CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will conduct an appropriate workup of low testosterone before considering prescribing testosterone replacement

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Male hypogonadism: More than just a low testosterone

ABSTRACT

Confronted with a low serum testosterone level, physicians should not jump to the diagnosis of hypogonadism, as confirmation and thorough evaluation are warranted before making the diagnosis or starting therapy. This review discusses how to approach the finding of a low testosterone value, stressing the need to confirm the finding, the underlying pathophysiologic processes, drugs that can be responsible, and the importance of determining whether the cause is primary (testicular) or secondary (hypothalamic-pituitary).

KEY POINTS

Blood samples for testosterone measurements should be drawn near 8 AM.

A low serum testosterone value should always be confirmed by a reliable reference laboratory.

The definition of a low testosterone level varies from laboratory to laboratory. In general, values less than 200 or 250 ng/dL are considered low, and values between 250 and 350 ng/dL may be considered borderline low.

If testosterone is low, determine if the cause is primary (testicular) or secondary (hypothalamic-pituitary).

Acute illness and treatment with opioids, anabolic steroids, or corticosteroids can result in transient hypogonadism.

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Editor's note: This article on the differential diagnosis of hypogonadism in men is the first of two articles. The second, to be published next month, focuses on the appropriate use of testosterone therapy.

A 54-YEAR-OLD MAN is referred for evaluation of low testosterone. He had seen his primary care physician for complaints of diminished libido and erectile dysfunction for the past year and worsening fatigue over the past few years. He has not been formally diagnosed with any medical condition. His serum testosterone level is 180 ng/dL (reference range 249–836 ng/dL).

On physical examination, he is obese (body mass index 31 kg/m^2) with a normal-appearing male body habitus, no gynecomastia, and normal testicles and prostate gland.

How should this patient be evaluated?

LOW TESTOSTERONE HAS MANY CAUSES

Male hypogonadism, ie, failure of the testes to produce adequate amounts of androgen or sperm, has become a common clinical finding, particularly in the older population. This is more likely the result of an increase in awareness and detection of the disorder by physicians rather than a true increase in prevalence.

The finding of a low serum testosterone value needs to be confirmed and thoroughly evaluated before starting treatment. It is important to determine whether the cause is a primary (hypergonadotropic) testicular disorder or secondary to a hypothalamic-pituitary process (hypogonadotropic or normogonadotropic).

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THE HYPOTHALAMIC-PITUITARY-GONADAL AXIS

Testosterone production is under the control of luteinizing hormone (LH), whereas sperm production is under the control of follicle-stimulating hormone (FSH) (FIGURE 1). Both of these pituitary hormones are regulated by the pulsatile secretion of hypothalamic gonadotropin-releasing hormone (GnRH).

Testosterone (produced by Leydig cells) and inhibin B (produced by Sertoli cells within the seminiferous tubules) result in negative feedback inhibition of gonadotropin (LH and FSH) secretion. Testosterone and estradiol (produced by aromatization of testosterone) act at both pituitary and hypothalamic sites and are the principal regulators of LH secretion.[1,2] Inhibin B is the major regulator of FSH secretion in men,[3] but steroid feedback also occurs.[2,4]

TO FOLLOW UP A LOW TESTOSTERONE, CONFIRM THE VALUE NEAR 8 AM

If a testosterone value is found to be low, it is important to determine the time that the sample was obtained. Serum testosterone levels follow a diurnal rhythm, at least in younger men, with values near 8 AM being, on average, 30% higher than the trough levels later in the day.[5–7] The timing of the diurnal variation may be different in night-shift workers, who may require assessment at a more appropriate time of the day (ie, upon awakening).

Commercially available testosterone assays are not well standardized, and some are frankly unreliable

Another factor affecting testosterone levels is the patient's health status at the time of testing. Values obtained in the hospital during an acute illness should be repeated once the event has resolved, as testosterone values decrease considerably in this setting.[8] Even in outpatients, particularly in men over age 60, one must be sure that the low testosterone level was not obtained during a period of decompensation of one of the many comorbidities seen in these patients, such as coronary artery disease, congestive heart failure, or uncontrolled diabetes.

