Thyrotropin-secreting Pituitary Adenomas: Pitfalls in Diagnosis and Management

Nicholas A. Tritos, MD, DSc

Presentation of a case

A 64 year old man was taken to the emergency room of a community hospital after experiencing a brief syncopal episode. Magnetic resonance imaging (MRI) of the brain was performed and showed a 2.5 by 2.0 centimeter sellar mass, abutting the chiasm (Figure 1).

Over the previous three years, he had noted recurrent palpitations lasting a few seconds at a time. He was evaluated by a cardiologist and was found to have no evidence of arrhythmia or structural heart disease. Serum thyrotropin was normal (2.1 mU/ml; normal, 0.4 to 5.0). He had been placed on metoprolol therapy, which alleviated these symptoms. Headache, visual symptoms, recent weight change, tremor, heat intolerance, acral enlargement were absent.

Past medical history was significant for sleep apnea and colon polyps, both diagnosed five years before. He had no history of known hypertension or hyperglycemia. Medications were metoprolol and low dose aspirin.

His blood pressure and pulse were normal. There were no visual field defects either on confrontation testing or formal perimetry. The mandible was prognathic. The thyroid was smooth, symmetric, and weighed approximately 20 grams. The rest of his examination was unremarkable.

Laboratory testing showed the following results: thyrotropin: 4.1 mU/ml; total thyroxine (T4): 14.9 mcg/dl (normal, 4.5 to 10.9); free thyroxine (fT4): 3.2 ng/dl (normal, 0.9 to 1.8); total triiodothyronine (T3): 200 ng/dl (normal, 60 to 180); insulin-like growth factor 1 (IGF-1): 529 ng/ml (normal, 71 to 290); prolactin: 8 ng/ml (normal, up to 15); alpha subunit: 0.50 ng/ml (normal, 0.05 to 0.53); sex hormone binding globulin (SHBG): 73 nmol/l (normal, 13 to 71). His serum testosterone and the cortisol response on cosyntropin stimulation testing were normal.

A presumptive diagnosis of a thyrotropin and growth hormone co-secreting pituitary adenoma was made. Octreotide LAR therapy was advised preoperatively to control thyroid hormone excess. He underwent transsphenoidal resection of the sellar mass, which was consistent with a pituitary adenoma on pathologic investigation, showing immunoreactivity for thyrotropin, growth hormone and alpha subunit. Six weeks later, there was no evident pituitary tumor on postoperative MRI examination. In addition, serum thyrotropin, fT4, total T3 and IGF-1 were normal.

Discussion

Thyrotropin-secreting pituitary adenomas (thyrotropinomas) account for approximately 1.0-2.0% of pituitary adenomas (1-3). They may secrete sufficient thyrotropin to cause clinical hyperthyroidism. Most patients have a goiter on examination. Extrathyroidal manifestations of hyperthyroidism, including Graves’ orbitopathy, pretibial myxedema or clubbing, are absent, except in rare patients with coexisting Graves’ disease. Unilateral proposis may occasionally occur as a result of direct tumor extension into the orbit.

Approximately 25% of these tumors co-secrete other pituitary hormones, including growth hormone, prolactin, or another glycoprotein (follicle stimulating hormone, luteinizing hormone or alpha subunit), leading to clinical syndromes of growth hormone (acromegaly) or prolactin excess (4). Of note, the majority of these tumors are macroadenomas at presentation, and may be associated with mass effect or hypopituitarism. Microadenomas appear to be more common in recent reports, likely reflecting earlier detection.

The biochemical hallmark of these tumors is the presence of high concentrations of thyroid hormones (thyroxine and triiodothyronine) with an inappropriately normal or elevated serum thyrotropin level (4). The diagnosis of hyperthyroidism may be missed if serum thyrotropin is the only hormone assayed in the assessment of the pituitary-thyroid axis. Conversely, there are several conditions characterized by high T4 and T3 levels and/or non-suppressed thyrotropin levels, which should be considered in the differential diagnosis of these patients (Table 1). The absence of suppressed thyrotropin levels should unequivocally exclude the diagnosis of Graves’ disease or toxic nodular goiter and avert the use of ablative therapies directed to the thyroid (including radiiodine therapy or

continued on page 2
thyroidectomy).

