associated with thyroid cancer)
- US characteristics associated with an increased risk of malignancy include; solid composition, hypoechoic pattern, irregular or interdigitating border, increased intranodular blood flow, micro- or macro-calcifications and the presence of abnormal cervical lymph nodes

Fine Needle Aspiration Biopsy

Fine needle aspiration biopsy (FNAB) is the most important procedure for determining the malignant potential of a thyroid nodule. Conscious sedation for younger children and anxiolytics for adolescents is appropriate and recommended. Ultrasound guided FNAB and bedside confirmation of sample adequacy are associated with a lower incidence of unsatisfactory samples. FNA of abnormal lymph nodes, in particular in the lateral neck, should be pursued prior to extending surgical dissection. An experienced thyroid cytopathologist is essential to improve the accuracy of diagnosis. Adjunct techniques, such as sending Tg level from washout of the FNA needle should be pursued to confirm lymph node metastasis if the cytology is equivocal. Current commercially available molecular panels performed off of FNA specimens have not been validated within the pediatric population.

Treatment of Patients With Suspicions for Malignancy or Malignant Cytology

Pre-operative Staging

Thyroid and Neck Ultrasound

Careful US investigation of the neck should be a routine part of the pre-operative evaluation, with the highest incidence of lymph node (LN) metastasis found in level III, IV and VI of the neck [3]. US has greater sensitivity to detect disease in levels II, III and IV, although, there is reduced sensitivity of detecting level VI disease in patients with a eutopic thyroid due to the thyroid obstructing a significant portion of this region. For patients with extensive LN metastasis by physical exam and/or US imaging, a neck MRI or CT is strongly recommended in order to optimize pre-operative surgical planning.

Pre-operative screening for evidence of pulmonary metastasis may also be considered but will rarely impact surgical planning. Routine chest x-ray has very low sensitivity at detecting metastatic disease. A 123-I whole body scan (WBS), performed after TT, is the

most sensitive method for detecting pulmonary metastasis, with the post-treatment WBS having greater sensitivity compare to the diagnostic-WBS.

Risk of surgical complications

The most common complications after thyroidectomy include transient or permanent hypoparathyroidism and recurrent and/or superior laryngeal nerve damage. In patients younger than 10 years of age, there is an increased risk of complications associated with the presence of extrathyroidal extension, lymph node dissection and repeat surgery [4].

Radioiodine Therapy

Radioiodine (RAI) therapy is traditionally performed 4-6 weeks after surgery, but can be conducted sooner depending on local protocol and individual patient circumstances. To optimize RAI uptake, TSH must be > 30 μIU/ml. In addition, induction of an iodine deficient state is recommended (see www.thyca.org for low-iodine diet recipes). Both of these can typically be accomplished over a 14-21 day time period.

The use of RAI is considered under two broad categories; RAI ablation and RAI treatment. There is little controversy over the use of RAI to treat local, or more commonly, distant disease that is not amenable to surgical resection. However, the method to prepare the patient for treatment (thyroid hormone withdrawal vs. rhTSH), the method to determine treatment activity (empiric vs. dosimetry) and the criteria to base when additional RAI may be beneficial is a matter of continuing investigation and discussion.

The use of RAI for ablation is under greater scrutiny, a particularly salient discussion in pediatrics where the risk of disease-specific mortality is low, the risk of recurrence high, and the risks associated with complications of therapy expressed over a greater number of years. The intent of ablation is to destroy any remaining residual healthy thyroid tissue as well as any residual microscopic thyroid cancer to enable improved sensitivity of post-operative WBS imaging as well as improved specificity in using serum thyroglobulin (Tg) as a biomarker during surveillance. Whether RAI ablation reduces the risk of recurrence is a matter of debate. The question over the potential lack of benefit is compounded by concerns that exposure to RAI may increase the risk of non-thyroid second malignancies [5, 6].

So, akin to efforts to reduce or eliminate the use of RAI in adult patients with 'low' risk disease, there are renewed efforts to define a similar subgroup in the pediatric population. In the absence of prospective studies examining the impact of withholding RAI ablation on disease-free or progression-free survival, the decision on whether a patient would benefit from RAI therapy may be based on the completeness of surgical resection, the pathological findings (American Joint Committee on Cancer TNM score; Tumor size, Lymph nodes affected, Metastases) and the post-operative staging. Post-operative staging is usually performed 4-6 weeks after surgery and includes assessment of a stimulated Tg, when the TSH is > 30 μIU/ml and a diagnostic radioiodine whole body scan. The incorporation of SPECT/CT is helpful in discerning thyroid bed remnant from lymph node metastasis as well as thymic uptake from metastasis to the mediastinum.

For patients with N0 or minimally involved N1a disease the use of RAI may be associated with greater risk than benefit. For patients with extensive N1a disease or N1b disease, there is an increased risk of persistent disease as well as distant metastasis and the benefits of RAI may outweigh the risks. Repeat surgery, performed by a high-volume thyroid cancer surgeon, should be considered for patients found to have extensive, persistent disease on post-operative staging prior to RAI treatment.

There are no standardized doses of RAI for children. Some adjust ^{131}I dose according to weight or body surface area (BSA) and give a fraction (e.g. child's weight in kg/70 kg) based on the typical adult dose used to treat similar disease extent. Others suggest that ^{131}I doses should be based entirely on body weight (1.0 – 1.5 mCi / kg). Dosimetry may be used to limit whole body retention to < 80 mCi at 48 hours and blood / bone marrow exposure to < 200 cGy and is useful in small children, children with diffuse lung uptake or significant

distant metastases, and those undergoing multiple treatments. Lesional dosimetry can be performed in children with substantial lung involvement or large tumor burden at other sites, such as bone [7]. A post-treatment scan to localize any metastatic disease should be obtained 5-8 days after RAI.

Long-Term Follow-Up

The mainstay of long-term therapy is TSH suppression. Physical exam with laboratory surveillance (TSH, T4 or fT4, thyroglobulin (Tg) and thyroglobulin antibody (TgAb)) is typically performed on a 3-month interval, with neck ultrasound performed 6 months post-initial treatment, then annually. For patients found to have regional or distant metastasis, a stimulated Tg and diagnostic whole body scan (^{123}I) one year after initial treatment is recommended.

Patients are considered to be in remission if they have an undetectable stimulated Tg (< 1 ng/mL) and a negative dx-WBS. Once remission is achieved, decreasing frequency of laboratory measurements and less-aggressive TSH suppression may be considered.

For patients with a suppressed Tg between 1-10 ng/mL assessing a stimulated level on an annual basis, along with repeat neck US, chest CT and/or dx-WBS is warranted. As a general rule, children appear to have more robust response to TSH stimulation and this otherwise 'grey' zone for suppressed Tg levels in adults may be reflective of a greater degree of persistent or progressive disease in a child.

For patients with suppressed Tg > 10 ng/mL a similar approach should be pursued. The most common location for persistent, recurrent and/or progressive disease is in the central (level VI) or lateral neck (III, IV) followed by the lungs. An increasing suppressed or stimulated Tg, in the setting of non-surgically resectable, iodine avid disease (previous (+) WBS) warrants re-treatment with additional radioiodine. If the Tg is stable, and the US and dx-WBS do not reveal evidence of persistent disease then MRI of the neck to evaluate for evidence of deep cervical, para- or retropharyngeal lymph nodes, and a CT of the chest to look for evidence of non-avid pulmonary metastasis should be considered. A 24 hour urine iodine should be performed to confirm adherence to the low-iodine diet. Although controversial, a one-time repeat dose of RAI, with post-treatment WBS, is also reasonable. The post-therapy WBS has higher sensitivity and specificity to detect disease and is a the test that defines non-RAI avid disease if negative. With the exception of pulmonary metastasis, if bulky disease is found on anatomic imaging it should be resected prior to administration of subsequent doses of RAI.

For patients with pulmonary disease, 1/3rd to 2/3rd of patients may continue to have persistent, but stable disease for decades. Pulmonary function testing should be a routine aspect of surveillance and dosimetry should be considered when calculating repeat doses of RAI. An unknown percent may ultimately progress, however, within this cohort, there is another subgroup of patients that may ultimately experience decreased disease burden, reflected by a downward trend in Tg levels, years after the last RAI dose has been administered. Unfortunately, there are no means to predict the eventual course of disease for the individual patient dictating that for patients without an obvious upward trend in Tg patience and extended follow-up may be the most reasonable option.

MAIN CONCLUSIONS

- With proper treatment, long-term survival for childhood and adolescents with thyroid cancer is excellent, even in children with pulmonary metastasis.
- However, while cancer specific mortality is low, standardized mortality ratios (observed vs. expected deaths) are up to 8-fold higher and the psychological impact of prolonged follow-up (repeat PE, I^{131} scans and US) and the risk of non-thyroid secondary malignancies from RAI is poorly defined.
- Efforts must focus on improving disease-free survival and optimizing individualized therapy to decrease the risk of complications. The formation of regional, pediatric thyroid centers capable of providing the full-spectrum of medical and surgical resources for evaluation and care will aid efforts to decrease potential short- and long-term complications for children

and adolescence with thyroid nodules and/or thyroid cancer.

CASES WITH QUESTIONS AND DISCUSSION OF CASES WITH ANSWERS

Case 1

A 15 year old Caucasian girl is noted to have a right-sided thyroid nodule during annual school physical exam. Thyroid US reveals a 4.4x1.9x3.22 cm mass.

Questions

1. ***What risk factors are associated with the development of thyroid nodules and thyroid cancer? What other aspects of the history and physical exam do you want to know?***
2. ***What is the next step in the evaluation and how do you counsel the family on the potential results of the fine needle aspiration (FNA) biopsy?***
3. ***The FNA returns with 'follicular lesion of undetermined cytology' (FLUS). What surgical approach would you recommend based on the results of the FNA? What ancillary tests are available to help predict the malignant potential in indeterminate cytology? What factors would you consider in making this recommendation?***
4. ***Patient undergoes a lobectomy but the pathology returns as a follicular variant of papillary thyroid cancer (fvPTC), 2.3cm in greatest dimension. What is your recommendation; clinical surveillance or completion thyroidectomy? Would you recommend a prophylactic central neck dissection: Yes or No? Ipsilateral or Bilateral?***
5. ***The patient undergoes a completion thyroidectomy with ipsilateral central neck dissection. The contralateral lobe and all LN are negative for metastasis. Would you recommend RAI ablation? What data would you use to make this decision? Would your recommendation have changed if the central lymph node dissection was positive?***

Answers

1. The patient falls into the pediatric group with the highest incidence of thyroid cancer; Caucasian girls, age 15-19 years of age. Otherwise, she has no other risk factors, to include; no history of previous radiation exposure, no history of autoimmune thyroid disease and no family history of thyroid cancer. With the exception of the thyroid nodule her exam is normal, to include no abnormal, palpable cervical lymph nodes.
2. After the US is reviewed, to include assessment for completeness of exam which should include transverse and long view of each nodule, Doppler assessment of the nodule(s) and evaluation for any abnormal lymph nodes (see text for criteria) in the central and lateral neck, a FNA should be the next step. The FNA should be completed at a center capable of performing the procedure with conscious sedation and/or distraction techniques, under US guidance and with bedside confirmation for sample adequacy. An experienced thyroid cytopathologist is essential to ensure accuracy of diagnosis. The family should be educated on the potential results and implications of the FNA.
3. The Bethesda System for Reporting Thyroid Cytopathology attributes a 5-15% risk of malignancy for the FLUS category [8]. The risk stratification of the system is based on adult data and the risk within pediatrics may be higher [9]. There are no commercially available, molecular biology tests for assessing the malignant potential of indeterminate cytology that have been validated in the pediatric population. Lobectomy is the most frequent surgical approach, but total thyroidectomy (TT) may be considered for patients with bilateral nodules and/or evidence of autoimmune thyroid disease.
4. Due to an increased risk of bilateral disease a completion thyroidectomy is recommended. Ipsilateral, central neck dissection should be considered due to an increased risk of regional metastasis. However, there are no prospective studies in the pediatric population to determine if this procedure decreases the need for RAI or decreases the risk of persistent or recurrent disease. As such, the risks and benefits of more extensive surgery should be discussed with the family and based on the experience

of the surgeon.

5. Six weeks after surgery the patient has a stimulated Tg of 0.2 ng/ml (TgAb-) and 1.2%, nonfocal uptake on DxWBS. Based on this data, no RAI is administered. Serial, nonstimulated Tg levels over the next year remained undetectable and a repeat neck US one year after surgery showed no evidence of persistent disease.

Case 2

A 13 year old girl is referred to your clinic after discovery of a large, left sided thyroid mass. Thyroid US reveals 2 nodules in the right lobe, the largest a 1.3cm mixed solid-cystic nodule, and the left lobe is completely replaced by a heterogeneous, mass with scattered hyperechoic foci. Several abnormal lymph nodes are noted in the left lateral neck.

Questions

1. ***The FNA is positive for papillary thyroid cancer; would you pursue any other imaging prior to surgery? If so, what?***
2. ***What surgical approach would you pursue? TT with central neck dissection? Lateral neck dissection? What data would you use to make the decision?***
3. ***The post-operative WBS reveals 35% uptake with a focus in the left central neck and right lateral neck. Stimulated Tg is 16 nglmL but TgAb are (+). How would you proceed? Give RAI or pursue surgical dissection?***

Answers

1. For patients with thyroid nodules that will undergo FNA evaluation (see concerning US characteristics above), complete US interrogation must include evaluation of the central neck (level VI) as well as the lateral neck (levels II, III, IV, and V. The finding of abnormal lymph nodes (see US characteristics listed above) is associated with an increased risk of malignancy for the thyroid nodule(s). The challenge, especially in pediatrics, is to discern reactive LN from malignant LN. The lateral neck US should be performed prior to FNA so that any concerning LN in the lateral neck can undergo FNA. This data is critical to make an informed decision on whether lateral neck dissection is warranted. A Tg level obtained after washing out the FNA needle with 0.5-1.0ml normal saline can aid in the diagnosis of LN metastasis if the FNA has equivocal cytology. TgAb positivity does not impact the sensitivity of measuring Tg obtained by FNA. For patients with pre-operative evidence of LN metastasis (bulky disease on exam or pre-operative US), cross-sectional imaging of the neck (MRI or CT) should be considered in order to optimize operative planning.
2. For patients with malignant cytology as well as patients with indeterminate cytology with bilateral disease, total thyroidectomy (TT) is the procedure of choice [10, 11]. A prophylactic central neck dissection, whether ipsilateral (for unifocal disease) or bilateral should be strongly considered secondary to the high incidence of metastasis to the central neck. The intent of this approach is to decrease the potential need for RAI, by decreasing the likelihood of uptake in the central neck on diagnostic WBS, and to decrease the risk of recurrence. This must be balanced with the increased risk of surgical complications (hypoparathyroidism and recurrent laryngeal nerve damage) and the parents should be counseled that there are no prospective studies in pediatrics to confirm the efficacy of this approach. The initial surgery is the most critical point of care. Referral to a high volume thyroid cancer surgeon is an absolute and is the only means to optimize the risks and benefits associated with attempts at complete surgical resection.

   A TT, bilateral central and lateral neck dissection is completed; 4/5 LN in the central neck, 6/13 in left lateral neck and 7/31 right lateral neck are (+) for PTC with lymphovascular and perineural invasion as well as extrathyroidal and nodal extension into regional soft tissues.
3. Post-operative staging is used to determine if a patient may benefit from radioiodine (RAI) therapy. Staging includes consideration of the extent of disease from pre-operative staging, review of histology, as well as the amount and location of persistent disease on post-operative staging.

The AJCC TNM classification system (*see above*) can be used to describe the tumor size and degree of LN metastasis, although the system is not valid for prognostic staging within the pediatric population. Post-operative staging includes assessment of a stimulated (TSH > 30 mIU/L) Tg and a diagnostic WBS. For patients with no evidence of extensive, bulky LN disease a post-operative US with a non—stimulated Tg may be reasonable with a stimulated Tg and DxWBS performed at a later time if data from surveillance suggests persistent and/or progressive disease (Tg > 1 ng/ml and/or abnormal imaging). Thyroid hormone withdrawal is the traditional approach for stimulation, however, rhTSH may be needed for patients with persistent functional disease, cancer survivors that have hypothalamic/pituitary dysfunction, or in an effort to decrease exposure of non-target tissues to RAI. Tg antibodies, found in ~ 15% of patients, interfere with multiple Tg assays (ICMA), most frequently associated with false lowering of the Tg. TgAb appear to have less interference on RIA Tg assays [12].

Post-operative staging reveals two challenges; TgAb positivity and bulky persistent disease. The presence of the TgAb decreased the utility of acutely using the stimulated Tg level to determine the extent of persistent disease. However, TgAb can be used as a surrogate marker of Tg and remaining disease during surveillance. The 35% uptake on DxWBS indicated the presence of remaining bulky, cervical disease. SPECT/CT (single photo emission CT) was performed and revealed two relatively large LN (>1cm). With decreased ability of RAI to destroy bulky disease radio-guided surgery was performed with post-surgery DxWBS decreasing to 10% uptake. The patient received 106mCi of 131-I and over the next 6-12 months nonstimulated Tg and TgAb decreased below detection limits.

Case 3

A 12yo girl presents after her mom noted an enlarged thyroid. She has a past medical history of VCUR s/p urethral reimplantation at 3 years of age, otherwise she is healthy and post-menarche. Her family history is negative for thyroid cancer, however her father has a history of thyroid nodules with benign FNA. Initial US reveals a diffusely heterogeneous gland with several bilateral nodules, the largest in the left lobe, measuring 3.3cm in greatest dimension. The majority of nodules are hypoechoic with ill-defined borders and increased intranodular flow on Doppler US. A total thyroidectomy, central neck and left lateral neck dissection are completed. Post-operative stimulated Tg is 922 ng/ml with a TSH 39.6 mIU/L. Diagnostic WBS reveals a single focus of uptake in the right lower neck. A decision is made to give 130mCi of 131-I. The post-treatment scan reveals uptake in right lower neck and bilateral lungs.

Questions

1. ***What is the likely explanation for the disparity between the high post-op stimulated Tg and the DxWBS?***
2. ***What patients are at increased risk for pulmonary metastasis?***
3. ***What options should be considered in deciding on the RAI activity to administer?***
4. ***For pediatric patients with pulmonary metastasis, what is the expected response to RAI treatment? How does one decide if andl or when to administer additional RAI? What additional testing should be followed for patients with pulmonary metastasis?***

Answers

1. When the post-op stimulated Tg is markedly elevated in relation to the findings on DxWBS on needs to consider that there is a significant amount of persistent disease, with pulmonary metastasis being the most likely location in pediatric patients.
2. The presence of extensive N1a and/or N1b disease should raise concern for an increased risk of pulmonary metastasis. In general, metastasis follows a predictable pattern, from metastasis to level VI to the lateral neck (levels II, III, IV, and less commonly V) followed by pulmonary metastasis. There are exceptions with patients occasionally presenting with 'skip'

metastasis.

3. There is no consensus for deciding on a RAI activity and no studies comparing efficacy, safety or long-term outcome for treatment of non-resectable disease in pediatric patients. The choices for deciding on the 131-I activity include empiric dosing adjusted to the % size of the patient compared to an adult, weight based, and dosimetry. For the former, both empiric and weight base, the activity is further adjusted by the location and amount of uptake on the DxWBS.
4. For patients with pulmonary metastasis (M1) RAI is considered therapeutic, and multiple doses may be required to achieve remission. Overall, only approximately 50-75% of patients achieve remission with the majority of the remaining patients developing persistent, stable disease that does not resolve despite repeated doses of RAI [13].

Determining the optimal frequency of treatment is the challenge. In a study by Biko et al. the response to RAI, measured by declining serum Tg, was observed several years after the last dose was administered (ref). This prolonged response to RAI therapy has also been observed in adult patients where the full-benefit, defined by the nadir of serum Tg achieved after RAI, may not be realized for 12 to 18 months after the last -I dose [14]. For patients with pulmonary metastasis, baseline pulmonary function testing should be obtained and repeated annually due to a potential risk of developing pulmonary fibrosis [15]. Chest CT should also be obtained for any patient found to have abnormal pulmonary functions.