If an 8 AM testosterone value is low, it is reasonable to obtain at least one confirmatory testosterone level on another day, near 8 AM, in the next few weeks, when the patient is in good health. Confirming the testosterone level is important, particularly since commercially available testosterone assays are not well standardized and some are frankly unreliable.[9,10] A repeat confirmatory level should always be performed by a reliable reference laboratory. If the testosterone level is still low, further evaluation is warranted.

TOTAL TESTOSTERONE VS BIOAVAILABLE TESTOSTERONE VS FREE TESTOSTERONE

Of the total circulating testosterone, 60% is bound to sex hormone-binding globulin (SHBG), 38% is bound to albumin, and only 2% is free. All of these fractions can be measured to assess for testosterone deficiency.

Free testosterone is the biologically active form of this hormone and, thus, the free testosterone level is considered to be a better representation of the true testosterone status. However, some clinicians believe that bioavailable testosterone (testosterone loosely bound to albumin + free testosterone) is a better reflection of the true level of the active hormone than the level of free testosterone alone.

There are situations in which the total testosterone level is low but bioavailable or free testosterone levels are normal. The level of total testosterone is affected by alterations in the levels of SHBG and albumin. A reduction in the level of SHBG can result in low total serum testosterone levels in patients with obesity or type 2 diabetes (states of insulin resistance), and also in cachexia, malnutrition, advanced cirrhosis, acromegaly, hypothyroidism, and nephrotic syndrome. SHBG can also be low in patients taking glucocorticoids, progestins, or androgenic steroids.[11] In these settings, checking the level of free testosterone (the active hormone), bioavailable testosterone, or both, by a reliable reference laboratory, may be more appropriate.[9,10]

But regardless of which measurement is chosen, all testosterone levels—especially bioavailable and free testosterone values—should be interpreted with caution if they are not measured at a reliable reference laboratory.[9,10] Interested readers may wish to

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Hormonal control of testosterone secretion