After artifactual abnormalities in thyroid function tests, excessive concentration or affinity of one of the thyroid hormone binding proteins, and medication effects are excluded, two major diagnostic considerations remain, including thyrotropin-secreting pituitary adenoma and resistance to thyroid hormone, which is usually caused by dominantly inherited, inactivating mutations of the beta subunit of the thyroid hormone receptor (TR) (1, 5).

Laboratory tests that may be useful in distinguishing between the two conditions are outlined in Table 2 (2-4). Patients with a thyrotropin-secreting pituitary adenoma will usually show biochemical evidence of hyperthyroidism, including elevated sex hormone binding globulin (SHBG) levels, abnormally high alpha subunit to thyrotropin molar ratio and lack of thyrotropin response to stimulation by thyrotropin-releasing hormone (TRH) (Figure 2) or suppression by triiodothyronine (Figure 3) (1, 6). In some cases, a dissociation between alpha subunit and thyrotropin responses to TRH stimulation has been reported (Figure 2) (1, 6). The lack of commercial availability of TRH preparations in the United States and the possible cardiovascular risks of triiodothyronine suppression testing (which is contraindicated in the elderly or patients with known cardiovascular disease) have limited the use of these dynamic tests in the diagnosis of thyrotropin-secreting pituitary adenomas.

Of note, genetic testing for mutations of the TR beta subunit is available and is positive in approximately 85% of patients with resistance to thyroid hormone. The reader is referred to www.genetests.org for a directory of laboratories where this test can be performed. As incidental pituitary lesions (generally microadenomas or cysts) are present in approximately 10% of the gen-

<table>
<thead>
<tr>
<th>Antibodies to T4 or T3 (leading to artifactually high thyroid hormone levels in analog assays)</th>
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<tr>
<td>Heterophilic antibodies to mouse immunoglobulins (leading to artifactually high thyrotropin levels)</td>
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<td>Increased concentration or affinity of thyroid hormone binding proteins (leading to high total thyroid hormone levels; free thyroid hormone levels are normal)</td>
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<td>Erratic compliance with thyroid hormone replacement in primary hypothyroidism</td>
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<td>Resistance to thyroid hormone</td>
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<tr>
<th>Test</th>
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<tr>
<td>High SHBG</td>
<td>94%</td>
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</tr>
<tr>
<td>High alpha subunit level</td>
<td>64%</td>
<td>2%</td>
</tr>
<tr>
<td>Increased (&gt;1) alpha subunit to TSH molar ratio*</td>
<td>81%</td>
<td>2%</td>
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<tr>
<td>TRH stimulation test (thyrotropin response present)</td>
<td>8%</td>
<td>96%</td>
</tr>
<tr>
<td>Triiodothyronine suppression test (thyrotropin response present)</td>
<td>12%</td>
<td>100%</td>
</tr>
<tr>
<td>Genetic analysis [TR beta subunit mutation]</td>
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<td>85%</td>
</tr>
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</table>

*This ratio is calculated as follows: [alpha subunit (in ng/ml) / TSH (in mcu/ml)] x 10
†TRH is not commercially available in the United States
SHBG: sex hormone binding globulin; TRH: thyrotropin-releasing hormone; TR: thyroid hormone receptor; TSH: thyrotropin.

Table 1. Conditions associated with high thyroid hormone [thyroxine (T4) and/or triiodothyronine (T3)] levels and/or non-suppressed [normal or elevated] thyrotropin levels.

Table 2. Laboratory tests used to distinguish between thyrotropin-secreting pituitary adenomas and resistance to thyroid hormone (1-4).
al population, genetic testing may be particularly advisable in patients with either a microadenoma or no obvious sellar lesion on MRI examination, but may be deferred in patients with macroadenomas. It may be noted that the two conditions (thyrotopinoma and resistance to thyroid hormone) may rarely coexist (7).

Transsphenoidal pituitary surgery is generally advisable in patients with presumed thyrotopin-secreting pituitary adenomas and may lead to a remission in 35-62% of patients, if performed by an experienced pituitary surgeon (3, 4). Postoperatively, patients with persistent tumor and/or hyperthyroidism can be treated with a somatostatin analog (octreotide LAR or sustained-release lanreotide), which can normalize thyroid hormone excess in approximately 75% of cases and decrease tumor size in about 45% (8-10). Somatostatin analogs may also be used preoperatively to control hyperthyroidism. Dopamine agonist therapy may be effective in controlling thyroid hormone excess in patients with tumors co-secreting prolactin. Radiation therapy may be helpful in patients failing surgical and medical therapy.