Together, these data suggest that aggressive use of RAI in children and adolescents with iodine-avid pulmonary metastases should be limited to patients who have evidence of disease progression. The end-point at which a child with persistent iodine-avid disease receives no further benefit remains unclear, but treatment to a negative Tg may not be a tenable goal in all cases. The decision to treat with another course of RAI should be individualized and based on 1) objective benefit from prior treatments and 2) evidence of progressive disease based on increasing Tg and/or imaging. The potential benefit of additional RAI must be weighed against the risks from greater cumulative RAI body burden [6]. For patients with stable disease (suppressed Tg not increasing and negative or non-progressive imaging studies) continued surveillance may be a better option.

For our patient, the following year her stimulated Tg decreased from 922 ng/ml (TSH 39 mIU/L) to 103 ng/ml (TSH 77 mIU/L) and a second dose of RAI was subsequently administered (124 mCi). One year later her stimulated Tg decreased further to 44.3 ng/ml (TSH 45 mIU/L) and her DxWBS showed no evidence of pulmonary uptake. In discussion with the family that patient did not receive a 3rd dose of RAI. For the past 2 years her nonstimulated Tg has remained in the 2-3 ng/mL range. Neck US x 2 have been negative. A chest CT revealed two non-specific lower lobe nodules, 3mm and 5mm in size. A repeat chest CT is pending with decision for additional dosing of RAI based on the results.

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Thyroid Hormone Replacement: T3, T4, or Both?

M42
Monday, June 17
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

At present, common practice and Endocrine guidelines indicate that hypothyroid patients should be treated with levothyroxine with periodic monitoring of TSH, Free T4 and TSH to ensure the TSH is within the normal range. (1) However, over the last several years there is increasing suggestion that serum T3 levels, which represent the active thyroid hormone, may play a more important role in thyroid hormone action than previously believed.(2) It is hypothesized that when T4 is administered, T4 to T3 conversion may be inadequate and that supplemental T3 should be given to help enhance quality of life and to ensure adequate thyroid hormone concentrations in tissues. There is discussion in the lay press indicating that administration of T4 alone gives insufficient T3 for many of the tissues resulting in decreased quality of life. However there are very few scientific, peer reviewed studies supporting this hypothesis. Approximately 20 million Americans are hypothyroid and the vast majority is being treated with levothyroxine alone. The significance of this clinical problem would be high if T4 administration alone is inadequate for these patients. Endocrinologists, also, are frequently put in a difficult position when patients read the lay literature and ask for additional T3 when they are taking T4. This Meet The Professor session will focus on the scientific evidence for T4 alone therapy or in combination with T3.

BARRIERS TO OPTIMAL PRACTICE

One barrier is lack of appropriate scientific studies comparing the pathophysiologic benefit of L-thyroxine alone versus L-thyroxine plus T3. The second barrier relates to the large amount of lay literature on the topic and physicians are put in the difficult position of trying to help the patient, but also to rely on evidence based medicine.

LEARNING OBJECTIVES

As a result of participating in this session learners should be able to:

1. understand the physiology of normal T3 and T4 synthesis and generation;
2. understand when it is appropriate clinically to use levothyroxine alone and when to use combination T3 and T4 therapy in the treatment of hypothyroid patients.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Hypothyroidism is common occurring in 4.6% of individuals in the U.S. according to NHANES data (0.3% clinical; 4.3% subclinical; n=17,353). (3) The symptoms are nonspecific and may include: fatigue, headaches, weight gain depression, irritability, fluid retention, hair loss, carpal tunnel syndrome, hives, poor memory, poor concentration, low libido, unhealthy nails, dry skin, cold intolerance, low motivation, low ambition, insomnia, allergies, and acne. It is frequently difficult to discern which of these symptoms could be related to thyroid function abnormalities or, perhaps, are related to other medical or psychological conditions.

Major questions arise: (1) can hypothyroid patients be optimally replaced be thyroxine therapy alone; (2) are there convincing data that combine T4 and T3 result in physiologic tissue concentrations of T4 and T3 and normalization of serum TSH levels; (3) is

improved clinical status associated with these changes; and (4) are there new data that may provide a rationale for combined T4 and T3 therapy. Arguments for T3 supplementation include the observation that the thyroid gland produces both T3 and T4. L-thyroxine therapy contains no T3 although, of course, there is conversion from T4 to T3. Patients taking T4 alone have higher than normal T4 /T3 ratios. Thus, peripheral conversion of T4 to T3 may be inadequate; selected biomarkers such as IGF-1 do not seem normalized in patients taking T4 alone.

There is evidence in animals that tissues may have deficient T3 levels. Escobar-Morreale et al. (4) studied tissue T4 and T3 content in hypothyroid rats subjected to thyroidectomy and radioactive iodine therapy. The rats were replaced with .9 ug/100gm plus T3 .15 ug/100gm; plasma and tissue T4 and T3 as well as plasma TSH and tissue deiodinases were measured. The tissue T4 and T3 content of the pituitary gland was significantly increased in animals taking T4 and T3 as was the liver content. These data suggest that combined T4 and T3 therapy normalizes plasma and tissue T4 and T3 concentrations. One caveat is that there is no proof based upon biologic end points that normal tissue levels of T4 and T3 provided by combined therapy are superior to those seen during T4 alone. Bunevicius et al. (5) studied 33 hypothyroid patients who were taking an average dose of l-thyroxine .175mg per day. Irrespective of the dose of l-thyroxine 12.5 micrograms of T4 was substituted for .05 mg of L-T4. This was a blinded, randomized crossover study with each arm lasting 5 weeks. While patients were taking both T4 and T3, there was significant improvement in terms of cognitive performance and mood scores, visual analogue scales and physical symptoms. There were no differences noted in Achilles tendon reflex time, neuropsychological tests, blood pressure or serum lipids. The authors concluded that partial substitution of T3 for T4 may have salutary effects on the brain and perhaps other tissues as compared to equivalent doses of T4. This article has been criticized for the following reasons. Psychiatric outcomes have not been validated for hypothyroidism. The dose of thyroid hormone was relatively high and, therefore, it is difficult to extrapolate to normal replacement therapy, and the timing of dosing the T4 and T3 dose and its relationship to breakfast is a potential issue. Patient in this study took the medication once daily, half an hour before breakfast. The patients reported to clinic at approximately 9 am having omitted breakfast but having taken their thyroid medication about two hours earlier. Nonetheless, when patients were asked 20 out of 33 preferred combination T4/T3 therapy, 2 out of 33 preferred l-thyroxine alone and 11 out of 33 had no preference.

Normal T4 production is approximately 56 mg per m2 per day considering an average surface area of 1.78 m2; the dose is approximately 100 micrograms per day with approximately 80% effective G.I absorption. Therefore the optimal replacement dose would be approximately 112 – 125 micrograms per day. Normal T3 production is 3.3 micrograms per m2 per day considering an average surface area of 1.78 m2 the T3 requirement would be approximately 5.9 micrograms per day. The daily T3 production rate is approximately 25 – 30 micrograms per day; 19 to 24 micrograms per day of T3 is derived from T4 deiodination. Therefore, the optimal pill in a normal weight individual having a body surface area of 1.78 m2is approximately T4 112 micrograms per day, 100 micrograms of which are bioavailable and with T3 content of 6 micrograms with about 22 additional micrograms derived from T4 conversion. Therefore, the Bunevicius et al. study (6) may not have used physiologic replacement doses. The question does remain to this day whether combination T4 and T3 therapy is more beneficial than T4 alone. Although Bunevicius et al. (6) showed some benefit, subsequent evaluation noted no benefit in multiple randomized, controlled trials. (7-11) Two meta-analysis studies were performed that noted lack of statistical power in many of the previous studies, small sample size, lack of homogeneity and brief duration of study period.(12, 13) These studies concluded that the benefit of adding T3 to T4 therapy could not be substantiated and that T4 should remain the treatment of hypothyroid patients.

The studies noted that utilized T3 in combination with T4 used commercially

available T3 which is relatively short acting. Serum T3 levels peak (generally above the normal range) within 2-4 hours after administration and return to baseline levels within 4-6 hours. Theoretically, a sustained-release T3 preparation would be advantageous and might give normal T3 levels throughout a 24 hour period. Hennemann et al. (14) studied this issue in a preliminary manner and showed "proof of principle" that a long acting T3 preparation could be developed. To our knowledge, no further studies in human appear in the literature

The T4 / T3 tablet ratio optimally would probably contain approximately a 14 to 1 molar ratio and it would be optimal to have a true slow release or constant release over 24 hours. Gullo et al. noted that T4 treatment alone does not guarantee euthyroidism as T4 ratios were abnormal in athyreotic patients treated with T4.(Gullo et al. PLoS one 6 (8):e22552; August 2011).

Panicker et al. (15) demonstrated that Type 2 deiodinase polymorphisms were present in selected patients and they postulated this could alter the response to T4 therapy being. They analyzed polymorphisms of the Type 2 deiodinase gene and identified them in approximately 16% of the population. Indeed, a group of these patients improved their quality of life and well-being scores while taking T4 and T3 combinations. It is speculated that polymorphisms may inhibit the ability to convert T4 to T3 and could, theoretically, help explain why some patients taking l-thyroxine do not feel normal on l-thyroxine alone. Further research into this area needs to be performed. Torlontano et al. (16) also showed that a Type 2 deiodinase polymorphism exists and that these patients required a higher dose of T4.

Celi et al. (2) has studied the issue of whether T3 therapy is more beneficial than T4 therapy. Fourteen hypothyroid patients were treated either with T3 or T4 in a randomized, double blind crossover study. The T3 was given TID to achieve target TSH with relatively stable serum T3 levels throughout the day. While taking T3 patients had a significantly greater (as compared to T4 alone) decrease in weight loss, total cholesterol, total LDL cholesterol, and apolipoprotein B. These authors concluded that T3 doses (that gave equivalent TSH serum levels as T4 alone) had greater beneficial effects on weight loss and lipid metabolism, without differences in cardiovascular function or insulin sensitivity.

MAIN CONCLUSIONS

Evidence of clear benefit of T3 plus T4 therapy remains uncertain. There are certain positive studies suggesting that T3 alone or in combination with T4 is more beneficial than T4 alone. However, there are multiple studies showing no differences. Further, supraphysiologic T3 doses have generally been used implying that beneficial clinical effects may be due to transient relative T3 excess. There are risks of over or under dosing with current short acting T3 preparations that preclude optimal results. To date, there is no satisfactory long acting T3 preparation available and even giving T3 doses several times daily may not achieve physiologic serum T3 levels over a 24 hour period. Recent studies showing genetic polymorphisms indicate subpopulations with normal TSH who may not achieve normal T4/T3 ratios when administered T4 alone. The development of a long acting T3 preparation may be useful, but, obviously, has to be subjected to appropriate clinical studies. Unfortunately it is still difficult to assess T3 or T4 action at the individual organ or cell level in humans.

CASES WITH QUESTIONS

Case 1

41year old man with Graves' disease undergoes radioactive iodine ablative therapy rendering him hypothyroid. He is seen in follow up 2 years later with the following thyroid function tests on l-thyroxine therapy. Free T4 1.5 ng/dl (normal .8-1.8); Total T3 98 ug/dl (normal 80 to 180.); TSH .9 uU/ml (normal .3 to 3.5). He complains of fatigue, weakness, and lethargy and he claims these symptoms have been a problem only since the radioactive iodine therapy. He wants to know why you are not treating him with T3 or thyroid extract.

Case 2
66 year old man has been treated with oral T3 for many years because of primary hypothyroidism. He feels well. His thyroid gland is not palpable. He takes oral T3 50 ug bid po at 7 am and 5 pm. He eats breakfast at 7:30 am. Laboratory tests drawn at 8:00 am show serum T3 140 ng/dl; FT4 1.1 ng/dl; TSH .6 uU/ml. You would like to change his replacement medication to levothyroxine alone, but he insists he feels well and his lab tests are fine. Therefore, he is reluctant to change. What do you tell him?

Case 3
A 30 year old woman is taking compounded long acting T3 to treat primary hypothyroidism. She feels well on this medication. She takes 30 micrograms daily at 7 am. At 9 am FT4 1.3 ng/dl; TT3 270 ng/dl; TSH .1 uU/ml. What advice do you give her?

DISCUSSION OF CASES AND ANSWERS

Case 1
As discussed above, there is little compelling evidence to date that adding T3 to T4 therapy increases psychological profile or tissue levels of T3.

Case 2
Oral T3 has a short serum half-life and general peaks at 2-4 hours post dose and returns to basal levels in 4-6 hours. Obtaining thyroid function tests at a single time during the day does not give a representative sample of T3 (or T4 and TSH) levels throughout the day. It would be better to obtain TFTs several times during the day. Further, for a period of time following a dose of T3, serum T3 levels may be elevated and this potentially could lead to adverse effects.

Case 3
At present, there are no FDA approved long acting T3 preparations. It needs to be proven that the compounded long acting preparation she is taking is, indeed, long acting.

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Subclinical Thyroid Disease

M40
Monday, June 17
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Subclinical thyroid disease is a common clinical problem. Epidemiologic studies suggest that subclinical hypothyroidism occurs in 4-20% of the population, depending on age, sex, dietary iodine intake, and the TSH cut-offs that are used to define the upper limit of the reference range. Subclinical hyperthyroidism is perhaps 1/10 as common as subclinical hypothyroidism, and again the population prevalence depends on iodine intake (perhaps tenfold higher in low iodine environments), age, and gender. While the clinical significance of subclinical hypothyroidism remains controversial, even in pregnancy, current data suggest strongly that subclinical hyperthyroidism is a risk factor for bone loss in postmenopausal women, and atrial fibrillation, heart failure, and cardiovascular mortality in older persons.

BARRIERS TO OPTIMAL PRACTICE

The clinical significance of these two forms of what could be thought of as mild thyroid dysfunction remains cloudy, since there is a paucity of prospective randomized controlled trial data to inform clinicians about the most appropriate management. Furthermore, unsettled and controversial issues regarding screening for thyroid disease, the importance of subclinical hypothyroidism in pregnancy, and the increases seen in serum TSH in normal healthy older individuals make the problem even more controversial.

LEARNING OBJECTIVES

As a result of participation in the session, learners should be able to:

- Provide better, more evidence based care to patients with subclinical thyroid disease
- understand the controversies surrounding the most appropriate management of subclinical thyroid disease

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Subclinical Hypothyroidism

Subclinical hypothyroidism is a term that is used to describe the situation in which serum thyroid stimulating hormone (TSH) levels are elevated, but serum thyroid hormone levels (free T4, T3) are normal. In most patients, serum TSH levels are <10 mU/l, although occasional patients may have levels between 10-20 mU/l, but can still have levels of free T4 that are within the range of normal (1). In most patients, the cause of subclinical hypothyroidism is autoimmune (Hashimoto's) thyroiditis, although many other causes have been identified (e.g., lithium therapy, external radiation, etc.). Indeed, anything that can cause overt hypothyroidism (defined as a low free T4 with a high TSH) can also cause subclinical hypothyroidism. Thus, it is correct to say that subclinical hypothyroidism is actually a form of "mild" hypothyroidism. From a clinical point of view, the main issue is whether this very mild form of hypothyroidism is clinically significant, and whether it even warrants detection by screening, and it diagnosed, whether it requires treatment. It is also true that there are some situations in which elevated serum TSH levels are not due to subclinical hypothyroidism. Obesity is the most important clinical example of

this situation, with high serum TSH likely mediated by central effects of leptin to stimulate hypothalamic TRH secretion (2).

While subclinical hypothyroidism is extremely common, occurring in 4-20% of adults depending on age, sex, race, dietary iodine intake, and other factors, recent data on the statistical distribution of serum TSH levels in normal healthy individuals has added to the controversy of how to define a "normal" serum TSH level. Re-analysis of data from the United States National Health and Nutrition Epidemiologic Survey (NHANES) has shown that serum TSH levels rise with age in normal healthy people who are free of thyroid disease (3). In fact, in people who are in their 70s-90s, the 95th percentile for TSH may go as high as 6-9 mU/l. Thus, an 80 year-old woman with a serum TSH of 6.3 mU/l and a normal free T4 level may be a normal healthy individual, rather than a person with subclinical hypothyroidism. Therefore, the frequently cited high prevalence of subclinical hypothyroidism in the general population, especially in the elderly, needs to be re-examined in light of these new data.

Most patients who have subclinical hypothyroidism feel well and have no symptoms to suggest hypothyroidism. On the other hand, there are patients who have typical symptoms of hypothyroidism, but in fact, the number and type of symptoms (e.g., cold intolerance, constipation, difficulty losing weight, etc.) are similar in frequency and severity to euthyroid age matched controls. This is in keeping with the very low specificity of typical "hypothyroid symptoms". In the elderly, several large studies have shown that subclinical hypothyroidism is not associated with physical function, cognitive dysfunction, depression, or anxiety (4). Indeed, one study showed that subclinical hypothyroidism in people aged 70-79 years was associated with increased walking speed, a measure of fitness, compared to euthyroid controls (5). Another showed that elderly persons over age 85 years with subclinical hypothyroidism had a lower mortality rate than "normal" euthyroid controls (6).

Potential cardiovascular risk is the major morbidity associated with subclinical hypothyroidism. Some studies have suggested a decrease in diastolic function with exercise and possible reduced exercise tolerance in patients with subclinical hypothyroidism (1). There is also impairment in vascular smooth muscle relaxation and arterial stiffness that has been observed, but the clinical significance of these observations is uncertain (1). Some studies have also shown that patients with subclinical hypothyroidism may have dyslipidemia, especially in those patients who also are smokers or who had insulin resistance (1). Some prospective studies have shown an increase risk of cardiovascular disease and cardiovascular mortality in subclinically hypothyroid patients, whereas other studies have not demonstrated this finding. A recent meta-analysis of the 11 prospective cohort studies did show an increased risk of coronary heart disease, but this increase was only seen in persons with serum TSH levels >10 mU/l (7). Another retrospective study has shown that treating subclinical hypothyroidism seems to have beneficial effects to lower cardiovascular morbidity in persons between ages 40 and 70 years, but not in persons aged 70 years or more (8). Finally, heart failure is more common in elderly people with serum TSH levels >8-10 mU/l (9).

Subclinical hypothyroidism in pregnancy

The prevalence of subclinical hypothyroidism in women of reproductive age ranges from 0.5-5%. In pregnant women, the prevalence of hypothyroidism, mostly subclinical hypothyroidism is around 2.5% (1). Various studies have shown an increase risk of miscarriage, preterm delivery, and gestational hypertension in women with subclinical hypothyroidism; although the frequency of these adverse outcomes is lower than is seen in women who have overt hypothyroidism (1). Thyroid hormone is also important for normal fetal brain development, and some have suggested that untreated maternal subclinical hypothyroidism is associated with a decrease in the intellectual potential of the offspring (10). However, a recent randomized prospective study was not able to confirm this finding (11), and also did not show a higher rate of adverse pregnancy outcomes in untreated women with

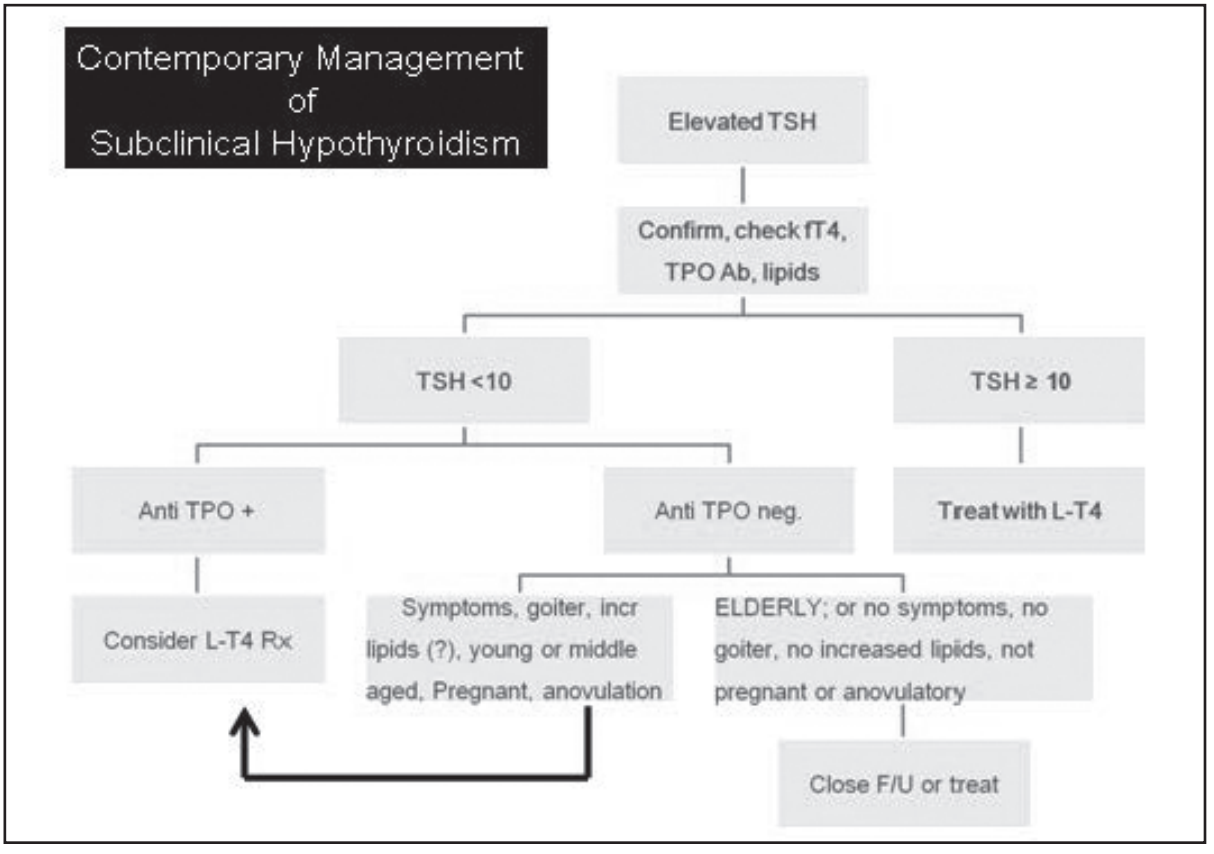
subclinical hypothyroidism.