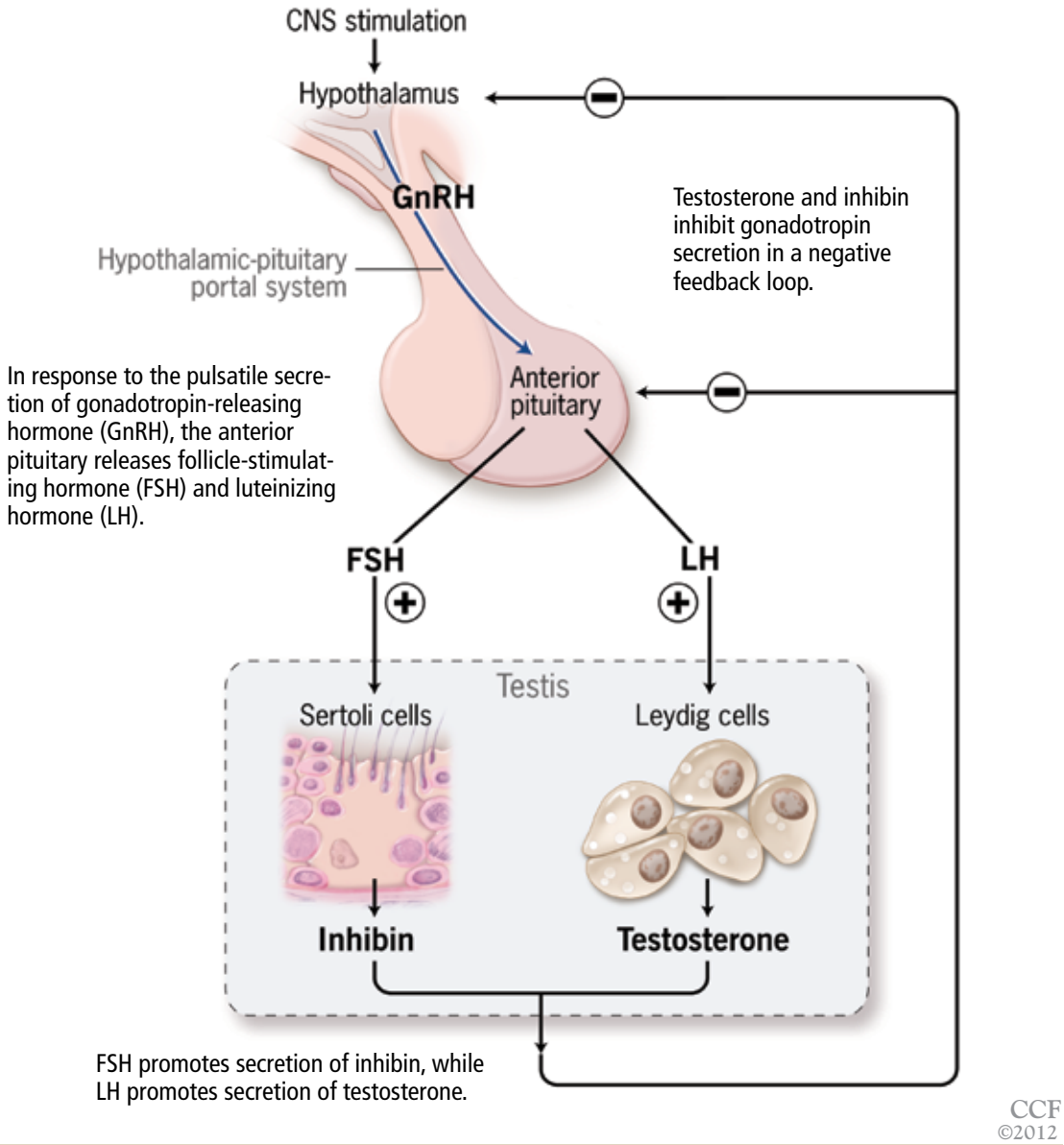

FIGURE 1

see the US Centers for Disease Control and Prevention (CDC) Hormone Standardization Program Web site (www.cdc.gov/labstandards/hs.html) for more details, including a list of CDC-certified laboratories.

CLINICAL FEATURES OF LOW TESTOSTERONE

A history of erectile dysfunction, decreased libido, and fatigue may be seen in patients with low testosterone. However, one must realize that these symptoms—as well as others reported by men with low testosterone, such as depression, difficulty concentrating, irritability, and insomnia—are nonspecific and may be related to other medical conditions.[12]

Likewise, physical findings such as muscle weakness, reduced body hair, and altered fat distribution (abdominal obesity) are seen in men with low testosterone, but also in those with a number of other medical conditions.

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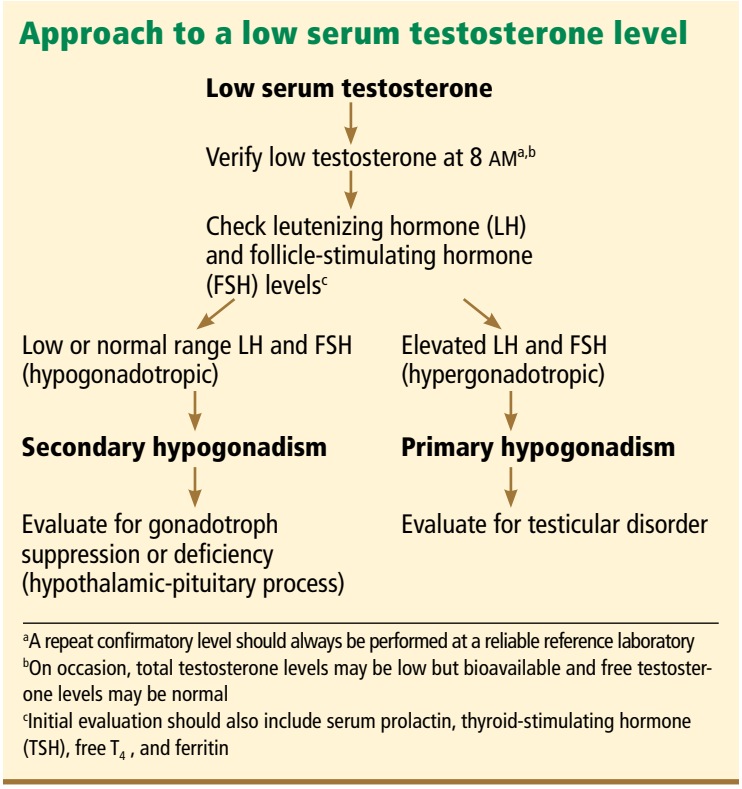