Antithyroid medications (methimazole or propylthiouracil) and beta adrenergic receptor antagonists may be used to control hyperthyroidism preoperatively. However, thyroid ablative therapies (radioiodine or thyroidectomy) are inadvisable, as their prior use may be associated with increased invasiveness of the sellar mass, reminiscent of the invasiveness of corticotropin-secreting pituitary adenomas in some patients with Nelson’s syndrome (4).

In summary, thyrotopin-secreting pituitary adenomas should be considered in patients with hyperthyroidism in the presence of non-suppressed serum thyrotropin levels. Resistance to thyroid hormone is an important diagnostic consideration, and can be differentiated from thyrotopinomas based on results of laboratory, genetic and imaging studies. Transsphenoidal pituitary surgery is the treatment of choice in most patients, and medical therapy with somatostatin analogs or dopamine agonists may be effective in patients with persistent disease postoperatively. Recognition of the diagnosis should help avert the use of thyroid ablative therapies and improve patient outcomes.

References
The Role of Growth Hormone in Bone and Mineral Metabolism: Lessons from Acromegaly and Growth Hormone Deficiency

Shirin Attarian, MD and Lisa Nachtigall, MD

Growth hormone and IGF-1 regulate skeletal growth and play important roles in the accrual of bone mass. The purpose of this review is to explore the role of GH in the regulation of bone and mineral metabolism as evidenced by studies in acromegaly and in growth hormone deficiency (GHD).

The GH axis and calcium metabolism in normal physiology

Mice with a GH receptor mutation (and low IGF-1) or with IGF-1 specific deletions exhibit more cortical than trabecular bone loss, suggesting that IGF-1 is more important for cortical than trabecular bone (1). GH and IGF-1 activate renal 1-alpha hydroxylase and inhibit 24-hydroxylase leading to greater production of 1,25-dihydroxyvitamin D3 (2). GH increases renal absorption of phosphate and thus increases serum phosphate levels (3). In addition, GH increases the sensitivity to PTH and possibly influences its circadian pattern of secretion (4). IGF-1 acts independently of GH to promote bone growth in the embryo. After birth and through puberty, both GH and IGF-1 play a critical role in linear bone growth (5). In addition, IGF-1 and GH are anabolic hormones which mediate bone remodeling and are important for bone homeostasis in adult life (6).

ACROMEGALY

Calcium and mineral metabolism

Hypercalcemia in acromegaly is rare, but there is a subgroup of acromegaly patients with hypercalcemia and/or hypercalciuria directly related to GH excess. As early as 1914 it was noted that acromegaly may be associated with an “increased absorptive power of the intestine for calcium salts” (7). More recently, increased 1,25-dihydroxyvitamin D3-dependent hypercalcemia in acromegaly, with normalization of calcium and 1,25-dihydroxyvitamin D3 levels after tumor resection and biochemical remission, was reported (8). IGF-1 and/or GH may also cause hypercalciuria independently of increased 1,25-dihydroxyvitamin D3. In one study of 27 patients with acromegaly, 22% had hypercalciuria without elevated PTH and 1,25-dihydroxyvitamin D3 (9). Thus, studies in patients with acromegaly suggest that hypercalcemia and hypercalciuria can occur independently of increased PTH.

Bone mass and fracture risk

The effect of GH excess on bone mass has been difficult to determine in acromegaly since co-existing hypogonadism is often a confounder in clinical studies on this topic. Most studies of patients with active acromegaly report that the bone mineral density (BMD) is normal or higher than expected for age or compared to normal controls (10-18). The study that concluded that acromegaly is associated with low bone mass and osteoporosis did not account for hypogonadism (9). However, when subgrouped by gonadal status, eugonadal acromegaly patients had normal (11) or increased (12,14,17) lumbar spine and/or femoral neck BMD compared to hypogonadal acromegaly patients and the general population. In contrast, BMD was reduced in hypogonadal acromegaly patients. Several studies reveal an inverse correlation between duration of hypogonadism and BMD (11, 19) or fracture (20). An increased bone turnover is consistently reported in acromegaly (9,10,12,16, 18-19).