Treatment of subclinical hypothyroidism

Based on the foregoing, replacement therapy for subclinical hypothyroidism, including in pregnant women, remains controversial. While prospective data show improvement in some cardiovascular risk factors (e.g., serum lipids, carotid intimal thickening), there are no prospective trials showing improved cardiovascular outcomes with treatment. Similarly, there are no prospective trials that have shown improvement in pregnancy outcomes in women with subclinical hypothyroidism who have been treated with levothyroxine, although recent clinical practice guidelines recommend treatment in this situation (12).

In general, most clinicians agree that patients who have serum TSH levels >10 mU/l should be treated, since they have an increased risk of progression to overt hypothyroidism, might be more frequently symptomatic, and might have an increased risk of cardiovascular disease (1). On the other hand, patients with serum TSH levels between 5 and 9 mU/l should be treated depending on the clinical situation (treatment more likely to be of benefit in young and middle-aged persons and persons with possible symptoms of hypothyroidism, depression, goiter, or cardiovascular risk factors). Elderly patients with a mildly elevated serum TSH might not be truly hypothyroid, and even if they are, they are less likely to benefit from treatment; indeed, they might even be harmed, since treatment is associated with often associated with inadvertent iatrogenic hyperthyroidism (13). In pregnancy, most endocrinologists advocate treating women with serum TSH levels above the reference range for pregnant women, or 2.5-3.0 mU/l, while most obstetricians do not recommend therapy. Only with well-designed, prospective randomized controlled trials, looking at clinically relevant outcomes such as cardiovascular morbidity or mortality, will the question of treatment be answered satisfactorily and convincingly.

FIGURE 1



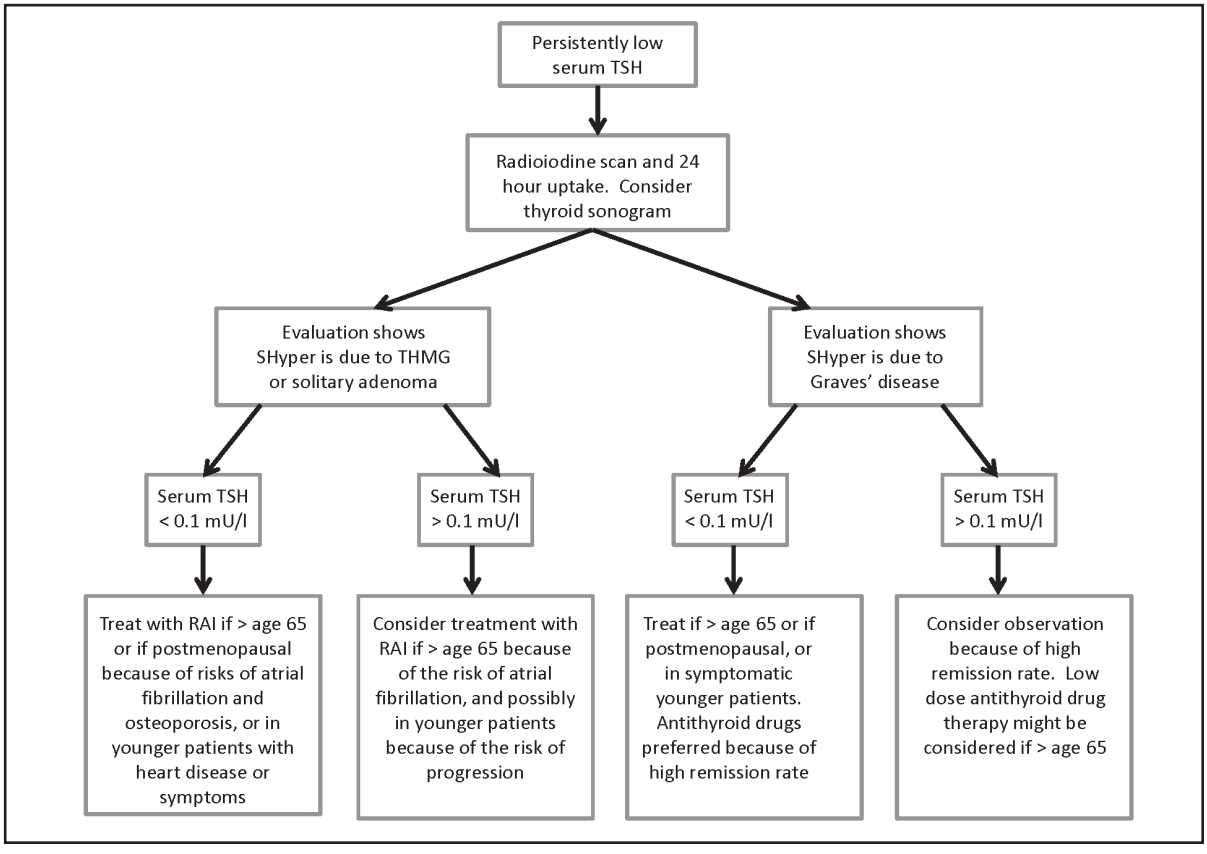
Subclinical Hyperthyroidism

Subclinical hyperthyroidism refers to a laboratory situation in which the serum TSH is subnormal, but the serum levels of free T4 and T3 are normal (1). Rare patients may have normal levels of these hormones, but elevated levels of free T3, which would not meet the definition of subclinical hyperthyroidism. Subclinical hyperthyroidism can be divided into two forms: "exogenous", due to intentional or inadvertent administration of excessive amounts of thyroid hormone therapy and "endogenous", due to the typical causes of hyperthyroidism (Graves' disease, toxic multinodular goiter, and solitary autonomously functioning thyroid nodules). Exogenous subclinical hyperthyroidism is far more common than endogenous causes, since, as noted above, a large minority of patients treated with thyroid hormone have subnormal serum TSH levels (13). Before the diagnosis of subclinical hyperthyroidism can be made, other causes of low serum TSH need to be excluded. These include changes in serum TSH seen in critically ill hospitalized patients and the normal physiologic lowering of serum TSH during pregnancy, especially at the end of the first trimester. Furthermore, there is a shift in TSH distribution to the left in individuals of African descent, so that some normal African-Americans have serum TSH levels that are below the reference range for Caucasians (14). For example, in the NHANES survey, 4% of black people had serum TSH levels <0.4 mU/l, versus only 1.4% of white people (14).

In order to establish a diagnosis of subclinical hyperthyroidism, serum TSH levels must be persistently low. Several studies have shown that low serum TSH levels are often transient (15). Graves' disease is the most common cause in young people, whereas toxic multinodular goiter is more common in the elderly. Interestingly, subclinical hyperthyroidism is quite frequent in patients with older persons with toxic multinodular goiter (>50%), but unusual (fewer than 10%) in older patients with Graves' disease (16).

The major clinical concerns surrounding

FIGURE 2



subclinical hyperthyroidism related to potential deleterious effects on the skeleton and the cardiovascular system in the elderly population. With respect to the skeleton, thyroid hormone has direct effects on osteoclast function, and there are also data suggesting, intriguingly, that there may be direct effects of TSH itself on bone health (17). In most studies, postmenopausal women (but not premenopausal women or men) with subclinical hyperthyroidism had diminished a bone mineral density compared to controls (1), and there is an increased risk of fracture in postmenopausal women with low serum TSH levels (18). In addition to increased 24-hour mean heart rate, increased left ventricular mass, and a possible hypercoagulable state, several prospective cohort studies of patients with subclinical hyperthyroidism who are over age 65 years have shown an increase risk of a atrial fibrillation (e.g., 19), heart failure (9), and cardiovascular mortality (1, 20). These risks (skeletal and cardiovascular) appear to occur in patients who have both exogenous and endogenous subclinical hyperthyroidism, especially when the serum TSH level is <0.1 mU/l.

Treatment of subclinical hyperthyroidism

Treatment of subclinical hyperthyroidism remains controversial, since there are no prospective randomized controlled trials. Several small prospective studies (not randomized) suggest improvements in bone mineral density in older women treated for subclinical hyperthyroidism. Another prospective study showed an increase in thigh muscle strength with treatment (21), and one randomized nonplacebo controlled trial showed that antithyroid drug treatment can improve hyperthyroid symptoms (22). For older patients with more significant degrees of TSH recommend treatment suppression (<0.1 mU/l), clinical practice guidelines sponsored by the ATA and AACE recommend treatment with radioactive iodine or antithyroid drugs (23). Treatment might also be considered in younger persons with hyperthyroid symptoms, as well as younger patients with toxic multinodular goiters or solitary hyperfunctioning nodules, since subclinical hyperthyroidism may progress over time to overt hyperthyroidism, whereas Graves' disease may actually remit with follow-up (24).

MAIN CONCLUSIONS

Subclinical thyroid disease is a common clinical problem. It remains controversial, since symptoms are nonspecific, and changes in serum TSH can be observed in relationship to age, race, and other non-thyroidal factors. Furthermore, there are few randomized controlled trials to document efficacy of thyroid hormone treatment for subclinical hypothyroidism or antithyroid drugs/thyroid ablation for subclinical hyperthyroidism.

CASES WITH QUESTIONS

Case 1

A 76 year-old Caucasian woman who is asymptomatic is found to have a serum TSH value of 4.3 mU/l, with a normal range of 0.5-4.1 mU/l.

She has a normal physical examination. There is no family history of thyroid disease.

A repeat set of thyroid function tests 3 months later shows the following: free T4 1.2 NG/ML, TSH 4.8 mU/l, antiTPO antibodies negative

Is this person hypothyroid?
What should be done?

Case 2

A 70 year old woman is referred for possible hypothyroidism, after her primary care provider ordered a screening serum TSH that was 5.5 mU/l. She feels well and has no major medical problems

She is taking no medications.

PE: P 80 BP 140/70 Wt 65 kg. The thyroid is normal to palpation. Skin cool, dry. Reflexes normal.

Repeat TSH 6.1 mU/l, FT4 1.0 ng/ml; antiTPO antibodies are positive

Should she have been screened?

Should she be treated with L-thyroxine?

Case 3

(read this sequence of emails and comment)

HI Dr. Cooper,

I am a second year pediatric resident with h/o of thyroid disease. You may remember that Dr. Plotnik had emailed you about my labs a few weeks ago when my TSH was undetectable and normal T4 around 13 weeks of pregnancy. I am currently 17.4 weeks pregnant. I had repeat levels done yesterday and my TSH increased to 5.3 with free T4 still being 0.9. I asked them to repeat today to confirm and TSH remained above normal at 4.6 (this lab was obtained in am vs. pm for other). I think they will likely start me on synthroid and recheck labs in 4 weeks. Am I correct that goals for TSH are less than 3? Does this sound appropriate? I would greatly appreciate your advice.
Thanks,
Courtney M. MD

Hi Courtney
I think it would be reasonable to shoot for a TSH of ≤ 2.5. So, yes, I agree with starting you on thyroid hormone. Let me know if you have any other questions.
David

Dr. Cooper
Thanks for the email. Ob will get back to me tomorrow about if they will actually treat me- it >turns out they use 4.5 as normal for TSH, so they seem a little hesitant about treating for 4.6. If they don't want to use your level would it be safest / better to see you in clinic?
Thanks
Courtney

Courtney
There is a complete disconnect between what OB's believe and what endocrinologists believe, based on the same data. I think you should be on medication.
I would recommend a dose of levothyroxine of 100 mcg/d. See if your OB would be willing to prescribe it.
David

Hi Dr. Cooper,
I finally was able to speak to the OB this evening. She would not prescribe me medication. She reports that they do not treat unless someone has overt hypothyroidism (even if my TSH were 9 and normal T4 she would not treat).
She was worried about causing undue harm and risk of over treating.
She also reported that this was the opinion of the department.
They suggested if I still felt strongly that I should go to endocrine clinic.
Is there any possibility that I could see you in clinic before I am too far along with my pregnancy? I know your schedule is super busy and you are booking into May according to your scheduler.
Please let me know.
I appreciate all of your help.

Courtney
Give me the number of your pharmacy and I will call in a prescription for you. I can see you on Tuesday 2/22 at 11:15. Please call my assistant at 2-4926 to set up the appt.
David

Case 4
A 70-year-old woman is referred for possible hyperthyroidism. She has no significant past history except for a goiter since she was in her 20's. She has no palpitations, heat intolerance, or weight loss.
Medications: calcium, multivitamins
Physical Exam: P 80, BP 130/85 wt. 156. no proptosis. The thyroid gland was enlarged with multiple bilateral nodules and a dominant 4 cm right thyroid nodule. The skin was warm and dry. Reflexes normal. no tremor.
Thyroid Function Tests: free T41.4,T3 135,TSH <0.02
Ultrasound: multiple benign-appearing nodules with a dominant 6 cm right lobe nodule
Radionuclide scan shows a large hypofunctioning area on the right corresponding to the dominant nodule. Biopsy of the right thyroid nodule is benign

Should she be treated?
If so, how should she be treated?

DISCUSSION OF CASES AND ANSWERS

Case 1
Answer: This is likely an age-related increase in serum TSH, rather than subclinical

hypothyroidism. Even if she were mildly hypothyroid, there is no evidence that treating her would be of any benefit. The most appropriate strategy would be to repeat thyroid function tests in one year.

Case 2

Answer: Screening for subclinical thyroid disease and asymptomatic persons is controversial. Some groups such as the American Thyroid Association recommend screening of adults after age 35, whereas other groups such as the US Preventative Services Task Force do not recommend screening because of lack of benefit of treatment, especially in the elderly. With regard to treating this patient, it might be considered because of possible progression to overt hypothyroidism with her positive antiTPO antibodies. However, some patients revert back to normal, and there is little evidence to document improvement in mood, cognition, or cardiovascular outcomes. Congestive heart failure is more common in elderly patients with subclinical hypothyroidism, but only when serum TSH values are higher.

Case 4

Answer: According to clinical practice guidelines, she should be treated to avoid a decrease in BMD and prevent atrial fibrillation, although there are no prospective trials documenting the efficacy of therapy. Given the fact that she has a multinodular goiter, radioiodine would be the preferred therapy. Antithyroid drug therapy would be a secondary choice. There is no evidence that pretreatment with antithyroid drugs is needed before radioiodine therapy of subclinical hyperthyroidism.

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RAI Remnant Ablation: When is 30 mCi Appropriate?

M57
Tuesday, June 18
11:15 AM to 12:00 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

There is a great deal of uncertainty regarding administration of radioiodine (RAI) for remnant ablation (RRA). This uncertainty begins with whether or not a particular patient should receive RRA, it then focuses on what the relative benefits and risks are of choosing such treatment, and further extends to what activity of RAI should be selected if RRA is chosen. This uncertainty is well illustrated by several studies of practice patterns that show the widely different activities that may be selected for achieving RRA.

The initial decision as to whether a particular patient should receive remnant ablation should be based on the potential benefits and risk of radioiodine administration. Widely quoted benefits include allowing accurate disease surveillance and providing information for accurate staging. Additional benefits that are desired include decreasing the risk of disease recurrence and increasing disease-specific survival. These benefits have only been demonstrated in some studies. They have not have demonstrated in randomized controlled trials of RRA. Ideally, these benefits would be achieved without excessive side effects. In general, the short-term risks of RRA are fairly easy to document, but the longer-term risks are harder to quantify.

Questions to consider include the following:

1. ***How can patients be stratified based on their risk?***
2. ***Is there any additional testing, in addition to clinic-pathologic stage that would be helpful in stratifying risk?***
3. ***Within the various risk categories, who needs RRA and who does not?***
4. ***What is the benefit of RRA?***
5. ***What are the side effects of RRA?***
6. ***How should the patient be involved in the decision-making?***
7. ***If RRA is chosen, how should patients be prepared?***
8. ***If RRA is chosen, what dose is optimal? (When is 30 mCi optimal?)***

BARRIERS TO OPTIMAL PRACTICE

Several factors add to the difficulty in weighing risk versus benefits of RRA. These include difficulty in assigning a disease stage or risk to an individual patient (i.e. risk stratification), difficulty in determining the theoretical versus proven benefits of RRA for low risk patients, difficulty in assessing and minimizing the risks of RRA.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to

1. Stratify patients in risk categories based on tumor characteristics and additional testing as necessary.
2. Based on risk, decide which patients would benefit from RRA.
3. Quantify the reduction in risk associated with RRA.
4. List the short-term and long-term side effects associated with RRA.
5. List potential ways to involve patients in decision-making regarding RRA.
6. Describe preparation for RRA.
7. Select an appropriate activity for RRA.
8. Determine when 30 mCi is the most appropriate activity.

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Risk Stratification

After a patient has undergone their initial surgical therapy, the next step is to assess their disease stage and/or risk in order to reach a decision about the need for RRA. Factors that affect risk include tumor size, extrathyroidal extension, vascular invasion, completeness of tumor resection, nodal disease, aggressive histologic subtypes, and distant metastases. In additional to these classic assessment tools, the thyroglobulin nadir after surgery may be an additional prognostic factor (1).

Benefits of RRA

Radioactive iodine can be administered in those without residual disease for remnant ablation, which involves destroying normal thyroid tissue to improve surveillance. Alternatively it can be given as adjuvant therapy, in which case the intention is to prevent future disease (2). Often these purposes are combined. The term therapy implies that the radioiodine is being given for residual disease.

A systematic review of studies of RRA was performed by Sawka and colleagues in 2008 (3). This review suggested that although RRA was associated with decreased thyroid cancer mortality in 3 studies, that an additional 8 studies were unable to show a mortality benefit. With respect to locoregional recurrences, 3 out of 4 studies suggested a benefit, whereas 2 out of 3 studies suggested a reduction in distant metastases. Heterogeneity of treatment effects made it difficult to determine an overall treatment effect on recurrences in this analysis. However, the calculated risk difference favored RRA. The benefit in two of the studies reporting a reduction in loco-regional recurrences was a relative risk of 0.29 (0.17–0.51), $p<0.001$ (4) and a hazard ratio of 0.5 (0.3-0.8), $p<0.007$ (5) associated with RRA.

The preponderance of data suggests that there is no benefit of RRA in low risk patients. A prospective registry study not included in the above analysis by Sawka because of its short duration of follow up showed that RRA improved overall survival in patients with stage II, III, and IV disease, but did not improve the survival of stage I patients (patients in this study were staged according to staging system specific to the registry) (6). RRA did not appear to be of benefit in a prospective non-randomized study of patients with microscopic foci of papillary thyroid cancer (7). A study of low risk patients who did not receive RRA and were followed over a 4-year period showed a 2.3% recurrence rate (8). This study was retrospective, but at least suggests that low risk patients who do not receive RRA do not have unexpectedly high recurrence rates. A recent systematic review performed by Sacks et al (9) suggested that most studies did not show a survival benefit of RRA in low risk patients, in contrast to a benefit being seen in stage III and IV patients. They concluded that the data was mixed with regard to recurrence rates in low risk patients, with approximately half of the studies showing reduced recurrence and the other half showing no impact on recurrence.