FIGURE 2

Testosterone levels at 8 AM are about 30% higher than the trough levels later in the day

Additional features suggest specific disorders, eg, anosmia in Kallmann syndrome; eunuchoid body habitus, gynecomastia, and small testes in Klinefelter syndrome.

Men with low testosterone may have low bone mineral density or anemia, or both.

Careful examination of the breasts for gynecomastia and the testes for size, consistency, and masses (testicular tumors) helps in formulating a differential diagnosis and in appropriately directing subsequent laboratory evaluation and diagnostic imaging.

LOW TESTOSTERONE: PRIMARY VS SECONDARY

A history of testicular trauma, systemic chemotherapy, or mumps orchitis should direct the physician's attention to a testicular etiology. On the other hand, darkened or tanned skin (suggesting hemochromatosis), galactorrhea (suggesting hyperprolactinemia), or visual field deficits (suggesting a sellar mass) should direct the physician's attention toward a pituitary-hypothalamic process.

Once the low testosterone value has been confirmed at least one time near 8 AM, one should obtain LH and FSH values to help direct further evaluation in deciphering the etiology (FIGURE 2). Elevated (hypergonadotropic) values indicate a testicular disorder (primary hypogonadism), whereas low (hypogonadotropic) or normal (normogonadotropic) values point to a pituitary-hypothalamic process (secondary hypogonadism). It should be emphasized that, in the setting of a low testosterone level, LH and FSH values within the normal range are "inappropriately normal" so that further investigation is required.

This evaluation should also include serum prolactin, thyroid-stimulating hormone (TSH, also known as thyrotropin), free thyroxine (T_4), and ferritin levels, the latter because hemochromatosis (iron overload) can cause both primary and secondary hypogonadism. If at any time in the evaluation the laboratory results suggest secondary hypogonadism, a full assessment of pituitary function should be undertaken.

Semen analysis is usually reserved for patients presenting with the primary complaint of infertility.

PRIMARY HYPOGONADISM

The patient should be carefully questioned about the age at which his problems began, about pubertal development, and about fertility. Causes of primary hypogonadism include:

- Karyotype abnormalities—Klinefelter syndrome (47, XXY syndrome) is the most common
- Toxin exposure, chemotherapy
- Congenital defects—anorchia, cryptorchidism[13]
- Orchitis (mumps, autoimmune)
- Testicular trauma or infarction
- Hemochromatosis
- Medications that inhibit androgen biosynthesis, eg, ketoconazole (Nizoral)[14]
- Increase in temperature of the testicular environment (due to varicocele or a large panniculus).

SECONDARY HYPOGONADISM

Causes of secondary hypogonadism include the following:

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Congenital disorders

These disorders are usually diagnosed in childhood or adolescence, often after the patient is brought to the physician because of short stature or pubertal delay.