The few studies that evaluate fracture rate in acromegaly suggest an increase risk, but also demonstrate lack of correlation between BMD and fracture incidence (19-21). However, these fracture studies included mixed groups of controlled and active acromegaly patients (19-20) or included only controlled patients after treatment for acromegaly (21). Of the three studies that showed increase fracture rates in acromegaly, one included only postmenopausal women with fractures solely based on thoracic and lumbar x-rays (19). A second study that showed increased fracture in acromegaly patients was performed only in men; the majority had controlled, treated acromegaly, some of whom may have had GHD and many of whom had hypogonadism (20). Although the control group was matched for hypogonadism, it was not matched for duration of hypogonadism, which correlated with increased fracture risk in this study. The third study did not control for hypogonadism (21). A single observational study suggested a decrease in fracture risk in acromegaly patients compared to a normal control population and this study included a large group of untreated men and women first evaluated at the time of diagnosis of acromegaly prior to surgical or other therapy but the prevalence of hypogonadism was unknown (15). Taken together, a variety of studies, mostly cross sectional and including de novo and treated acromegaly patients, show increased vertebral fracture rates. The risk is not predicted by BMD but does correlate with duration of hypogonadism. Few data are available on the fracture risk in eugonadal patients with growth hormone excess.

ADULT GROWTH HORMONE DEFICIENCY

Calcium and mineral metabolism

GHD is associated with PTH resistance, delayed response to PTH and changes in circadian rhythm of PTH secretion (4,22). In children, GH replacement raised 1,25-dihydroxyvitamin D concentration acutely but not chronically (23). In adults receiving 6 months of GH replacement, plasma phosphate increased and calcium
increased slightly with GH treatment (24). Small increases were observed in plasma calcium and phosphate concentrations at 12 months of GH therapy (25).

**Bone mass and fracture risk**

Adults with GHD exhibit reduced bone mass attributed to low turnover osteoporosis and have increased fracture risk (26-29). Patients with GHD have greater cortical than trabecular bone loss and the degree of bone loss is related to the age of onset of GHD, the severity of GHD and the age of the patient (30-31). The risk of nonvertebral fracture is significantly increased in untreated GHD and often involves the radius, suggesting a predilection for cortical bone loss (32-33). However, an increased incidence of vertebral radiographic deformities, possibly reflecting an increased rate of vertebral fracture has also been reported (34), Fig 1. Fracture prevalence in GHD correlates with severity of GHD but not with BMD (33-34). Fracture risk was associated with longer duration of disease among patients with GH deficiency in the KIMS database (35).

The effects of GH replacement on bone mass and fracture risk

Men and women with GHD have different responses to GH replacement regarding BMD (27). In addition to gender, age of onset of GHD, severity of bone loss, GH dose and duration of therapy play a role in the determining the extent to which GH therapy improves BMD (27,36). An increase in BMD of the hip and lumbar spine associated with GH replacement in adults is evident after at least 18 months of GH therapy (37-39), and persists for up to 10 years of continuous treatment (40). In men, the increase in the spine has been greater than that seen in women (38,41) and spinal and hip BMD can be sustained for up to 18 months after the discontinuation of GH (36). Few studies have evaluated whether GH replacement decreases fracture risk in GHD and conflicting results have been reported regarding a decreased fracture rate associated GH replacement (27). A shorter time between GHD diagnosis and starting GH therapy was associated with a greater reduction in vertebral radiographic fracture rate (34), Fig 1.

In summary, both GHD and GH excess are associated with changes in calcium and bone mineral metabolism. Further research is needed to explore the role of gonadal status on the bone effects of acromegaly and GH deficiency. In addition, studies are needed to address how BMD can be optimized and fracture risk reduced in both of these growth hormone disorders.

**References:**

Hypothalamic-Pituitary Complications of Anorexia Nervosa

Elizabeth Lawson, MD

Anorexia nervosa (AN), a disorder characterized by restrictive eating and severe undernutrition, affects up to 1% of college aged women. AN is associated with significant medical problems, including severe bone loss and comorbid depression, and the highest mortality of any psychiatric disease. Hypothalamic-pituitary dysfunction is common and may contribute to symptoms of this devastating illness (1).