As suggested by many investigators a randomized controlled trial of RRA in low risk patients would provide vitally needed results. One estimate of the numbers of patients needed to perform such a trial to study recurrence rates is 528 patients followed for a period of 5 years (3).

Risks of RRA

There are several studies that show that patients suffer both short-term and long-term side effects from RRA. Sialadenitis, xerophthalmia, epiphora, epistaxis, radiation thyroiditis, decreased sperm count, premature menopause, and secondary malignancies are all potential consequences of receiving treatment with RAI. The incidence of sialadenitis, xerophthalmia, epiphora, and nasal symptoms is difficult to quantify as these symptoms are likely under-reported. In one study 38/46 had evidence of xerostomia and 9/46 had evidence of xerophthalmia after 100 mCi RAI, compared with no such dysfunction after 25-50 mCi RAI (10).

In a large European study of 6841 patients the authors found an excess relative risk of both solid tumors and leukemia. The authors estimated that a treatment dose of 3.7 GBq

(100 mCi) RAI would induce an excess of 53 solid malignant tumors and 3 leukemias in 10,000 patients during 10 years of follow-up (11). A study using the SEER database also found a significantly greater risk of second primary malignancies over that expected in the general population for patients treated with radioisotopes (12). The observed/expected risk was 1.20 (95% CI, 1.07–1.33). The absolute excess risk per 10,000 person-years was 11.8. The dose of RAI could not be examined in the second study

Patient Participation

The uncertainty that exists regarding whether or not to pursue RRA clearly affects patients as well as physicians. Some studies of patients who have received RRA show dissatisfaction regarding their therapy or regret regarding their choice. Patients who were more involved in decision-making appear to express less regret regarding their choice (13). A computerized decision aid may be helpful to patients who are considering whether or not to pursue RRA (14).

Preparation for RRA

Preparation for RRA has traditionally involved iodine depletion, in addition to TSH elevation. A low iodine diet reduces urinary iodine excretion and increases iodine uptake, and is generally recommended. However, there is mixed evidence regarding the value of a low iodine diet for improving RRA. One study suggests that a low iodine diet improved the success of RRA based on an assessment of iodine scanning and thyroglobulin measurement 6 months later (15). Another showed no association between the success of RRA and urinary iodine excretion (16).

Most data show that either withdrawal or recombinant TSH can be used to prepare patients for RRA and that these methods appear to be similar when evaluated on the basis of diagnostic scans and stimulated thyroglobulin values 8-12 months later (17, 18). Preliminary results also show similar short-term outcomes (19).

Practice Patterns

Two different studies can be used to illustrate practice patterns of radioiodine use in the US and Canada. In one study of the National Cancer Database 28-47% of low risk patients received RAI treatment depending on the geographic area of the US (20). In a survey of physicians who were presented with a case of a 38 year old with a single 1.6 cm focus of papillary thyroid cancer, there was a spectrum of opinion regarding RAI dose selection. 0-10% of those surveyed recommended no RAI, 6-25% recommended 29.9 mCi, and 30%-62% recommended a dose of 100 mCi (21).

Dose Selection

A systematic review comparing doses of RAI used for RRA was published in 2007 (22). At that time it was not possible to conclude whether doses of 30 mCi and 100 mCi achieved comparable rates of successful remnant ablation. Since then several randomized trials have been performed and the most studies suggest that equivalent success rates can be achieved with lower doses (23-28).

Randomized trials of RAI doses for Remnant Ablation				
Study	25-30 mCi	50 mCi	100 mCi	Comment
Success rates based on RAI scanning				
Pilli, 2007	n/a	89	89	rTSH
Bal, 2012	82	85	89	WD, no LID
Mallick, 2012	93	n/a	95	rTSH and WD
Schlumberger, 2012	94	n/a	96	rTSH and WD
Success rates based on TG stimulation				
Pilli	n/a	79	67	
Mallick, 2012	86	n/a	88	rTSH and WD
Schlumberger, 2012	90	n/a	93	rTSH and WD
Caglar, 2011	89	n/a	86	WD only, low dose = 21 mCi
Success Rates based on Combined Criteria				
Fallahi, 2012	39.2	n/a	64	WD only, TSH <25 in 20%
Caglar, 2011	81	n/a	73	WD only, low dose = 21 mCi

MAIN CONCLUSIONS

Patients who are at low risk of recurrence and negligible risk of death from thyroid cancer can be identified. Such patients do not appear to benefit from RRA, although a trial randomizing patients to follow up with and without RRA has not yet been performed. In patients with an intermediate risk of recurrence, current evidence suggests that 30 mCi of RAI will achieve effective remnant ablation based on follow up diagnostic scanning and measurement of stimulated thyroglobulin measurements. Use of recombinant TSH as preparation for RAI administration appears to be comparable to withdrawal from thyroid hormone as preparation. Choice of 30 mCi would be likely to avoid exposing patients to the unnecessary risks of RAI that appear to be dose related. Involvement of patients in the decision-making regarding RRA appears to improve patient satisfaction with therapy. Long-term outcomes of patients who have been specifically treated with 30 mCi for RRA are lacking.

CASES WITH QUESTIONS

1. A 44-year old female with PTC presents for further management after a total thyroidectomy. She was found to have microscopic multifocal PTC. There were 4 foci of PTC ranging between 2 and 7 mm in size. Two foci were the follicular variant of PTC. No lymph node involvement was identified. a) What disease stage is this patient? b) Would you recommend RRA? c) If yes, what dose would you select?
2. A 56-year old male presents for further management of PTC after he underwent a total thyroidectomy and central neck dissection. He was found to have an 8 mm PTC with minimal extrathyroidal extension into perithyroidal soft tissues that was resected with clear surgical margins. 1 out of 28 central compartment lymph nodes were affected by cancer. a) What disease stage is this patient? b) Would you recommend RRA? c) If yes, what dose would you select?
3. A 24-year male with a diagnosis of PTC presents after a total thyroidectomy and right neck dissection. His surgical pathology shows a necrotic 3.7 cm lesion with the viable cells having the characteristics of the tall cell variant of PTC. There was capsular invasion, but no extrathyroidal extension, and the surgical margins were clear. 21 out of 26 resected lymph nodes contained PTC. a) What disease stage is this patient? b) Would you recommend RRA? c) If yes, what dose would you select?

DISCUSSION OF CASES AND ANSWERS

The patient presented in case 1 has stage I disease. Although her disease has multiple foci, she does not have any evidence of residual disease and has no documented lymph node involvement. She probably would not benefit from RRA (7).

The second patient has a T3 tumor. As he is older than 45 years, both the T3 tumor and the central compartment lymph nodes place him in stage III. Such a patient would have been eligible for randomization to receive either 30 or 100 mCi in the two recent clinical trials (25, 26). However, arguably, this patient might be unlikely to have additional central nodes or lateral lymph node disease and could be considered at low-intermediate risk for having residual disease or recurrence. A dose of approximately 30 mCi might be considered in such a patient.

The final patient has stage I disease because of his young age. Although many stage I patients do not benefit from RRA, this particular patient has prognostic features that are perhaps not in keeping with his stage designation. These include the tall cell variant of PTC, and the fact that the large number of central compartment nodes that are positive many be predictive of lateral compartment nodal disease too. A dose higher than 30 mCi might be advisable in such a patient.

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Evaluation of Thyroid Nodules

M48
Monday, June 17
1:00–1:45 PM & 3:00–3:45 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Thyroid nodules are a commonly encountered referral reason for endocrine consultation. Although palpable nodules are present in only 5-7% of the population, imaging detects thyroid lesions in up to 50% of those over age 50. The majority of these are incidental findings, identified when imaging is performed for another medical indication, e.g. carotid ultrasound, neck CT scanning. Since the cancer risk (7-9%) is relatively independent of nodule size, it is important for the clinician to identify the subset of nodules that may be potentially clinically significant thyroid cancers so that fine-needle aspiration (FNA) for cytology can be performed. The selection of nodules for FNA is based upon patient specific risk factors for thyroid cancer, nodule sonographic features, and nodule size. Furthermore, although FNA is the recommended procedure for diagnosis of thyroid cancer, up to 30% of cytology results will fall into one of three indeterminate categories, using the Bethesda classification [1]. Although only the minority of these patients (20-25%) will subsequently be found to have thyroid cancer, diagnostic surgery (generally lobectomy) has been the traditional treatment paradigm. Therefore, up to 80% of patients with indeterminate cytology results undergo surgery, with its potential associated complications, for subsequent diagnosis of benign disease.

BARRIERS TO OPTIMAL PRACTICE

1. Performance and interpretation of thyroid ultrasound (US). Evidence based guidelines from the American Thyroid Association (ATA) [2] and the American Association of Clinical Endocrinologists (AACE) [3] recommend thyroid sonography for characterization of thyroid nodules because certain individual sonographic features and US patterns are associated with lower or higher cancer risk. However, performance and interpretation of thyroid sonography is subject to interobserver variation that can lead to misclassification of sonographic features and subsequent inaccurate recommendations for FNA. In addition, lack of access to real time imaging can compound misinterpretation of US findings.
2. Adoption of the standard Bethesda classification system for consistent reporting thyroid cytology. Since its inception in 2008, the 6-tiered Bethesda system is more widely used but there is still significant interobserver variation cytology interpretation [4] that can lead to misdiagnosis.
3. Understanding the malignancy risk associated with each cytology classification, specifically for nodules with the indeterminate cytology diagnoses of follicular lesion of undetermined significance (FLUS) and follicular neoplasm (FN). Recent publications have reported a wide range of associated malignancy rates (6-48% for nodules with FLUS cytology) [5] leading to confusion among endocrinologists about how to manage these patients.
4. Role of molecular testing. Currently there are several commercially available molecular tests or testing panels that have been proposed for use to better risk stratify patients with indeterminate thyroid nodules cytology. The optimal algorithm for using these tests is not defined [6].

LEARNING OBJECTIVES

As a result of participating in this session learners should be able to:

1. Identify the various sonographic imaging features of thyroid nodules and their association with thyroid cancer
2. Appreciate common pitfalls in interpretation of thyroid sonography
3. Understand the Bethesda classification of FNA cytology
4. Recognize the potential for molecular testing to improve cytologic diagnoses and understand the results of the current available tests

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

The recently published ATA) [2] and AACE [3] guidelines summarize the optimal approach to patient found to have thyroid nodules, with the goal of risk stratification for thyroid cancer as a rationale for FNA decision making.
A serum TSH level should be measured to assess thyroid function. If suppressed this may indicate that the nodule (s) is functioning and a radionuclide scan should be performed for evaluation. Nodules that accumulate I-123 more than the extranodular tissue are considered functioning and FNA is not recommended because of the very low risk of malignancy. However, some patients will have both functioning and nonfunctioning nodules present and the I-123 scan must be directly correlated with US imaging to determine nodule functionality. If nonfunctioning nodules are identified that meet sonographic criteria for FNA, then US-FNA should be performed prior to definitive therapy for hyperthyroidism since an indeterminate or suspicious cytology result may lead to surgery that would address both the thyroid structural and functional issues.

For euthyroid or hypothyroid patients, the next step in evaluation is thyroid US performed with a high frequency linear probe (10-14mHz). This technology has been widely adapted by endocrinologists caring for patients with thyroid nodules. In multivariable analyses, nodule sonographic features consistently associated with thyroid cancer include a solid composition, hypoechogenicity, presence of microcalcifications, irregular margins and a taller than wide shape (*see Table 1 [7]*).

The interobserver variability assessment of US features is dependent upon operator experience and the use of real time imaging or "clips". One of the most common errors is misidentification of microcalcifications in mixed cystic/solid nodules. Two pitfalls account for the most common misclassifications of hyperechoic spots within these nodules as microcalcifications. First, the back walls of the spongiform (see definition of spongiform below) nodule's internal small cystic components exhibit posterior acoustic enhancement that appears as a bright linear streaks (*Figure 1*). Second, although real time scanning demonstrates the classic comet tail or reverberation artifact of colloid crystals within cyst fluid, static images may capture just the "bright spot" without the reverberation.

Because of the recognition that certain sonographic characteristics are more likely to cluster together [8], risk assessment is optimally done by definition of US patterns rather than by single individual features

TABLE 1: Grayscale sonographic features reported to be associated with thyroid cancer [7]

	Median Sensitivity [range]	Median Specificity [range]
Hypoechoic c/w surrounding thyroid	81% [48-90%]	53% [36-92%]
Marked hypoechogenicity c/w strap muscle	41% [27-59%]	94% [92-94%]
Microcalcifications	44% [26-73%]	89% [69-98%]
Macrocalcifications	10% [2-17%]	94% [84-98%]
Absence of halo	66% [33-100%]	43% [30-77%]
Irregular, mircolobulated margins	55% [17-84%]	79% [62-85%]
Solid consistency	86% [78-91%]	48% [30-58%]
Taller than wide shape on a transverse view	48% [33-84%]	92% [82-93%]

(*Figure 2*).

- High risk: solid, irregular margins, microcalcifications, iso- or hypoechoic, taller than wide; presence of sonographically suspicious lymph nodes for metastatic thyroid cancer
- Intermediate risk: predominantly solid iso/hyper/hypoechoic nodules encapsulated nodules with a thick halo or a smooth border; cystic nodules where the solid component is uniformly solid
- Low risk: pure cyst, spongiform nodules (nodules with microcystic areas that comprise more than 50% of the nodule volume); mixed cystic solid nodules with a spongiform solid component

Based upon the high specificity >90% of the high risk US pattern, the recommended size cut-off for FNA of these nodules is lower than that for those with other US patterns. However, with the exception of a pure cyst, no sonographic pattern can exclude thyroid cancer and FNA is recommended for nodules with intermediate and low risk US patterns, but at higher size cut-offs. FNA recommendations have to be balanced with the recognition that up to 20% of nodules will yield indeterminate cytology, often leading to surgery and another 5-10% will be nondiagnostic with need for repeat FNA. Furthermore, ultrasound examination should include evaluation of the regional cervical lymph nodes, both in the lateral compartments (levels II-V) as well as the visualized central paratracheal area (level VI). Identification of sonographically abnormal cervical lymph nodes in the presence of a thyroid nodule strongly suggests thyroid cancer and FNA of the abnormal lymph node takes precedence over nodule FNA. The most current 2009 ATA recommendations [2] for FNA are listed in *Table 2* and include assessment of individual patient risk factors for thyroid cancer, such as family history, or history of childhood external beam radiation to the neck area as well as sonographic imaging features and nodule size cut-offs.

US guidance for FNA has become standard practice. Studies have reported both lower nondiagnostic and false negative rates with

FIGURE 1

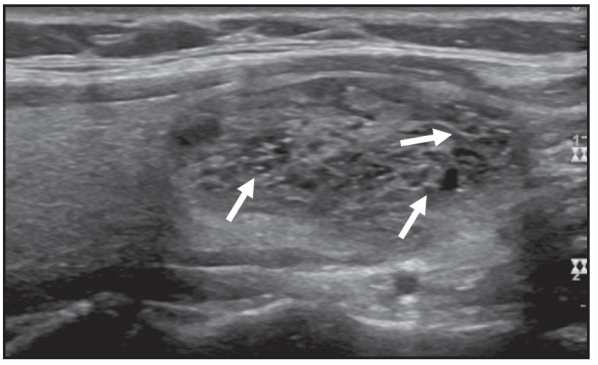


FIGURE 2

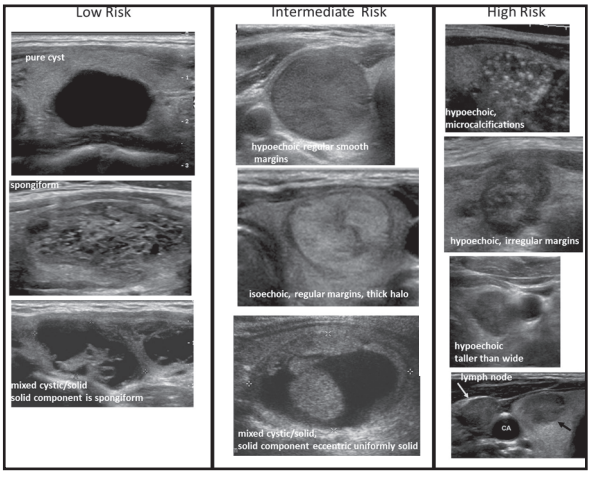


TABLE 2: ATA Guidelines for FNA of thyroid nodules [2]

Nodule sonographic/ Clinical Features	**Recommended nodule threshold size for FNA Strength of recommendation**
High risk history with suspicious sonographic features	>5 – 9 mm Recommendation level A
Abnormal cervical lymph nodes	All Recommendation level A
Microcalcifications present OR Solid and hyperechoic	≥1 cm Recommendation level B
Solid and iso- or hyperechoic	≥1 – 1.5cm Recommendation level B
Mixed cystic/solid and any suspicious ultrasound feature	≥1.5 – 2.0cm Recommendation level B
Predominantly cystic or spongiform nodule without suspicious ultrasound features	≥2cm Recommendation level C
Purely cystic lesion	FNA not indicated Recommendation level B

ultrasound guidance compared to FNA procedures performed by palpation. It is an office-based procedure that allows continuous real time visualization of the needle tip during the FNA procedure. Two methods for US FNA are employed. With the perpendicular approach, the needle enters perpendicular to the long axis of the transducer. With the parallel approach, the needle approaches the nodule just under the transducer and parallel to its long axis; it can be visualized along its length as it enters the nodule. A specimen for cytology is obtained either with the capillary technique, without applying suction, or with aspiration. The cytological specimen is prepared by making a slide smear or rinsing the needle in a liquid preparation.

FNA biopsy of thyroid nodules provides essential cytology information that allows the clinician to better stratify the likelihood of malignancy, reducing the number of surgeries for patients with benign nodules and appropriately triaging those with a higher likelihood of cancer to surgery. After ascertaining that adequate cellularity is present, cytology results had traditionally been categorized as benign, malignant and indeterminate, but terminology has varied significantly among laboratories, with some using subclassifications within the indeterminate group. To address these inconsistencies in reporting, in 2008 the National Cancer Institute (NCI) of the National Institutes of Health organized a conference of expert cytopathologists to standardize the reporting of FNA cytology, which led to the resulting 6 category scheme called the "Bethesda System" [1]. Each of its 5 diagnostic categories is associated with a risk estimate for thyroid cancer, and the indeterminate group was separated into three distinct diagnostic groups: atypia of uncertain significance (AUS)/follicular lesion of uncertain significance (FLUS) (cancer risk 10-15%); follicular neoplasm (FN) (cancer risk 20-30%); and suspicious for malignancy (SUSP) (cancer risk 50-75%) [1].

Over the last 5 years, the Bethesda system has been widely adapted and with recent estimates that about 15-20% of all FNA cytology results are diagnosed as FLUS or FN [9]. The traditional paradigm of care for this group of patients has involved diagnostic lobectomy for definitive histologic diagnosis. Recent studies have reported that repeat FNA cytology should be an option for patients with FLUS cytology because the repeat FNA can yield a benign cytology result in up to 50% [10]. The negative predictive value of a benign cytology result in such cases has a higher negative predictive value (NPV) than any of the currently available molecular tests.

In addition, molecular testing is rapidly emerging as a useful test in the evaluation of these cytologically indeterminate nodules with FLUS or FN results. Two commercial tests are available, with different test performance characteristics that can aid clinicians in either recommending surveillance or surgery. Both require RNA obtained from nodule FNA for analysis.

One approach is to identify specific mutations associated with key cell-signaling cascades known to be strongly associated with thyroid cancer. These include testing for point mutation in BRAF and RAS, both involved in the MAP Kinase pathway, as well as for rearrangements of RET/PTC (a tyrosine kinase proto-oncogene) and PAX8/PPARg (a transcription factor). Overall 70-75% of papillary thyroid cancers (PTC) harbor one of these mutations, with BRAF V600E being most common (present in 40%). The prevalence of the mutation/rearrangement also varies with the specific PTC subtype. For example, 60% of tall cell PTC is associated with BRAF mutations but RAS mutations are more common in the follicular variant of PTC (20%). Furthermore, about 70% of follicular thyroid cancers harbor mutations in KRAS codon12/13, HRAS or NRAS codon 61 or a PAX8/PPARg rearrangement [11]. However, since 30% of thyroid cancers do not express a mutation, this molecular test panel does not have optimal sensitivity, and the false negative rate is high. Hence, a negative result from this test panel does not assure benignity. In addition, since the majority of nodules with FLUS or FN cytology are benign (over 70%) the frequency of detecting these mutational markers is low for these cytology groups, but increases if applied to SUSP cytology

nodules. On the other hand, this panel has high specificity (>95%) and hence high positive predictive value (PPV), with the only false positive results associated with RAS mutations that prove to be follicular adenomas at surgery [12]. Therefore, the results from this test should not be used to counsel against surgical intervention, but the test can be helpful when deciding whether the initial surgical procedure should be lobectomy or thyroidectomy. In this scenario, it has been found to be cost effective, provided the cost of the test is less than $870.00 [13].