- Kallmann syndrome (anosmia and GnRH deficiency)[15]
- GnRH receptor mutation and deficiency[16]
- Genetic mutations associated with pituitary hormone deficiencies, eg, *PROP-1* mutation.[17]

Acquired disorders that suppress gonadotrophs

Drugs. Long-term therapy with common medications such as opioids or corticosteroids can result in secondary hypogonadism.[18–20] Others are GnRH analogues such as leuprolide (Lupron), which are used in treating advanced prostate cancer. The hypogonadism is usually transient and resolves after stopping the offending agent.

Obesity and related conditions such as obstructive sleep apnea, insulin resistance, and type 2 diabetes mellitus are associated with low testosterone levels.[21] Treatment should be directed at these underlying conditions and should include lifestyle measures such as weight loss and exercise, rather than simple prescribing of testosterone supplementation, as these efforts may provide multiple health benefits in addition to raising testosterone levels.[22]

Insulin resistance. In the setting of obesity, the total testosterone level may be low but the bioavailable and free testosterone (active hormone) levels may be normal. This is due to the effect of hyperinsulinemia on the liver, which results in a reduction in SHBG production.[23] Low levels of both total and free testosterone can be seen in morbid obesity,[24] but the cause remains unclear.

Type 2 diabetes mellitus. Testosterone levels have been reported to be lower in obese men who have diabetes than in those with obesity alone.[24] This decrement, comparable in magnitude to that seen with other chronic diseases, suggests that low testosterone may simply be a marker of poor health.[22,25,26]

Sleep apnea. Disturbances in the sleep cycle, regardless of the underlying cause, can result in decreases in serum testosterone levels. Often, correcting the underlying sleep disturbance can result in a normalization of serum testosterone levels.[27,28] A caveat about testosterone therapy: a thorough evaluation for sleep apnea should be undertaken in patients at high risk, since testosterone replacement therapy can adversely affect ventilatory drive and induce or worsen obstructive sleep apnea.[29]

Aging. Most reports have shown an age-related decline in both total and free serum testosterone levels (commonly referred to as "andropause"), particularly in men over 60 years of age. There also appears to be a loss of circadian rhythm,[30] although not all reports agree.[6] It appears that factors such as functional status and overall health may play a more important role in the pathophysiology of hypogonadism in men of advanced age than age alone.

Hemochromatosis. Iron overload, regardless of the cause, can result in hypogonadism via deposition of iron in the hypothalamus, pituitary, or testes. Hereditary hemochromatosis is a common autosomal recessive disease characterized by increased iron absorption. Although both primary and secondary hypogonadism can occur with long-standing iron overload, the latter is much more common.[31] Some cases of hypogonadism have been reported to reverse with iron depletion therapy.[32]

Hyperprolactinemia. Recognized causes of hyperprolactinemia in men include medications (dopamine antagonists, antipsychotics, metoclopramide [Reglan]), pituitary adenomas (microadenomas < 10 mm, macroadenomas ≥ 10 mm), lactotroph hyperfunction (stalk compression interrupting or reducing the tonic suppression of prolactin secretion by dopamine), hypothyroidism, stress, chronic renal failure, cirrhosis, chest wall injury (trauma), and active herpes zoster. The ensuing hypogonadism may be due to the compressive effect of a sellar mass or the direct effect of the prolactin elevation alone, since prolactin disrupts the pulsatile release of GnRH from the hypothalamus,[33] required for normal LH and FSH secretion.

Estrogen excess can be either exogenous (from exposure to estrogen-containing contraceptives and creams) or endogenous (from testicular[34,35] or very rare adrenal[36] estrogen-secreting tumors). Of note, some cases of testicular neoplasms may be detectable only

Testosterone replacement therapy can adversely affect ventilatory drive and induce or worsen sleep apnea

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TABLE 1

Causes of male hypogonadism

Primary hypogonadism

Karyotype abnormality (eg, Klinefelter syndrome)
Toxin exposure (chemotherapy)
Congenital defect
Orchitis
Testicular trauma or infarction
Hemochromatosis
Medications—eg, ketoconazole (Nizoral)
Increased temperature of testicular environment