Reproductive dysfunction
Amenorrhea for at least three months is currently a criterion for diagnosis of AN (DSM-IV) (2). Reproductive dysfunction in AN is secondary to hypothalamic amenorrhea. There is a reversal of normal gonadotropin pulsatility to prepubertal patterns, resulting in cessation of menstrual cycles and hypoestrogenemia (3). Low estrogen levels contribute to osteopenia and osteoporosis in these women. However, the more severe bone loss seen in women with AN compared to normal-weight women with hypothalamic amenorrhea suggests additional factors (4). Moreover, in randomized placebo-controlled trials, oral estrogen/progestin therapies have been ineffective in improving AN-induced bone loss (5-6). Hypothalamic amenorrhea in AN is likely an adaptive response to conserve energy for vital functions in the setting of chronic starvation and, in most cases, nutritional repletion results in restoration of normal reproductive function. The weight at which menstrual cycles stop is often predictable of the weight at which menstrual cycles will resume (7).

Hypercortisolism
Dysregulation of the hypothalamic-pituitary-adrenal “stress” axis is common in AN. Increased levels of serum, salivary and urine free cortisol levels have been demonstrated (8-10). Hypercortisolism may be due to the physical stress of starvation. These patients are extremely low weight and do not have a Cushingoid body habitus, likely due to lack of substrate.

Interestingly, during weight regain, there is a preferential increase in truncal fat that is associated with urine free cortisol levels (11). High cortisol levels may also contribute to symptoms of AN, including bone loss and depressive symptoms. In a study of 18 women with AN, 13 normal-weight women with hypothalamic amenorrhea, and 21 normal-weight healthy women, we found that higher overnight serum cortisol levels were associated with lower bone mineral density at the spine and hip, and more symptoms of depression (10).

Growth hormone resistance
AN is characterized by low levels of IGF-1 despite dramatically increased growth hormone secretion (12-14). This is attributed to starvation-induced resistance to growth hormone at the liver, where IGF-1 is normally produced. Growth hormone resistance may contribute to bone loss in AN. Increased growth hormone secretion is associated with low bone mineral density, and low IGF-1 is associated with decreased markers of bone formation (13, 15). In a randomized, double placebo-controlled study of IGF-1 or IGF-1 plus an oral contraceptive pill (OCP) in 60 women with AN and bone loss, there was a significant increase in spine bone mineral density in those who received IGF-1 (6). Those who received both IGF-1 and an OCP had the greatest increase in bone density (difference of 2.8% vs. controls over nine months).

However, IGF-1 is not approved for treatment of AN-induced bone loss and further research will be important to confirm the efficacy and safety of this therapy.

Sick euthyroid
The pattern of thyroid hormone levels associated with chronic starvation, termed “sick euthyroid”, is characteristic of AN. The TSH is typically normal with a low T3, high rT3, and high T4/T3 ratio (16-17). This is considered a normal adaptation to starvation in order to reduce the metabolic rate in an effort to conserve energy. Treatment with levothyroxine is not indicated. Thyroid function test abnormalities are reversible with weight restoration.

Posterior pituitary dysfunction
Vasopressin and oxytocin are homologous nonapeptide hormones produced in the hypothalamus and delivered to the posterior pituitary gland, where they are stored and eventually secreted peripherally. The syndrome of inappropriate antidiuretic hormone (SIADH) due to excessive vasopressin release into the bloodstream can occur in AN, resulting in low serum sodium levels. Hyponatremia can be exacerbated in these patients by psychogenic polydipsia, psychiatric medications and diuretic abuse (18). Sodium should be monitored in at risk patients as severe hyponatremia can lead to seizures, coma and death. Oxytocin, long recognized as a hormone important in induction of labor and milk letdown, has recently been implicated in appetite regulation, prosocial behavior, and bone formation. We have demonstrated decreased nocturnal oxytocin levels in women with AN,

References
associated with low bone mineral density (19). Further investigation will be important in characterizing the clinical manifestations of low oxytocin levels in AN.