Another available test is a proprietary multigene expression classifier (GEC) developed in the USA that analyzes cellular RNA expression signatures based upon the pattern of expression of 142 different genes. The test was developed to have high sensitivity for detection of thyroid cancer, with the ultimate goal of leading to a high negative predictive value (NPV) in cytologically indeterminate nodules (FLUS or FN, malignancy risk ~25%) so that diagnostic lobectomy could be avoided if the test is considered negative. The GEC was recently validated in a prospective multicenter study [14]. Based upon GEC results, the nodule is classified as either benign or suspicious. For nodules with FLUS or FN cytology, the NPV of a benign result was 94%. However the NPV decreases significantly if the test is used for cytologically SUSP nodules where the a priori cancer risk is higher (60-75%); therefore, the GEC should not be performed for these nodules. In the validation study, the missed cancers among the FLUS or FN cytology nodules were largely attributed to borderline follicular cell nucleic acid content in the submitted samples. Cost effectiveness analysis of this test must take into account all of the costs of continued surveillance over a patient's lifetime and the possibilities of additional FNA, as well as the costs of missed cancers. The one published cost effectiveness analysis employed only a 5 year follow up period and was computed using higher sensitivity and specificity estimates than reported in the final validation study [15]. Therefore, it likely overestimates the cost savings of avoiding surgery with a benign GEC result compared to what should be expected in real practice.

Currently, both clinical experience with molecular testing and publications investigating the application of these molecular methods are limited. The performance of both the GEC and the mutation analysis panel are dependent upon the now well recognized interobserver classification of indeterminate nodule cytologies into the specific subcategories of FLUS, FN or SUSP [4]. This directly impacts the associated histologic malignancy rates and subsequently the NPV and PPV estimates associated with each molecular test. Ongoing research in this field will continue to identify new molecular markers and future clinical trials are needed that will better refine both the utility and limitations of these markers in clinical practice.

MAIN CONCLUSIONS

- Thyroid nodules are a common reason for endocrine referral, with a majority presenting as incidental findings on imaging studies performed for other indications
- Thyroid US is indicated for all patient with thyroid nodules to characterize the sonographic features of the nodule, assess nodule size, and to evaluate regional lymph nodes.
- The US pattern of the nodule's appearance confers a risk of malignancy, and this, in conjunction with nodule size and patient-specific risk factors for thyroid cancer, leads to recommended nodule size cut-offs for US FNA
- FNA cytology results should be reported using the Bethesda 6-tiered classification.
- Molecular marker testing should be considered for nodules with FLUS or FN cytology. Combined with cytology, these tests can better assess likelihood of benignity or malignancy and both reduce the number of lobectomies performed for benign disease and identify those patients for whom bilateral surgery is appropriate. Additional studies evaluating the performance of these tests in diverse clinical settings will better define their optimal use.

FIGURE 3

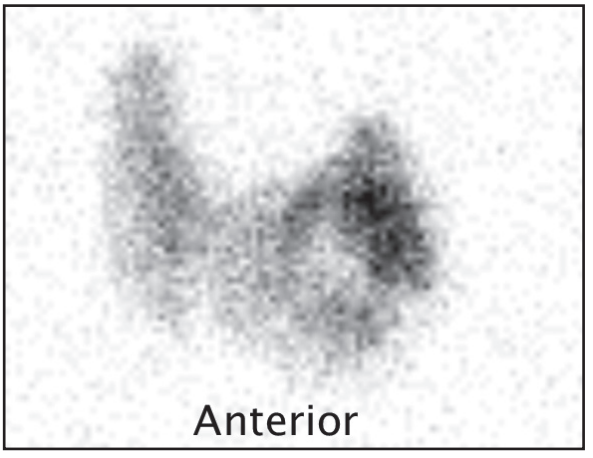
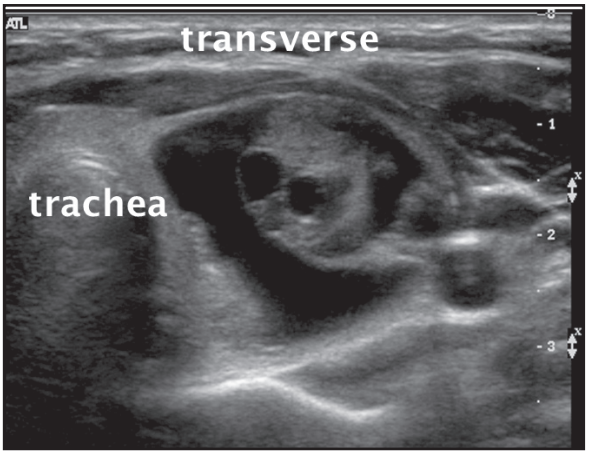


FIGURE 4



CASES WITH QUESTIONS AND DISCUSSION OF CASES AND ANSWERS

You are evaluating a 46 year old man whose primary care doctor palpated a nodular thyroid. He has no family history of thyroid cancer and no personal history of head or neck radiation. On questioning, he has noticed that when he runs his daily 5 miles, that his pulse is faster over the last 6 months and he has lost 3 pounds during the same period. On examination, his BP is 134/74 and his pulse is 88 bpm, which he says is above his historic baseline. You palpate a 3cm left mid/lower thyroid nodule. No enlarged cervical lymph nodes were detected. The rest of his exam was showed normal reflexes and no tremor.

Laboratory Results
Serum TSH 0.15mIU/L
Serum FT4 1.1ng/dL
Serum total T3 197ng/dL

What is the best next step in management?

A. Thyroid ultrasound
B. FNA of the left palpable nodule
C. I-123 thyroid scan
D. Start methimazole

Answer: C I-123 scan
The low serum TSH (in conjunction with the slightly elevated total T3) in the presence of thyroid nodular disease is indicative that the potential cause of the subclinical hyperthyroidism is autonomous nodule(s). Therefore, the next step should be to obtain an I-123 scan to assess the cause of the subclinical hyperthyroidism. Performing a diagnostic ultrasound most likely will also be required (see below) but this test should only be ordered after the I-123 scan if there is uncertainty about interpretation.

I-123 scan anterior view below (*Figure 3*); 24 hour radioiodine uptake 32%

What is the next best step in management?

A. US guided FNA of the cold nodule in the left mid to lower pole
B. Thyroid US
C. I-131 therapy of hyperthyroidism
D. ^{99m}Tc Pertechnetate thyroid scan

Answer: B Ultrasound imaging with real time correlation with the thyroid scan
The scan does not show the proverbial "hot" nodule which would appear as an area of uniform increased uptake of I-123. Rather at the location of the left palpable nodule, there are areas of both increased and decreased isotope uptake. Real time US scanning should be performed and compared with the I-123 scan to correlate location and composition of nodules (*Figure 4*). In the left mid/lower thyroid lobe, a mixed cystic solid nodule is identified on US. The solid component of this nodule is located superiorly and laterally, corresponding with the area of increased uptake on the I-123 scan. The remainder of the nodule's volume is cystic, corresponding with areas of decreased I-123 uptake. Since determination of nodule functionality is based

upon assessment of the isotope accumulation in the solid cellular component of the nodule, this patient has a Left mid/lower 3cm functioning nodule with cystic degeneration and FNA is not indicated for this left nodule.

US imaging of the right lobe detects 2 nodules. A right mid solid noncalcified isoechoic nodule measures 1.4x1.5x1.7cm. A right lower mixed cystic/solid noncalcified nodule 1.8x1.6x1.9cm

What do you next recommend?

A. US guided FNA of the RM nodule
B. US guided FNA of the RL nodule
C. Right lobectomy
D. Total thyroidectomy

Answer: A. RM nodule. See US imaging to be shown during MTP. Based upon the US of RM nodule, this falls into the intermediate risk for malignancy sonographic pattern. ATA guidelines recommend FNA for such nodules at a size cutoff of 1-1.5cm. The RL pole nodule has a spongiform appearance, an US pattern associated with a low malignancy risk and ATA guidelines recommend a size cutoff of 2cm for FNA consideration

US FNA is performed of the RM nodule is performed and the cytology is interpreted as "follicular lesion of undetermined significance" Bethesda classification class III.

What are the next options for this patient?

A. Right lobectomy
B. Repeat US FNA for cytology in 2-3 months
C. Repeat US FNA for molecular marker testing
D. Near total thyroidectomy

Answer: Several possibilities that will be discussed. See discussion in MTP for evaluation of nodules with FLUS cytology, including role of repeat FNA for cytology and molecular marker testing.

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Unusual or Perplexing Thyroid Cases

CMF01
Sunday, June 16
1:00–1:45 PM & 3:00–3:45 PM

Carla Moran, Mark Gurnell, Krishna Chatterjee
Institute of Metabolic Science, Addenbrooke's Hospital
Cambridge, UK

SIGNIFICANCE OF THE CLINICAL PROBLEM

The differential diagnosis of thyrotoxicosis with low uptake on thyroid scintigraphy includes both commonly and rarely encountered conditions; distinguishing between these can be challenging, and may involve investigations which clinicians only use rarely.

Raised thyroid hormones [TH: thyroxine (T4), triiodothyronine (T3)] with non-suppressed thyrotropin (TSH) levels are an important, and relatively commonly encountered, pattern of discordant thyroid function tests (TFTs); many cases are explained by confounding intercurrent illness, concomitant medication use, or analytical interference in TH or TSH assays, but differentiating between these and other rarer causes [e.g. Resistance to Thyroid hormone (RTH), TSH-secreting pituitary tumour (TSHoma)] can be difficult.

Misdirected investigation of these entities results in wastage of resources and/or incorrect therapeutic intervention.

BARRIERS TO OPTIMAL PRACTICE

Lack of familiarity with the rarer causes of thyrotoxicosis associated with low uptake on thyroid scintigraphy, and the investigations required to differentiate between these.

Limited knowledge/understanding of the conditions that cause hyperthyroxinaemia with non-suppressed TSH; failure to recognize the inherent susceptibility of commonly used laboratory assays for T4, T3 and TSH to analytical interference; relative rarity of RTH and TSHoma—differentiating between these conditions is often challenging, and typically requires a combination of investigations, several of which are only rarely undertaken in routine clinical endocrine practice.

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Identify potential causes of, and instigate relevant investigations to distinguish between, the different causes of thyrotoxicosis with low tracer uptake on thyroid scintigraphy.
- Reliably exclude common causes of hyperthyroxinaemia with non-suppressed TSH; adopt a systematic approach to distinguishing between RTH and TSHoma; appreciate the challenges inherent in managing cardiac hyperthyroidism in the setting of RTH or TSHoma.

STRATEGIES FOR DIAGNOSIS, THERAPY AND MANAGEMENT & CLINICAL PEARLS

Thyrotoxicosis With Low Uptake on Thyroid Scintigraphy

In the context of Graves' disease or toxic nodular goitre, a "falsely negative" thyroid uptake scan can occur following prior administration of iodinated contrast media; a recent study indicated normalization of raised urinary iodine levels 4 weeks after contrast investigation. Iodine-induced thyrotoxicosis usually occurs in patients with pre-existing foci of autonomy in a nodular gland or from iodine deficient areas.

Hyperthyroidism due to release of stored hormone, occurring in acute/subacute thyroiditis, can be associated with neck pain, raised ESR and thyroglobulin levels, and

reduced echogenicity and vascularity on ultrasound; thyrotoxicosis is self-limiting and may evolve to hypothyroidism if inflammation is severe.

Ectopic thyroid tissue may occur in any location from the mandible to the diaphragm and can be visualized by radioiodine scintigraphy. Hyperfunctioning autonomous nodules within ectopic thyroid tissue intensify tracer uptake, with corresponding reduced uptake in the eutopic location. Struma ovarii, a rare ovarian tumour (teratoma or dermoid) containing functional thyroid tissue, is infrequently (<8% of cases) associated with thyrotoxicosis. Isotope scanning reveals reduced thyroid uptake but abnormal pelvic tracer activity, congruent with local pain or a mass. Thyroglobulin levels are elevated.

The pattern of TFTs and hyperthyroidism (except with raised T3 and low T4 levels following liothyronine ingestion) in factitious thyrotoxicosis is not distinctive, such that making the diagnosis can be difficult and is one of exclusion—unless the patient admits to excess TH intake. Isotope scanning shows absent eutopic uptake and thyroglobulin levels are low with reduced gland vascularity. Faecal and urinary iodine excretion is increased. Management is challenging: ATD treatment is not effective, with abuse of this a possibility. If confidence in the diagnosis is high, symptomatic control with beta-blockade, together with psychiatric evaluation and counseling to prompt cessation of TH ingestion, is a rational approach.

Hyperthyroxinaemia With Non-suppressed TSH: Differential Diagnosis and Investigation

Altered serum binding proteins

1. Quantitative: Pregnancy, oestrogens (e.g. COCP, HRT, tamoxifen), hepatic disorders or, rarely, hereditary thyroxine-binding globulin (TBG) excess can raise TBG levels and hence total T4 and T3 (but free T4 and T3 are normal).
2. Qualitative: Dominantly-inherited genetic variants of albumin [familial dysalbuminaemic hyperthyroxinaemia (FDH)] or transthyretin [transthyretin-associated hyperthyroxinaemia (TTR-AH)], which alter affinity for iodothyronines, can cause FT4 (and less frequently FT3) to be overestimated, particularly in 'one-step' analogue hormone assays.

Assay Interference

TSH measurement

Most TSH assays use a 'sandwich' format with two antibodies—capture and (labeled) detection—directed against different epitopes on TSH, with the TSH moiety acting as a bridge between the two. The presence of human anti-animal antibodies (HAAs) in a patient's serum can interfere with TSH measurement if directed against the same species as the assay antibodies: thus, a HAA that blocks TSH binding to either capture or detection antibodies will result in 'negative interference', causing a falsely low TSH readout; conversely, a HAA that is capable of cross-linking the capture and detection antibodies may cause 'positive interference', leading to a falsely high TSH. Heterophile (weak, polyspecific) antibodies may cause similar interference. Laboratory strategies for confirming interference include the demonstration of the following:

1. Discordant TSH results in different assays that utilize different antibody pairs
2. Altered TSH result following immunosubtraction [using PEG or protein G/A]
3. Non-linear TSH measurement following sample dilution.

Free T4/T3 measurement

The relatively small size of T4 (and T3) precludes use of a 'sandwich' assay format, so 'competition assays' are commonly used; here, labeled T4 (the tracer) competes with serum T4 for a fixed number of anti-T4 antibody binding sites. Free hormone assays are designed such that the equilibrium between T4 and its binding proteins is conserved during measurement, so the amount of tracer displaced reflects the 'free' rather than 'total' hormone concentration. The presence of factors in serum which affect this equilibrium will confound hormone measurement. Examples include the following:

1. Fractionated and unfractionated heparin: both can cause an artifactual elevation

in measured concentrations of FT4 and FT3 by displacement of T4 and T3 from their carrier proteins; the mechanism is poorly understood, but is likely to involve generation of free fatty acids (FFAs) via heparin-mediated activation of endothelial lipoprotein lipase (LPL), with FFAs displacing TH from albumin.
2. Anti-iodothyronine antibodies which bind the tracer
3. HAAs or heterophilic antibodies that block the assay antibody
4. Variant TH binding proteins (e.g. FDH) with altered affinity for T4.

The use of a 'two-step' ('back titration') assay method or equilibrium dialysis (ED), which is less susceptible to such interference, is useful in confirming/excluding this possibility.

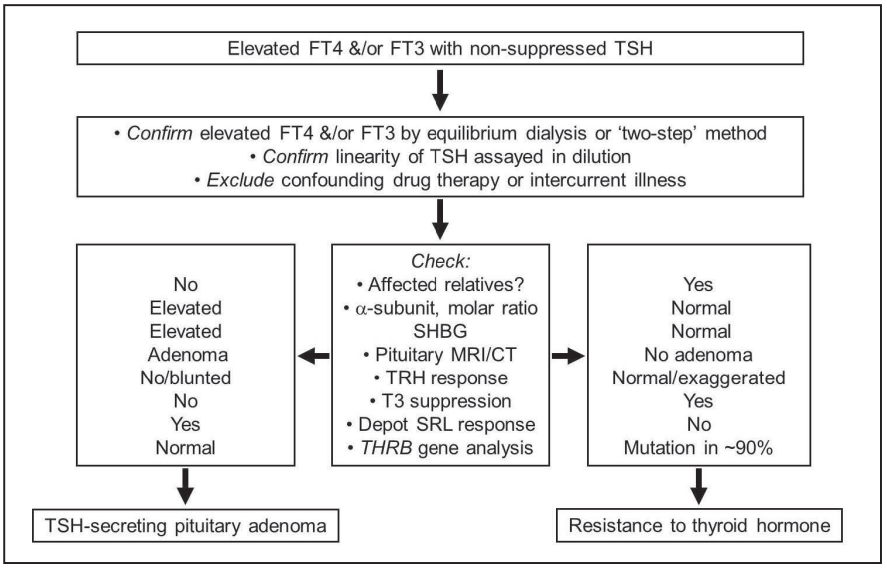
Thyroxine Therapy ± Poor Compliance
It is well-recognized that L-T4 replacement in physiological dosage to optimize TSH may be associated with mildly elevated FT4 (but normal FT3) levels in some patients. Owing to their differing half-lives, intermittent hormone ingestion may result in normal or even elevated TH levels, but fails to normalize TSH.

Drug Treatment
Amiodarone
Patients on amiodarone alone, or in combination with exogenous thyroxine, can exhibit elevated FT4 with normal TSH, but FT3 levels are usually normal.

Other agents
Propylthiouracil, glucocorticoids, propranolol and some iodinated contrast media or iodine-containing supplements/non-prescription medications can also reduce T4 to T3 conversion via a similar mechanism to amiodarone.

Non-thyroidal Illness (NTI)
Raised TH levels with non-suppressed TSH are a recognized pattern during non-thyroidal illness (NTI) including acute psychiatric states, but the abnormalities (which reflect a secondary adaptive response rather than primary hypothalamic-pituitary thyroid dysfunction) usually revert with recovery. If available, measurement of TH levels on a sample taken prior to the onset of NTI may confirm previously normal thyroid status.

Resistance to Thyroid Hormone (RTH) Versus TSH-secreting Pituitary Tumour (TSHoma)
RTH (estimated incidence 1 in 40-50,000 live births) and TSHoma (estimated incidence 1 per million) occur in patients of a similar age range and either gender. A subset of patients with predominant central/pituitary resistance (PRTH) also exhibit thyrotoxic symptoms and signs, such that these features are not discriminatory. An algorithm for distinguishing RTH and TSHoma is shown below:



However, several potential pitfalls should be kept in mind, including:

- Serum α-subunit: elevated levels are also found in non-functioning and GH-secreting pituitary tumors, while normal levels are a recognized finding in TSH-secreting microadenomas.
- SHBG: falsely low levels can occur in mixed GH/TSHoma due to inhibition of its synthesis by growth hormone; conversely, synthetic oestrogen therapy in RTH can falsely elevate SHBG.
- Pituitary imaging: TSH-secreting microadenomas may be difficult to visualize, while patients with RTH do harbor 'incidental' abnormalities on imaging; in addition, persistently elevated TSH levels following thyroid ablation in RTH, results in thyrotroph hyperplasia and pituitary enlargement.
- TRH test: 10–20% of patients with TSHoma show a preserved TSH response.
- THRB gene analysis: ~15% of RTH cases are not associated with THRB mutations.

Cardiac Hyperthyroidism in RTH and TSH-secreting Pituitary Tumour

The clinical phenotype of RTH is variable: asymptomatic individuals are classified as having generalized resistance (GRTH); patients with hyperthyroid features are deemed to have greater central or pituitary resistance (PRTH) than in peripheral tissues. Recognized hyperthyroid features in childhood include failure to thrive, accelerated growth and hyperkinetic behavior; in adults, lack of weight gain, palpitations, anxiety, insomnia and heat intolerance may be present. Although GRTH and PRTH can be associated with the same receptor defect—even within the same family—certain receptor mutations (R338W, R383H, R383C, R429Q) are more frequently associated with a PRTH phenotype.