**Bone loss**

In a study of 214 outpatient women with AN, mean age 25 yrs old, fewer than 14% had normal bone mineral density at all sites (20). There are currently no established medical therapies for prevention or treatment of AN-induced bone loss. Weight restoration and resumption of menstrual cycles are effective in improving, but not normalizing, bone mineral density (21-22). It is important to address other contributing factors, such as inadequate calcium and vitamin D intake, smoking, excessive alcohol, and excessive exercise. Studies of potential therapies, including IGF-I in combination with estrogen/progesterin therapy and bisphosphonates, are promising but further efficacy and safety data are needed. Medical treatments are under active investigation in the Neuroendocrine Unit (see Research Studies at right).

**Summary and conclusions**

Anorexia nervosa is characterized by hypothalamic-pituitary dysfunction in the setting of chronic starvation. Endocrine abnormalities contribute to symptoms, including osteopenia. Currently there are no approved medical therapies for AN-induced bone loss. However, there are several promising treatments that are under active investigation. Typically, hypothalamic-pituitary dysfunction is reversible and bone density improves but does not normalize with weight recovery.

See page 6 for References.

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**RESEARCH STUDIES AVAILABLE**

Patients may qualify for research studies in the Neuroendocrine Clinical Center. We are currently accepting the following categories of patients for screening to determine study eligibility. Depending on the study, subjects may receive free testing, medication and/or stipends.

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<th>SUBJECTS</th>
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<td>Adults with GHD</td>
<td>• Diagnostic testing for GHD</td>
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<td>Adults with Cushing’s</td>
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<td>Adolescent and young adult athletes</td>
<td>• Investigating impact of hormonal alterations on menstrual function and bone density</td>
<td>Madhu Misra, MD Anne Klibanski, MD</td>
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<tr>
<td>Obese adolescent girls</td>
<td>• Investigating impact of growth hormone on body fat distribution and metabolic function</td>
<td>Madhu Misra, MD Anne Klibanski, MD</td>
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<tr>
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<td>Women with anorexia nervosa</td>
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<td>Karen K. Miller, MD Anne Klibanski, MD</td>
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<td>Women ages 18-30 with a history of anorexia nervosa</td>
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<td>Elizabeth Lawson, MD Anne Klibanski, MD</td>
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<td>Men ages 18-45</td>
<td>• Investigating body weight and GH secretion GH treatment in abdominal obesity</td>
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<td>Girls and women with current anorexia nervosa or a history of anorexia nervosa, ages 10 and up</td>
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<tr>
<td>Obese men and women</td>
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<tr>
<td>Overweight children</td>
<td>• Effects of exercise on mitochondrial function</td>
<td>Amy Fleischman, MD Steven Grinspoon, MD</td>
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<td>HIV positive men and women</td>
<td>• Assessment of coronary artery atherosclerosis with and without metabolic abnormalities • Lifestyle modification strategies, including exercise and insulin sensitization • Growth hormone and growth hormone releasing hormone • Assessment of long-term GHRH • Assessment of brown fat • Assessment of menopausal transition • Statin therapy for coronary plaque</td>
<td>Steven Grinspoon, MD Janet Lo, MD Katie Fitch, ANP Takara Stanley, MD</td>
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</table>
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Madhusmita Misra, MD, MPH

Facilities
The Neuroendocrine Center is located on the 1st floor (Suite 112) of Zero Emerson Place at the Massachusetts General Hospital. A test center is available for complete outpatient diagnostic testing, including ACTH (Cortrosyn) stimulation; insulin tolerance; CRH stimulation; oral glucose tolerance and growth hormone stimulation testing. Testing for Cushing’s syndrome can also be arranged, including bilateral inferior petrosal sinus ACTH sampling for patients with ACTH-dependent Cushing’s syndrome.

Neuroendocrine Clinical Conference
A weekly interdisciplinary conference is held to discuss new patients referred to the Neuroendocrine Center and to review patient management issues. It is a multidisciplinary conference, attended by members of the Neuroendocrine, Neurology, Neurosurgery, Psychiatry and Radiation Oncology services. Physicians are welcome to attend and present cases.

Physicians’ Pituitary Information Service
Physicians with questions about pituitary disorders may contact Dr. Biller or Dr. Klibanski at 617-726-3965 within the Boston area or toll free at 888-429-6863, or e-mail to pituitary.info@partners.org.

Scheduling
Outpatient clinical consultations can be arranged by calling the Neuroendocrine Center Office at 617-726-7948.

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