Resting tachycardia is a feature in ~75% of GRTH and almost all cases of PRTH. Atrial fibrillation has been documented in 6% of RTH cases. Both of these features are less prevalent in RTH than conventional thyrotoxicosis; consistent with this, some (but not all) indices of cardiac contractility are in the thyrotoxic range in RTH, suggestive of a partially hyperthyroid myocardium in this disorder. Beta-blockade is the mainstay of controlling either tachycardia or ventricular response in AF associated with RTH; propranolol has the added benefit of inhibiting T4 to T3 conversion. In RTH cases with both cardiac and generalized hyperthyroid features, the use of triiodothyroacetic acid (TRIAC), a hormone analogue with greater central than peripheral thyromimetic activity, which inhibits TSH secretion and thereby lowers TH levels, is effective. Except in cases of severe cardiac failure, thyroid ablation (surgical, radioiodine) is not advocated: postablation, under-replacement with thyroxine is associated with chronically raised TSH levels, with attendant risk of pituitary hyperplasia; conversely, supraphysiological hormone replacement risks cardiac hyperthyroidism and recurrent AF.

Although tissue sensitivity to TH is normal in patients with TSH-secreting pituitary tumours (TSHomas), clinical features of hyperthyroidism are less evident than expected. Thus, their resting heart rate is comparable to RTH or thyrotoxicosis, with atrial fibrillation or cardiac failure occurring in ~6% of cases. Pituitary surgery or primary/adjunctive long-acting somatostatin analogue therapy are effective therapeutic approaches in this disorder.

Future prospective studies in RTH and TSHoma are warranted to determine whether the risk factors for developing AF and cardiac complications are similar to those identified (age, hypertension, cardiac hypertrophy, metabolic dysfunction) in conventional thyrotoxicosis.

CASES WITH QUESTIONS

Case 1

A 28-year-old woman presented with palpitations and breathlessness. She had a family history of thyroid disease. Examination revealed a fine tremor, warm peripheries and a resting tachycardia (120bpm). Thyroid function tests (TFTs) showed: TSH <0.03 mU/L (RR 0.35–5.5), free T4 (FT4) >150 pmol/L (RR 10–19.8), free T3 (FT3) >30 pmol/L (RR 3.5–6.5). The anti-TSH receptor antibody (TRAb) titre was 0.4 IU/L (NR 0–1). A thyroid isotope scan revealed no uptake.

Questions

1. ***What are the potential causes of thyrotoxicosis in this patient?***
2. ***How would you investigate further?***

Answers

1. The clinical features and TFTs are consistent with thyrotoxicosis. The negative TRAb result and absent uptake on isotope scan are not consistent with either Graves' disease or autonomous thyroid function (e.g. toxic nodular goitre). Thyroiditis (acute/subacute or postpartum) is a possibility. Iodine-induced thyrotoxicosis, following exposure to this trace element in drugs (e.g. contrast agents, amiodarone) or diet (e.g. kelp, nutritional supplements) should be considered. Rarely, autonomous hyperfunction of ectopic (mediastinal, struma ovarii) or extrathyroidal neoplastic thyroid tissue has been described. Finally factitious thyrotoxicosis should be considered.
2. An antecedent history of prodromal illness, neck pain, pregnancy or excess iodide exposure (drug, dietary) should be sought. Ancillary investigations that may aid discrimination include ESR (raised in acute/subacute thyroiditis), vascular flow on Doppler ultrasound (reduced in thyroiditis, factitious), serum thyroglobulin (raised in thyroiditis, struma ovarii; low in factitious) and whole body radioiodine scan to detect ectopic or extrathyroidal tissue. Markedly elevated faecal thyroxine or urinary iodine levels can indicate factitious thyrotoxicosis.

Case 2

A 50-year-old woman was diagnosed with a 5cm papillary thyroid cancer and underwent total thyroidectomy followed by ablative radioiodine treatment. She was commenced on suppressive levothyroxine (L-T4) therapy, but despite taking up to 350 mcg/day (body weight 65kg), which resulted in marked thyrotoxic features (tremor, palpitations, weight loss, heat intolerance) and raised TH levels [FT3 8.1 pmol/L (RR 3.5–6.5)], TSH remained unsuppressed [lowest TSH=0.59 mU/L (RR 0.35–5.5)].

Questions

1. ***What are the possible causes for a non-suppressible TSH in this patient?***
2. ***How would you investigate and manage this case?***

Answers

1. The patient has discordant TFTs, with exogenous hyperthyroxinaemia failing to fully suppress pituitary TSH secretion. Intermittent compliance with L-T4 therapy should be considered (intake of L-T4 just prior to testing results in elevated TH levels, but fails to suppress chronically raised TSH). Otherwise, the clinical features and elevated FT3 indicate the patient is genuinely thyrotoxic, suggesting that the TSH is the discordant test result. Analytical interference in the TSH assay may result in measurable TSH, even when its levels are completely suppressed. If true hyperthyroxinaemia with non-suppressed TSH is confirmed, the possibility of a second disorder, in particular Resistance to Thyroid Hormone or a TSH-secreting pituitary tumour (TSHoma), confounding management of the thyroid cancer, must be considered,.
2. Before embarking on further investigations (laboratory, radiological and possibly genetic), check the patient's compliance with L-T4 therapy (ensure she understands the rationale for using higher, suppressive, doses of thyroxine in this setting). Next, consider the possibility of artifactual laboratory results—either FT4 and FT3, or TSH; initially, TSH assay interference should be excluded, either by serial sample dilution or immunosubtraction. Once true hyperthyroxinaemia with non-suppressed TSH is confirmed, measurement of sex hormone binding globulin (SHBG), alpha-subunit, TSH response to TRH (± L-T3 suppression), THRB gene screening and pituitary imaging help discriminate RTH from TSHoma. In either case, complete TSH suppression may prove difficult to achieve even with targeted therapy [e.g. supraphysiologic L-T4 in RTH; pituitary surgery ± somatostatin receptor ligand (SRL) in TSHoma], and careful surveillance

(thyroglobulin, RAI scan, neck ultrasound) to detect thyroid cancer recurrence is required.

Case 3

A 19-year-old man presented with atrial fibrillation (AF). FT4 was elevated [30 pmol/L (RR 10–24)] with non-suppressed TSH [1.8 mU/L (RR 0.4–4). Subsequently, he suffered recurrent episodes of AF (aged 25, 28 & 30 yrs), which were refractory to cardioversion until treatment with amiodarone was introduced. Eleven months later, FT4 levels were markedly raised (>100 pmol/L) with suppressed TSH (<0.1mU/L). Amiodarone was discontinued. After six months of carbimazole therapy TFTs reverted to the previous pattern (FT4 32 pmol/L, TSH 1.3 mU/L) and the antithyroid drug (ATD) was discontinued. However, two months later, raised TH [FT4 35 pmol/L (RR 10–25), FT3 10 pmol/L (RR 2.6–7)] and subnormal TSH (0.02 mU/L) were again noted, and ATD treatment was restarted. Although his FT4 normalized [19 pmol/L (RR 10–25), TSH levels rose (11 mU/L (RR 0.35–5) and his AF recurred.

Questions

1. ***What is the differential diagnosis of this case at first presentation?***
2. ***Why will management of his recurrent hyperthyroidism and AF be a challenge?***

Answers

1. The patient had elevated FT4 with inappropriately normal TSH levels. Congruence of this biochemical abnormality together with refractory atrial fibrillation (a known feature of hyperthyroidism), suggests that FT4 levels are truly raised; following exclusion of a falsely normal TSH due to assay artefact, the differential diagnosis is between Resistance to Thyroid Hormone (RTH) and a TSH-secreting pituitary tumour (TSHoma). Cardiac hyperthyroidism, including AF, is a recognized feature of both entities.
2. In the context of recurrent hyperthyroidism, the likelihood of long-term maintenance of sinus rhythm is low. A further course of ATD therapy is one option, but a previous course of treatment failed to induce sustained remission. Thyroid ablation (surgical, radioiodine) is an alternative option: however, if undertaken in the context of RTH, appropriate dosage of subsequent thyroxine therapy is difficult to determine and under replacement risks chronically elevated TSH levels with attendant pituitary thyrotroph hyperplasia; thyroid ablation in the context of TSHoma may result in tumour progression. Whether additional risk factors (e.g. aberrant conduction pathways) predispose to AF in the context of RTH or TSHoma remains unknown.

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The Papillary Microcarcinoma Epidemic: Ignore, Observe, or Treat?

M9
Saturday, June 15
3:00–3:45 PM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Micropapillary cancers are defined as papillary cancers 10 mm or less. They represent an increasing percentage of all patients with thyroid cancer. A full understanding of their natural history is essential to prevent overzealous treatment and associated complications.

Autopsy studies:

Up to a 13% prevalence in the United States (average 6%)
Up to a 36% prevalence in Europe (Finland)
Not significantly dependent on age
7% under age 50 or over age 80 in Sweden
3% in young adults in Wisconsin
Incidental finding at time of thyroid surgery
2-24%
Increasing papillary cancer incidence in the United States (all sizes), especially women
4.85 / 100,000 in 1975
11.99 / 100,000 in 2007
Percentage of micropapillary cancers among all papillary cancers excised

5 %	1960-1980	Queen Elizabeth Hospital, Hong Kong
22 %	1991-2000	Queen Elizabeth Hospital, Hong Kong
40 %	2006	University Ferrara, Italy
43 %	2006	University Wisconsin, US
50 %	2008	Jewish General, Montreal, Canada

BARRIERS TO OPTIMAL PRACTICE

- Cancer phobia
- Overzealous treatments
- Case reports that demonstrate the exception, rather than the rule

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

1. Appreciate the natural history of papillary microcarcinoma
2. Formulate a rational approach for surgery and adjunctive radioiodine

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Scope of the Problem

- US population is over 300 million
- 6 % prevalence of micropapillary cancer in the US = 18 million people
- Prevalence of all sizes of papillary cancer in 2007 = 434,256 (SEER database)
- Therefore only 2.5 % of micropapillary cancers have come to clinical attention!
- Improved imaging and diagnostics will allow us to find the rest of them?
- Observational Trial (Ito et al, Japan) 340 of 1395 patients with biopsy-proven micropapillary cancer agreed to observation
- Exclusion criteria: tumors adjacent to trachea or possibly adjacent to the nerve (posterior), tumors associated with lateral nodes, high grade histology 28 % were multifocal and 9 % had suspicious central nodes on ultrasound
- With up to 10 years of follow-up (mean 74 months), over 60 % did not grow, and over 10 % regressed. 9% grew to >10 mm, 9% grew by 3 mm, and 2% developed lateral nodes.
- No difference in outcomes among those patients having surgery at diagnosis, and those in whom surgery was delayed.

- Data support concept of avoiding FNA in subcentimetric nodules (even suspicious nodules) under 10 mm.

Clinical Series

Mayo Clinic: average follow-up 17 years (6 to 89 years)
- Multifocal 23 %
- Bilateral 17 %
- Extrathyroidal 2 %
- Nodal involvement 30 %
- Distant metastases 0.3 %
- 40-year disease specific mortality 0.7 %
- all three patients who died had lymphadenopathy, massive in one
- one had pulmonary metastases on presentation
- recurrence rate: 8 %
  - 1.5 % in thyroid bed, the rest in nodes
  - 0.8 % if no nodes at presentation and 16 % of patients with nodes at presentation
  - 11 % in patients with multifocal disease, 4% in those with unifocal tumors

Noguchi Thyroid Clinic: average follow-up 15 years
- 0.2 % distant metastases
- 3.5 % recurrent disease
- recurrence more likely if tumor >5mm, nodal disease, or extrathyroidal invasion

Queen Elizabeth Hospital, Hong Kong
- 1 % pulmonary metastases and death
- 5 % nodal recurrences
- 1 % recurrence in the bed
- recurrence risk increased 6.2 times if nodes present initially and 5.6 times when multifocal

Asan Medical Center, Seoul, Korea
- 4.8 % recurrence
- no deaths reported, but one patient (0.3 %) with progressive disease

Yonsei University, Seoul, Korea
- 24 % central nodes
- 4 % lateral nodes

Initial Surgery

National Thyroid Cancer Treatment Cooperative Study Group (NTCTCSG)
- 6.2 % recurrence, 38 % multifocal
- patients who had less than a total thyroidectomy
- recurrence rates
  - multifocal disease 18 %, unifocal disease 4 %
  - patients with multifocal disease
  - total thyroidectomy 6 %, less than a total thyroidectomy 18 %

SEER database 1988 to 2005
- 99.9 % 15-year disease-free survival regardless of total versus lobectomy

Completion Thyroidectomy

No data. Assess contra-lateral lobe with ultrasound.

Node Dissection

Therapeutic—if nodes detected on pre-op imaging

Prophylactic?

One study (Wada et al) compared three groups for recurrence:
- Therapeutic n=24 recurrence rate 21 %
- Prophylactic n=235 recurrence rate 0.4 %
- None (incidental) n=155 recurrence rate 0.7 %

Argument A

If you do a central node dissection and nodal disease is detected the patient will benefit from radioiodine (but see below)

Argument B

If you do a central node dissection, you have removed potentially persistent disease and the patient does not need radioiodine.
- Ito et al: stage 1 papillary thyroid cancer
- 96 % had central node dissection
- 57 % positive nodes
- 0.1 % had radioiodine
- recurrence rates 2 % after a mean 91 months (range 6 to 240 months)
- Benefit: recurrence rate falls from 6 to 2 %
- Risks: increased hypoparathyroidism and recurrent laryngeal nerve injury
- Reserve central node dissection for those with central node recurrences
- Radioiodine

NTCTCSG
- Recurrence was higher in multifocal (7 %) versus unifocal (2 %) disease
- Radioiodine did not reduce recurrence rates in multifocal disease
- Radioiodine did not reduce recurrence rates in patients with positive nodes

Mayo Clinic
- Radioiodine did not alter recurrence in patients with node-negative disease
- Recurrence was increased in patients with node-positive disease who received radioiodine

SEER Database (1998 to 2005)
- 99.9 % 15-year disease-free survival regardless of the use of radioiodine

MAIN CONCLUSIONS

Since observed micropapillary cancers demonstrate indolent growth over many years, routine biopsy of subcentimetric thyroid nodules should be discouraged.

Where high-volume thyroid surgeons are available, a total thyroidectomy is the surgical treatment of choice for micropapillary cancer due to the high incidence of multifocality, and a reduction in recurrence rates with more extensive surgery.

The complications associated with prophylactic central node dissection may exceed the benefit of this procedure.

Radioiodine is rarely indicated for treatment of micropapillary cancer.

CASES WITH QUESTIONS

Case 1

28 year-old woman felt something in her throat. Ultrasound—8 mm hypoechoic nodule with microcalcifications.

Questions

1. Should she have an FNA?
2. FNA was suspicious for papillary cancer. Should she have BRAF?
3. There were no nodes seen on her ultrasound. What surgery should she have?
4. Pathology shows an 8 mm papillary cancer, classic variant
5. There was a 1 mm metastatic focus in a perithyroidal node. Would you give her radioiodine? How much?

Case 2

42 year-old woman with a 2 cm thyroid nodule, biopsy was FLUS and she had a hemithyroidectomy. Pathology was a benign 2 cm adenoma, and a 3, 2, 2, and < 1 mm papillary cancer. No nodes were dissected. Pre-operative ultrasound shows a 1.5 mm nodule in the contralateral lobe.

Questions

1. Should she have a completion thyroidectomy?
2. If one were done, would you then give her radioiodine?

DISCUSSION OF CASES AND ANSWERS

Case 1

FNA should be discouraged in patients with subcentimetric nodules in the absence of nodal metastases. Data on the use of BRAF are controversial, but even if one could convincingly demonstrate that BRAF patients are more likely to have nodal metastases, the overall excellent prognosis in these patients suggests that it is premature to use BRAF as an excuse to treat patients more aggressively. If a high-volume thyroid surgeon is available, the patient should have a total thyroidectomy. There is no data to suggest a benefit of radioiodine for this patient, especially for such a trivial metastatic focus. Over half of these patients will have minimal nodal involvement.

Case 2

There are no data regarding the use of a completion thyroidectomy in this setting. While one could argue for it, based on data demonstrating reduced recurrences in patients who have had a total versus less than a total thyroidectomy (see above), the issue is whether the benefit justifies the potential cost and complications. It may be more rational to monitor and repeat surgery only when a recurrence is documented. There is no evidence that radioiodine improves outcome in multifocal disease.

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Thyroglobulin Assays: Are They Sensitive Enough?

M20
Sunday, June 16
8:00–8:45 AM & 5:45–6:30 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

Thyroglobulin (Tg), the glycoprotein precursor for the thyroid hormones Thyroxine (T4) and Triiodothyroinine (T3) is only synthesized by the thyroid gland. The recognition of the tissue-specific origin of the circulating Tg concentration has led to serum Tg measurement becoming firmly established as the primary tumor-marker for monitor patients with differentiated thyroid cancer (DTC) (1) in whom recurrences can occur decades after initial thyroidectomy. As shown in *Table 1*, over the last four decades Tg measurement methodology has involved Radioimmunoassay (RIA), Immunometric Assay (IMA) and most recently Tandem Mass Spectrometry (LC-MS/MS) (2-5). Each class of method (RIA, IMA or LC-MS/MS) has inherent sensitivity and specificity limitations that impact the clinical utility of the test. In particular, sensitivity can vary 10-fold among different manufacturer's assays belonging to the same class of method. It is important for physicians to understand how Tg assay sensitivity is determined in order to facilitate dialogs with the laboratory concerning the clinical need for Tg method sensitivity and how changes in the Tg method can disrupt the monitoring of DTC patients.

BARRIERS TO OPTIMAL PRACTICE

The interface between laboratories and the physicians they serve is often weak, such that physicians have little say in the Tg method selected by the laboratory despite a ten-fold difference in sensitivity between methods that can negatively impact patient care. It is well established that Tg monitoring of DTC patients may be disrupted inadvertently by changing the method as a result of the patient changing physicians or insurance. As shown in *Figure 1*, the mean serum Tg concentration in euthyroid normal individuals approximates 12 ng/mL (μg/L) (6). After thyroidectomy, approximately one gram of normal remnant tissue is left around critical structures. This is expected to produce approximately 1.0 ng/mL (μg/L) Tg in the circulation when TSH is in the euthyroid range, and approximately 0.5 ng/mL (μg/L) when TSH is suppressed. Given that the thyroid size of such subjects approximates 12 grams; this suggests that the relationship between thyroid mass in grams and serum Tg concentration is as follows:

1.0 gram of thyroid tissue produces 1 ng/mL (μg/L) Tg in the circulation

As shown in *Figure 1*, the functional sensitivity FS of most assays still only approximates 0.5 to 1.0 ng/mL (μg/L)—very close to the lower limit of euthyroid subjects with an intact thyroid gland. This level of sensitivity is clearly inadequate for detecting low amounts of Tg secreted by small thyroid remnants or persistent/recurrent tumor – especially when the tumor is an inefficient Tg secretor (7).

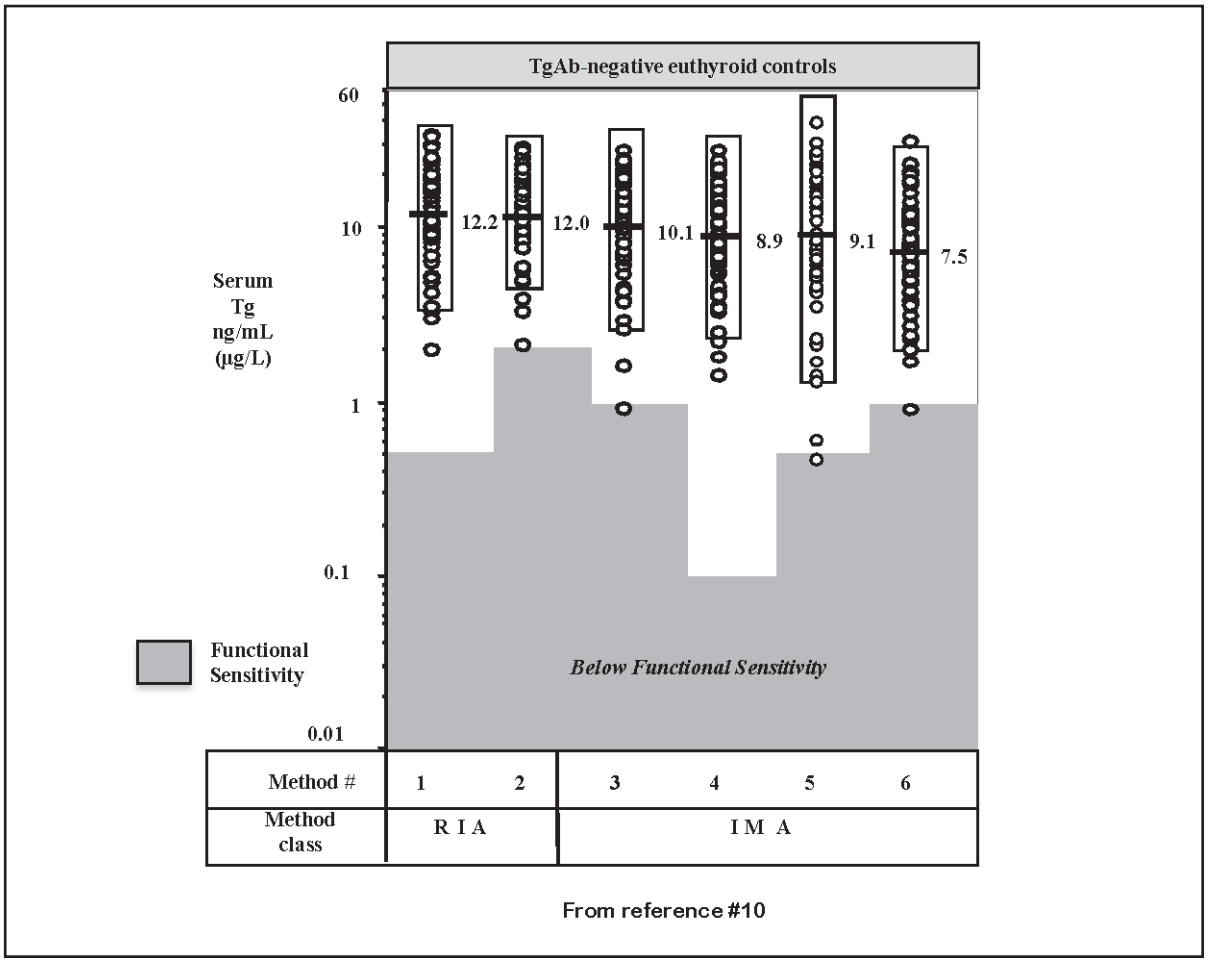
LEARNING OBJECTIVES

- To recognize that the functional sensitivity potential of the three classes of Tg method (IMA, RIA and LC-MS/MS) are different
- To understand how generational Tg assay nomenclature relates to functional sensitivity
- Recognize the advantages of monitoring 2nd generation basal Tg trends vs. rhTSH-stimulated Tg

TABLE 1: Classes of Thyroglobulin (Tg) Methodology

assay class	Principle	Turn-around time	• Functional Sensitivity (FS) • Strengths/Pitfalls
Immunometric Assay (IMA) (1990-present)	Format: Non-competitive Uses monoclonal Abs (MAbs)	hours *(can be automated)*	• FS between 1.0 and 0.05 ng/mL • prone to HAMA & TgAb interferences • limited MAb epitope specificity to detect abnormal tumor Tgs
Radio immunoassay (RIA) (1973-present)	Format: Competitive Uses apolyclonal Ab (PAb)	~6 days *(difficult to automate)*	• FS~0.50ng/mL • broad PAb specificity for detecting abnormal tumor Tgs • no HAMA interference • resistant to TgAb interference
Tandem mass spectrometry LC-MS/MS (2009-present)	**SpecimenPreparation:** 1. +/- immunoaffinity PAb enrichment 2. reduction+/-alkylation 3. Trypsin digestion 4. Tg peptide immunoaffinity enrichment **Analysis:** 1. target peptide detected by LC/MS/MS	? 1-2 days *(specimen preparation difficult to automate)*	• FS ? 1.0-2.0 ng/mL • no TgAb or HAMA interference expected • ? target peptide(s)may not be produced when there are Tgpolymorphisms

FIGURE 1



SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

Strategies for Determining Tg Assay Sensitivity and Overcoming Assay Insensitivity

When the sensitivity of the measurement for an analyte critically impacts the clinical utility of the test (e.g. TSH and Tg measurements), laboratories and manufacturers have a tendency to misrepresent assay sensitivity by using meaningless descriptive terms like "ultrasensitive" and "supersensitive" for marketing purposes. These descriptive terms do not help laboratories distinguish between the sensitivity of different manufacturers' methods or allow laboratories and physicians to select between methods based on their functional performance in clinical practice.

Analytical sensitivity: A within-run sensitivity parameter

The within-run mode of measurement obviously gives the best precision (lowest coefficient of variation, % CV) across the range of measurement. Analytical sensitivity is a within-run parameter that is most favored by manufacturers and the one typically cited in the kit package insert. Analytical sensitivity is usually calculated as the 97.5 percentile of the signal generated by 20 replicates of the zero calibrator matrix. This measure of sensitivity is a far more optimistic estimate than achieved by the method used under typical clinical practice conditions, where serum is the matrix and often the clinical question is: "has the Tg concentration risen into the detectable range over time between specimens drawn and measured months apart?" Over time there may have been instrument and reagent-lot changes as well as other variables that affect the precision of low range measurement.

Functional sensitivity: between-run sensitivity parameter

The discordance between the reliability of detecting low analyte concentrations under conditions encountered in clinical practice and the overly-optimistic analytical sensitivity estimate has necessitated establishing a scientific definition for assay "functional sensitivity". This functional sensitivity parameter is designed to represent the lowest analyte concentration that can be reliably detected using the analyte-specific clinical interval between specimens - which in the case of serum Tg used to monitor DTC patients for recurrence is 6 to12 months. In short, functional sensitivity is defined as the serum Tg concentration associated with 20 percent coefficient of variation (CV) taking into account the fact that the precision profile of any assay erodes over time, especially in the low range because of differences in reagent lots, instrument recalibrations, temperature effects and intangible operator and other factors (9).

The wide differences in functional sensitivity between assays shown in *Figure 1* has prompted adopting a generational nomenclature system for Tg assays, similar to that now established for TSH, whereby each subsequent generation has an order of magnitude (10-fold) greater functional sensitivity (FS):

- 1st generation Tg assays characterized by FS between 0.5 and 1.0 ng/mL (μg/L)
- 2nd generation Tg assays characterized by FS between 0.05 and 0.10 ng/mL (μg/L)
- 3rd generation Tg assays characterized by FS between 0.005 and 0.01 ng/mL (μg/L) (*Box 1*)

Recombinant human TSH-stimulated Tg testing: Used to overcome 1st generation Tg assay insensitivity.

The profound TSH stimulato ry effect on Tg secretion has been recognized for more than 40 years (9). In many cases, TSH stimulation can unmask persistent/recurrent DTC in patients hitherto believed disease-free who have a low basal Tg measured when TSH is suppressed. Historically, thyroid hormone withdrawal prior to radioiodine administration has been used to raise endogenous TSH, or in the 1970s 10 IU bovine TSH was administered by i.m. injection. Subsequently this practice has been abandoned after it became recognized that bovine TSH induced anti-TSH antibodies (10).

Following the approval of recombinant human TSH (rhTSH) for clinical use in 1999 (11), rhTSH-stimulated Tg testing became widely adopted as a means to overcome 1st

BOX 1

Functional Sensitivity (FS) reflects the low-end, between-run assay precision – i.e. it represents the lowest analyte concentration that can be reliably detected in serum under typical clinical conditions used for patient testing (8).
For serum Tg measurement, functional sensitivity is defined as the serum Tg level that can be measured:

- using direct IRP "CRM-457" standardization
- with 20% between-run coefficient of variation (CV)
- in a low Tg human serum pool (not an artificial matrix)
- in multiple runs made over 6-12 months (typical clinical interval)
- using ≥ 2 lots of critical reagents, calibrators and instruments (if > than one instrument employed)

Note: TgAb+ pools are needed for determining FS for RIA and LC-MS/MS used for TgAb+ sera

generation Tg assay insensitivity and stimulate radioiodine uptake, while maintaining the patient's quality of life by not interrupting L-T4 therapy (12). Early multicenter studies found rhTSH stimulation was comparable to thyroid hormone withdrawal, using a I^{131} diagnostic whole body scan (WBS) as the endpoint to detect either disease or remnant tissue in the thyroid bed (11). This study evaluated serum Tg cutoffs of 2 versus 5 ng/mL to detect thyroid tissue and found that rhTSH was equivalent to thyroid hormone withdrawal for detecting normal thyroid tissue and metastatic tumor (11). A consensus cut-off of 2 ng/mL (μg/L) was subsequently widely adopted and became recommended by current guidelines (1,13).

There are a number of limitations to using the rhTSH-stimulated Tg consensus cutoff of 2.0 ng/mL (μg/L) to detect persistent/recurrent DTC. These include:

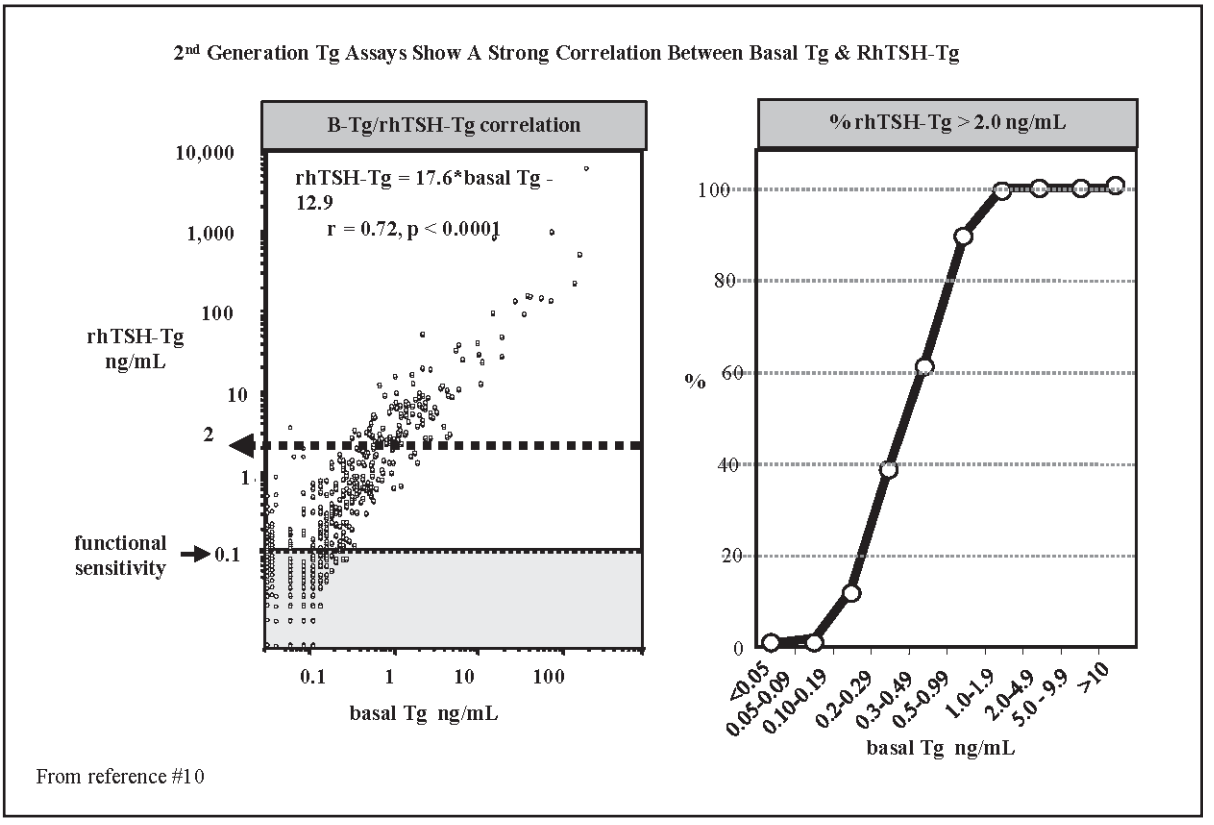
- Despite a high negative predictive value (>95 percent), the positive predictive value of rhTSH-Tg is low (< 50 percent) (14).
- The use of a fixed Tg cutoff is problematic given the two-fold difference in the numeric values reported by different Tg assays (2,3).
- The magnitude of rhTSH-Tg stimulation varies depending on the absorption from the injection site, surface area and patient age (15-17).
- The magnitude of the rhTSH-Tg fold response (rhTSH-Tg/basalTg) is patient-specific and depends on the TSH sensitivity of the Tg-secreting tissue, - and thus relates to the degree of differentiation of the tumor (7, 18,19)

Monitoring basal Tg measured by 2nd generation assays [FS 0.05 – 0.10 ng/mL (μg/L)] vs. rhTSH-stimulated Tg.

Second generation assays with FS between 0.05 and 0.10 ng/mL (μg/L) have been available for more than ten years (20-22). When these assays were used for rhTSH-stimulated Tg testing they initially sparked controversy because many patients hitherto thought to have an "undetectable" serum Tg using a 1st generation method had detectable both basal and rhTSH-Tg in the 0.10 – 1.0 ng/mL (μg/L) range when measured by a more sensitive 2ndgeneration method (23). The problem was that historically an "undetectable" serum Tg has been considered indicative of the absence of disease, without taking account that Tg "undetectability" is merely a reflection of assay functional sensitivity. Obviously, when "undetectable" is used as a Tg cutoff an increase in the assay's FS will increase diagnostic sensitivity at the expense of a loss in diagnostic specificity (3).

There is clearly a strong relationship between the basal Tg concentration (measured in the low TSH state) and TSH-stimulated Tg (*Figure 2*) (24). This relationship is in accord with the basal Tg/bovine TSH stimulated-Tg relationship described in the 1970s. It follows that the likelihood of having a rhTSH-stimulated Tg value reach the consensus cutoff of 2.0 ng/mL is directly proportional to the basal Tg concentration. Studies have now determined that the magnitude of the rhTSH fold response (rhTSH-Tg/basal Tg) is patient-specific, probably reflecting the TSH sensitivity of thyroid tissue (normal remnant +/- tumor) (19). It is now recognized that following the first rhTSH test subsequent tests yield little

FIGURE 2



information, especially when basal Tg can be detected using a 2nd generation assay (25,26).

Early studies made with 2ndgeneration methodology reported the superior clinical sensitivity of monitoring the basal Tg trend (without TSH stimulation) as compared to using TSH stimulation (21). More recently the basal Tg doubling time has been reported to have prognostic value (27). This concept is in accord with other tumor marker tests such as calcitonin doubling time used for as a prognostic factor for medullary thyroid cancers.

MAIN CONCLUSIONS

Current Tg methods are based on IMA, RIA or LC-MS/MS methodology. Each class of method differs with respect to its sensitivity potential. It is critical that sensitivity be determined as functional sensitivity calculated according to current guidelines. The IMA class of methods is most widely used, however, individual methods within this class can display ten-fold differences in functional sensitivity, FS [1st generation FS = 1.0 to 2nd generation assays FS = 0.10 ng/mL (µg/L)]. Thyroid tumors differ in their efficiency for secreting Tg and responding to TSH stimulation, especially when less well-differentiated, as suggested by having impaired iodine uptake or BRAF mutations. Papillary thyroid cancers tend to metastasize to lymph nodes which may be too inefficient a Tg secretor to give rise to a circulating Tg concentration above 1.0 ng/mL (µg/L), even when stimulated with rhTSH. It follows that assay sensitivity will critically impact the clinical utility of the Tg method. Basal Tg monitoring using 2nd generation methods [FS ~ 0.10 ng/mL (µg/L)] is rapidly becoming the standard of care. With this level of functional sensitivity inconvenient and expensive rhTSH-stimulated Tg testing is unnecessary. In the future, 3rd generation assays with functional sensitivities between 0.05 and 0.005 ng/mL (µg/L) may further improve the ability to detect metastatic lymph nodes and tumor tissue that is inefficient in secreting Tg.

BOX 2

Treatment	FNA	Before Tx.	L-T3 50ug	RAI 5.6 mBq	L-T4 125 µg
Date	8/10/09	9/3/09	10/20/09	11/2/09	5/10/10
Serum Tg (2nd gen) ng/mL (µg/L)		12.50	0.90	7.80	0.31
Serum TSH mIU/L		3.10	0.10	45	0.05
Fold response (rhTSH-g/bTg)				8.7	

Treatment	72hr rhTSH	L-T4 125 µg	72hr rhTSH	L-T4 125 µg	72hr rhTSH
Date	5/14/10	11/15/10	11/19/10	4/11/11	4/15/11
Serum Tg (2nd gen) ng/mL (µg/L)	1.20	0.48	1.52	0.62	1.89
Serum TSH mIU/L	35	0.03	47	0.07	49
Fold response (rhTSH-g/bTg)	3.9		3.2		3.0

Treatment	UZT - LN met	LN resection	L-T4 125 µg
Date	5/2/11	5/17/11	6/7/11
Serum Tg (2nd gen) ng/mL (µg/L)	0.65	0.72	0.09
Serum TSH mIU/L	0.04	0.08	0.06
Fold response (rhTSH-g/bTg)			

CASES WITH QUESTIONS AND DISCUSSION OF CASES AND ANSWERS

Case 1

By 2nd generation assay while taking 125 µg q.d L-T4 and TSH in the 0.03 - 0.09 mIU/L range. 42 year old female with no family history of thyroid disease presented with a 3-month history of an enlarging anterior neck mass.

Diagnosis: Ultrasound: 4.0cm left thyroid mass + calcifications. FNA confirmed papillary thyroid carcinoma (PTC).

Treatment: Total thyroidectomy + Level VI neck dissection. Pathology: 4.3 x 3.5 cm PTC (BRAF +) with 18 metastatic lymph nodes removed from the central compartment.

Post-operative Management: Patient placed on L-T3 therapy (25µg b.i.d.) prior to L-T3 withdrawal and radioiodine (RAI) Rx. (5.6 mBq) after 6 weeks.

Post Rx. Scan: Uptake in the thyroid bed but no evidence of metastases. Monitoring: Periodic basal + rhTSH-stimulated Tg testing and 0.15 mBq RAI whole body scans.

1. ***Question: Were the multiple rhTSH-stimulation tests necessary?***

Answer: When serum Tg is measured using a 2nd generation assay (functional sensitivity 0.05 ng/mL) the rising basal Tg trend between 5/10/10 and 5/17/11 provided more information than the rhTSH-stimulated responses (which were comparable and all below the consensus cut-off of 2.0 ng/mL).

2. ***Question: Was the preoperative serum Tg useful?***

Answer: The preoperative serum Tg was low relative to tumor size and the presence of multiple metastatic lymph nodes, suggesting the tumor was an inefficient Tg secretor. This was consistent with BRAF-positivity and the blunted rhTSH-stimulated fold responses (~3.0 compared with expected ~10-fold characteristic of normal tissue) seen after the RAI treatment had decreased the contribution from the normal thyroid remnant. (*Box 2*)

Case 2

TgAb-negative patient. A 25 year old female patient sees you for a first visit on 9/10/12 for follow-up. She is s/p thyroidectomy for papillary thyroid cancer in 2010. The patient states she did not receive radioiodine treatment after surgery and her past records are unavailable.

Current Medications

0.112 μg L-T4.

Neck ultrasound

Two benign-appearing lymph nodes but no other thyroid tissue visible

Serum Tests:	9/10/12	12/4/12	1/10/13	2/27/13
Tg (ng/mL)	1.5	0.9	0.15	<0.10
TSH (mIU/L)	9.3	1.3	0.42	0.06

Target TSH

0.05 - 0.3 mIU/L

The patient was counseled regarding the need for medication compliance in light of the 9/10/12 TSH result. After three more follow-up visits TSH became suppressed into the target range.

1. Question: Does the 9/10/12 serum Tg of 1.5 ng/mL suggest the presence of disease?

Answer: No. In the absence of radioiodine therapy the patient has a 1-2 gram normal thyroid remnant that is responding to chronic TSH stimulation caused by non-compliance. Only if the Tg failed to fall in response to TSH suppression would disease be suspected. The undetectable 2nd generation serum Tg on 2/27/13 is consistent with a very low risk for persistent/recurrent disease.

2. Question: Is the 2/27/13 undetectable serum Tg (< 0.10 ng/mL) consistent with a patient not receiving radioiodine?

Answer: Yes. The USC experience finds that a significant number of thyroidectomized DTC patients receiving L-T4 suppression (TSH < 0.05 mIU/L) develop an undetectable serum Tg (< 0.10 ng/mL using a second generation assay) within the first 3-6 months following thyroidectomy.

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Graves Ophthalmopathy

M63
Tuesday, June 18
12:15–1:00 PM

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SIGNIFICANCE OF THE CLINICAL PROBLEM

The significance of Graves' ophthalmopathy (GO) for the patient is self-evident from this quote "From a beautiful woman I changed into a 'creep' who stared at people pop-eyed. Children backed away, adults nudged one another. Having a squint made me quit my hobbies and make mistakes at work". It is thus not surprising that health-related quality-of-life (assessed by MOS-SF24/SF36) is substantially impaired in GO, even to a greater degree than in patients with diabetes, emphysema or heart failure. The widely used and well-validated disease-specific quality-of-life questionnaire, the so-called GO-QoL, likewise shows that GO can have a major negative impact on QoL. What is worrisome, is that QoL questionnaires frequently indicate unsatisfactory outcomes of treatment: after 10 years, 32% of patients said their eyes still did not appear normal, and 28% were not satisfied with the appearance of their eyes (1).

(1). The significance of GO for public health has recently become more clear from studies in Germany. Among unselected GO patients, 21.9% were temporarily disabled, and 5.6% were permanently disabled; 2.3% had lost their job, and 4.2% had retired early. Mean duration of sick leave was 22.3 d/yr, compared with the German average of 11.6 d/yr. Diplopia was identified as the principle predictor for work disability. Indirect costs due to sick leave and disability ranged between 4,153 and 8,437 U.S. $ per patient per year. Direct costs per patient per year were 418, 469 and 1,491 U.S. $ in mild, moderate-to-severe and sight-threatening GO respectively. Both direct and indirect costs correlated with answers on the GO-QoL questionnaire

(2). The significance of GO for the treating physician can also be approached from an epidemiological point of view. The prevalence of Graves' hyperthyroidism is about 0.5%, but only a subset will develop clinical manifestations of GO. A recent single-center survey from Italy reported that among 346 patients with Graves' hyperthyroidism seen over an 8-year period, at presentation 255 (73.7%) had no ocular involvement, 70 (20.2%) had mild and inactive GO, 20 (5.8%) had moderate-to-severe and active GO, and 1 (0.3%) had dysthyroid optic neuropathy (DON). Among patients without GO, at last visit of 18-month follow-up 87.1% still had no GO, 10.3% had mild GO, and 2.6% moderate-to-severe and active GO. Among patients with initially mild GO, at last visit 58.1% experienced complete remission of GO, 39.5% still had mild GO, and 2.4% had progressed to moderate-to-severe and active GO. Most patients without GO at diagnosis of Graves' hyperthyroidism do not develop GO during 18-month follow-up, and mild GO disappears in the majority of cases (3). Thus, even in a big (nontertiary referral) center just 27 incident cases of moderate-to-severe GO/DON were observed over an 8-yr period, that is about 3-4 cases per year. The low number is in line with the declining prevalence and severity of GO among patients with Graves' hyperthyroidism, most likely due to a decrease in smoking prevalence. The figures are in line with a recent Danish study reporting that approximately 5% of patients with Graves' disease develop moderate-to-severe GO, with an incidence rate of 16.1/million/per year (women 26.7, men 5.4). It follows that experience of individual

endocrinologists with more severe GO is limited.

BARRIERS TO OPTIMAL PRACTICE

1. Limited experience in the structured assessment of severity and activity of GO by endocrinologists.

   In view of the secular trend towards a decrease in prevalence and severity of GO, experience of individual endocrinologists remains limited. Severity and activity, however, are highly relevant for delineating an appropriate management plan.
2. Outcome of GO is influenced by the chosen treatment modality of Graves' hyperthyroidism, whereas immunosuppressive or surgical treatment of GO requires consultation of the endocrinologist.

   It matters for the eyes how euthyroidism is restored. Conversely, surgical treatment of GO should not be entertained when the patient is still not euthyroid or GO is still active, otherwise surgical results might be lost.
3. Limited efficacy of current nonsurgical treatment modalities of GO.

   There remain a number of nonresponders to steroids and retrobulbar irradiation, and surgical procedures are frequently required to restore the premorbid state of the eyes. Also, about 20% of patients are not satisfied with the final outcome of GO treatment.

   One solution for these barriers to optimal practice is to refer moderate-to-severe GO patients and patients with DON to combined thyroid-eye clinics. Investigation of patients simultaneously by endocrinologists and ophthalmologists/orbital surgeons in such clinics is likely to maximize the chances of a successful outcome. It facilitates coordination in the selection and timing of therapies required to restore the euthyroid state and to ameliorate the ophthalmopathy. Besides the obvious advantage of ease of communication, combined thyroid-eye clinics stimulate learning and research. Patient satisfaction also is greater for those who attend such clinics compared to those who do not (4).

LEARNING OBJECTIVES

As a result of participating in this session, learners should be able to:

- Diagnose Graves' ophthalmopathy, including a fair assessment of its severity and activity
- Treat Graves' hyperthyroidism in the presence of GO
- Treat Graves' ophthalmopathy according to severity and activity

SUCCINCT REVIEW-STRATEGIES FOR DIAGNOSIS, THERAPY, AND/OR MANAGEMENT

The European Group On Graves' Orbitopathy (EUGOGO) has published recommendations on the diagnosis and treatment of GO (5,6). Recent ATA guidelines on the management of thyrotoxicosis give largely similar recommendations (7). EUGOGO also published a book covering all aspects of GO in the format of 205 questions and answers (8).

Usually the diagnosis of GO is self-evident from the bilateral symmetrical eye changes in a patient with Graves' hyperthyroidism. Atypical presentations, however, do occur. Schematically the diagnosis of GO is based on three lines of investigation:

Investigation of Eye Changes (According to Severity and Activity)

Assessment of severity can be done using NO SPECS as a mnemonic (*Table 1*). It allows to classify patients as having mild, moderate-to-severe or very severe (sight-threatening) ophthalmopathy (*Table 2*). Assessment of activity can be done by the clinical activity score (CAS) based on the classical features of inflammation (*Table 3*). A clinical activity score of 3 or higher is a reasonable but no perfect indicator of active disease. A short duration of the eye changes (<18 months) increases the likelihood the ophthalmopathy is still active. Sophisticated methods employing orbital imaging (like T2-relaxation time in orbital fat and muscles on MRI) provide more objective activity measures, but are expensive and not widely available. Stable eye signs for a period of 6 months or longer indicate inactive disease. Detailed instructions for the assessment of eye signs can be downloaded

TABLE 1. Assessment of severity of GO (using No SPECS as a mnemonic)

No signs or symptoms	
Only Signs, no symptoms	Lid aperture in midline in mm
Soft tissue involvement	Swelling and redness of eyelids and conjunctiva
Proptosis	Hertel in mm
Extraocular muscle involvement	Eye muscle ductions, diplopia*
Corneal involvement	Punctate keratopathy, ulcer
Sight loss (due to optic nerve involvement)	Best-corrected visual acuity, colour vision, optic disk, visual fields
*Score: 0=no diplopia, 1=intermittent diplopia, i.e. when tired or upon awakening, 2=inconstant diplopia, i.e. at extremes of gaze, 3=constant diplopia, i.e. in primary or reading positions.	

for free from the website www.eugogo.eu and going to the section "evaluation."

Investigation of Thyroid Function

The presence of Graves' hyperthyroidism in a patient with ophthalmopathy supports the diagnosis of GO. However, about 10-15% of all GO patients are euthyroid and 3% are hypothyroid at the time of presentation. The detection of TSH receptor antibodies (TBII) in such patients provides circumstantial evidence but does not prove the eye changes are due to Graves' disease. It is unknown why only about 25% of euthyroid GO patients progress to overt hyperthyroidism.

Orbital Imaging

Orbital imaging is indicated in case an alternative diagnosis cannot be ruled out. This applies specifically to unilateral eye changes: although GO presents in about 10% as unilateral opthalmopathy and GO is the most frequent cause of unilateral exophthalmos, another disease might exist like orbital meningioma, non-Hodgkin lymphoma, orbital myositis, or idiopathic orbital inflammatory disease (formerly called pseudotumour orbitae). For similar reasons orbital imaging is also recommended in euthyroid or hypothyroid patients. Further indications are suspicion of dysthyroid optic neuropathy (to look for apical crowding) and prior to surgical orbital decompression. It follows that only in a minority of patients orbital imaging is required for the diagnosis of GO.

Treatment of GO can be difficult in view of the interdependence of therapies for Graves hyperthyroidism and GO itself. Schematically management of GO is based on three interventions aiming at:

To stop smoking

This goal is not easily reached, but current guidelines give clues how the physician may help patients to quit smoking (9 ,10).

To restore and maintain euthyroidism

This goal can be reached by either antithyroid drugs, radioactive iodine or thyroidectomy. However, the evidence base which option is preferable in patients presenting with both conditions, is rather limited (11). It appears that antithyroid drugs and thyroidectomy are rather neutral with respect to the course of GO, but that 131I therapy carries a risk of worsening GO, especially in the presence of risk factors like smoking, severe hyperthyroidism (T3 > 5 nmol/l), active

TABLE 2. Classification of GO according to severity.

	Mild	Moderate-to-severe	Sight-threatening
• Lid retraction	<2 mm	≥2 mm	-
• Soft tissue Involvement	mild	moderate	-
• Proptosis*	<3 mm	≥3 mm	-
• Diplopia	Score 0 or 1	Score 2 or 3	-
• Corneal exposure	absent	mild	+
• Optic nerve	normal	normal	compression
*above upper normal limit (in African American F/M=23/24 mm, in White F/M=19/21 mm, in Asians F/M=16/17 mm Thai or 18.6 mm Chinese).			

TABLE 3. Assessment of activity of GO (using the clinical activity score CAS).

• Spontaneous retrobulbar pain
• Pain on attempted up, side or down gaze
• Redness or the syslids
• Redness of the conjunctiva
• Swelling of the eyelids
• Swelling of the caruncle and/or plica
• Chemosis
CAS is the sum of all items present with a maximum score of 7; a CAS of ≥3 indicates active GO

ophthalmopathy, and high TBII. The risk can be substantially reduced by steroids. According to a recent worldwide survey, the presence of GO in a patient with Graves' hyperthyroidism shifts the preferred treatment option away from radioactive iodine towards prolonged treatment with antithyroid drugs or thyroidectomy (12). If 131I therapy is chosen, low-dose oral prednisone might be considered in mild active GO and high dose steroids in moderate-to-severe active GO (13).

To restore visual functions and appearance
Simple local measures can be very helpful for the patient, and should always be considered. A liberal use of artificial tears is effective against surface symptoms like grittiness. Lubricant ointments protect the cornea during sleep. Sunglasses ameliorate photophobia and excess lacrimation, and prisms may correct diplopia. Further medical or surgical treatment depends on the severity and activity of GO (*Table 4*). Whereas mild GO might be followed by the endocrinologist, urgent referral to an expert center is required in case of sight-threatening GO. Clues necessitating urgent referral could be unexplained deterioration in vision or changes in intensity or quality of color vision in one or both eyes (suspicious for DON), a history of eyes suddenly "popping out" (globe subluxation), and obvious corneal opacity or a still visible cornea when the eyelids are closed (lagophthalmos, risk of corneal breakdown).

TABLE 4: Management of Graves' Ophthalmopathy according to its severity and activity

Mild GO • wait-and-see policy • selenium
Moderate-to-Severe GO, active • intravenous pulses of methylprednisolone • upon failure, low-dose prednisone + retrobulbar irradiation of cyclosporin • in desperate cases, rituximab
Moderate to Severe, Inactive • orbital surgery as required, in the sequence ° orbital decompression ° eye muscle surgery ° eyelid surgery
Sight-Threatening GO • urgent referral for surgical decompression or • intravenous pulses of methylprednisolone

Management of Graves' Ophthalmopathy According to Its Severity and Activity
Selenium
In mild GO a wait-and-see policy is usually recommended in view of spontaneous improvement of GO during the natural history of the disease, observed in at least 30%. A recent randomized clinical trial, however, concluded that treatment with selenium selenite 100 microgram twice daily for 6 months improves quality of life (GO-QoL), clinical activity (CAS), eyelid aperture and soft tissue signs, and prevents progression to more severe GO (14). The effect was maintained at 12 months evaluation. The trial was performed in a number of European countries, which are mostly selenium deficient. It remains to be seen whether the same favorable results are obtained in areas with sufficient selenium intake.

Steroids
Glucocorticoids remain the hallmark for the treatment of moderate-to-severe active GO. Intravenous pulses of methylprednisolone are more effective and have less side effects than high-dose oral prednisone. The preferred treatment schedule of pulse therapy is: 500 mg methylprednisolone intravenously once weekly for 6 weeks, followed by 250 mg methylprednisolone intravenously once weekly for another 6 weeks (cumulative dose

4.5 gram). Iv pulses have been associated with a mortality of 0.6%, which however was largely observed at cumulative doses exceeding 8 gram. It is thus prudent not to exceed 8 gram, to avoid administration on consecutive days (except in DON), and to screen patients for recent hepatitis, liver dysfunction, cardiovascular morbidity, severe hypertension, inadequately managed diabetes, and glaucoma (15). A recent randomized clinical trial on the optimal dose of iv pulses comparing cumulative doses of 2.25, 4.98 and 7.47 gram, concluded that most improvement was seen in the 7.47 gram group, albeit at the expense of greater toxicity (16). The results suggest that an intermediate-dose regimen (like the 4.5 cumulative dose) be used in most cases and the high-dose regimen be reserved to most severe cases. The study also observed that about 30% of patients had relapsing GO at 24 weeks after improvement at 12 weeks. Whether the outcome of iv pulses can be improved by simultaneous retrobulbar administration or mycophenolate is presently investigated. In case of steroid failure and still active GO, one may opt to continue immunosuppressive treatment with a low dose of oral prednisone (e.g. 20 mg prednisone daily) in combination with either retrobulbar irradiation or cyclosporin until the disease has become inactive. In such rather severe cases that may take 6-12 months. Steroids are most effective in improving CAS, soft tissue signs, diplopia and visual acuity, but their effect on exophthalmos is disappointing. It follows that rehabilitative surgery is frequently required in order to restore premorbid appearance.

Retrobulbar irradiation

Available data suggest that retrobulbar irradiation is a safe treatment, particularly effective on soft tissue signs, ocular motility impairment and diplopia but less so on exophthalmos. The combination or retrobulbar irradiation with oral prednisone is more effective than oral prednisone alone. Current treatment schedule is mostly 20 Gy, delivered as 10 daily doses of 2 Gy over a period of 2 weeks. Other schedules might be equally effective, like a lower dose of 10 Gy over a 2-week period or 20 Gy fractionated as 1 Gy weekly over 20 weeks. Retrobulbar irradiation should be avoided in patients with diabetic retinopathy or severe hypertension as well as in patients younger than 35 years (17).

Rituximab

Rituximab, as the first in a line of novel drugs, potentially increases remission rate of Graves' hyperthyroidism and improves the course of GO (11). The usual dose is 1 gram twice with a 2-week interval. In view of its side effects which can be serious, the use of rituximab should be restricted to GO patients not responding to other therapy. The results of two randomized clinical trials are expected end of 2013: one compares rituximab with placebo, the other compares rituximab with steroids.

MAIN CONCLUSIONS

1. Graves' ophthalmopathy (GO) is usually easily diagnosed in a patient with Graves' hyperthyroidism. In patients presenting with eye changes who are euthyroid or hypothyroid, the presence of autoimmune thyroid disease (notably the finding of TSH receptor antibodies) supports but does not prove a diagnosis of GO. In such patients, as well as in case of unilateral eye changes, orbital imaging is recommended to exclude an alternative diagnosis.
2. A fair assessment of the severity and activity of GO (highly relevant for the management plan) can be done by the endocrinologist in his/her own office by simple means.
3. All patients with Graves' disease should be encouraged to quit smoking, as smoking is associated with worse outcomes.
4. In selecting the most appropriate treatment of Graves' hyperthyroidism in a patient with GO, antithyroid drugs and thyroidectomy appear to be neutral with respect to the course of GO. Radioactive iodine, however, carries a risk of worsening GO, which can be prevented by steroids. If 131I therapy is considered in GO patients, co-administration of prednisone should be considered dependent of risk factors (active GO, severe hyperthyroidism, high TBII, smoking).
5. Mild GO can be followed in view of high chances of spontaneous improvement;

treatment with selenium may be considered. Sight threatening cases of GO should urgently be referred to expert centers. Moderate-to-severe GO may benefit from consultation in combined thyroid-eye clinics. Active GO qualifies for immunosuppression: intravenous methylprednisolone pulse therapy is more effective and has less side effects than oral prednisone. Remaining eye changes can be remedied by rehabilitative orbital surgery, once GO has become inactive.

CASES WITH QUESTIONS

Case 1

This 41-yr old woman presents with Graves' hyperthyroidism and mild GO. She prefers treatment with antithyroid drugs. She loves smoking, and puffs away 10 cigarettes per day already for 20 years.

Q. Which arguments related to Graves' disease, are you discussing in order to convince her it is better to stop smoking now?

Case 2

This 54-yr old man had Graves' hyperthyroidism and moderate-to-severe active GO. His hyperthyroidism has been treated with antithyroid drugs for 2 years. His GO has in the meantime become inactive after treatment with steroids, and he is satisfied with the outcome. Three months ago he discontinued treatment with antithyroid drugs, but now experiences a relapse of his hyperthyroidism. You are planning 131 I therapy. Patient is proud he managed to quit smoking already for one year.

Q. Does this patient need a preventive course of steroids?

Case 3

This 55-yr old man is euthyroid on levothyroxine after total thyroidectomy for his Graves' hyperthyroidism. Despite iv steroid pulse therapy for moderate-to-severe active GO, his opthalmopathy remained active and he suffered from persistent significant exophthalmos and inconstant diplopia. When he developed dysthyroid optic neuropathy, surgical bony orbital decompression was done. Visual functions and proptosis improved after surgery, but visual acuity deteriorated three months later. Repeat orbital CT scan demonstrated adequate surgical decompression. He is unable to stop smoking. His ophthalmopathy is still active, he has persistent double vision and is on sick leave already for a long time. TBII serum concentrations remain high. This is clearly a severe case of therapy-resistant GO.

Q. What do you do?

DISCUSSION OF CASES AND ANSWERS

Case 1 Answers

1. Aftercourse of antithyroid drugs, recurrence rate of Graves' hyperthyroidism is higher in smokers than in non-smokers.
2. In case she experiences a relapse of Graves' hyperthyroidism and needs 131I therapy, chances of worsening GO are higher in smokers than in nonsmokers.
3. Heavy smoking is related to more severe GO.
4. Outcome of GO treatment with steroids or retrobulbar irradiation is worse in smokers compared to non-smokers.

Case 2 Answer

No, there is reasonable evidence that in patients whose GO has been rendered inactive by specific treatment, 131I therapy can be safely given. Moreover, he does not smoke any longer.

Case 3 Answer

This particular patient was treated with 20 mg prednisone orally in combination with cyclosporin. Retrobulbar irradiation was also administered. His ophthalmopathy slowly improved, and became inactive after one year. At that time, first cyclosporine and afterwards prednisone was discontinued. Patient declined surgery for remaining complaints of inconstant diplopia and soft tissue signs. Nowadays he might be a candidate for experimental treatment with rituximab.

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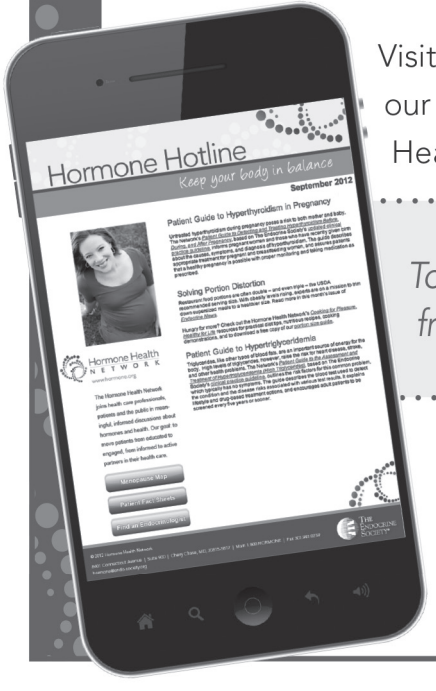

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