Secondary hypogonadism—congenital

Kallmann syndrome
Gonadotropin-releasing hormone (GnRH) receptor mutation or deficiency
Genetic mutation associated with pituitary hormone deficiency

Secondary hypogonadism—acquired, causing gonadotroph suppression

Medications (opioids, corticosteroids)
Obesity, insulin resistance
Type 2 diabetes mellitus
Obstructive sleep apnea
Aging
Hemochromatosis
Hyperprolactinemia
Estrogen excess
Anabolic steroid abuse
Anorexia nervosa
Acute illness
Human immunodeficiency virus infection
Chronic medical conditions
Alcohol abuse
Severe primary hypothyroidism
Pubertal delay

Secondary hypogonadism—acquired, causing gonadotroph damage

Sellar mass or infiltrative lesion
Metastatic lesion
Trauma (head injury)
Radiation exposure
Surgery
Stalk severance
Pituitary apoplexy

with ultrasonography. Computed tomography may be performed if an adrenal lesion is suspected.

Anabolic steroid abuse. Exposure to anabolic steroids, deliberately or inadvertently, can result in secondary hypogonadism and testicular atrophy, both of which may persist for years after stopping the anabolic agents. If you suspect anabolic steroid abuse, a urine anabolic steroid screen can be obtained.

Anorexia nervosa is far less common in men than in women.[37,38] Elements in the history that suggest this disorder include excessive exercise and a low body mass index. Chronic malnutrition (cachexia), regardless of the cause, can result in secondary hypogonadism.

Acute illness (gonadotroph sick syndrome). Hypogonadism is a relatively common finding in any critical illness (analogous to euthyroid sick syndrome with respect to the hypothalamic-pituitary-thyroid axis).[8] Testosterone levels are invariably low, so that assessment of testosterone status is not recommended in this setting. The low testosterone phase is usually transient and resolves with resolution or improvement of the underlying medical condition, such as sepsis or myocardial infarction.

HIV. Human immunodeficiency virus (HIV) infection can result in primary or secondary hypogonadism. It can occur with active HIV infection, in patients in whom control of viral replication has been achieved with highly active antiretroviral therapy, and even in patients who have normalized CD4+ cell counts.[39] Hypogonadism in HIV patients is multifactorial and may be related to weight loss, opportunistic infections of the pituitary-hypothalamus or testes, or medications such as opioids (licit or illicit), ganciclovir (Cytovene), ketoconazole, the appetite stimulant megestrol (Megace), or cyclophosphamide (Cytoxan). Testosterone replacement therapy does not adversely affect the HIV disease process and in fact may help to avoid complications.

Chronic medical conditions such as cirrhosis, renal failure, and rheumatoid arthritis commonly result in hypogonadism, the pathogenesis of which may involve dysfunction at all levels of the hypothalamic-pituitary-gonadal axis.[40–45] Hypogonadism in the setting of chronic disease is multifactorial, being due not only to the metabolic disturbances seen with these illnesses (uremia in renal failure, elevated circulating estrogens in liver cirrhosis), but also to recurrent acute illness and hospitalization for infection in these immuno-

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compromised hosts, either from the underlying medical condition or as a result of medications (corticosteroids).

Alcohol abuse. Alcohol can have adverse effects at all levels of the hypothalamic-pituitary-gonadal axis, resulting in low serum testosterone and reduced spermatogenesis.[46]

Severe chronic primary hypothyroidism, manifested by an extreme elevation of serum thyroid-stimulating hormone (TSH), can result in hypopituitarism. Pituitary function usually recovers with restoration of euthyroidism.[47,48]

Pubertal delay. Depending on the age of presentation, differentiating pubertal delay from permanent hypogonadotropic hypogonadism can be challenging.

Acquired disorders that damage gonadotrophs

- Sellar mass or cyst—pituitary adenoma, craniopharyngioma, Rathke cleft cyst, meningioma
- Infiltrative lesion—lymphocytic hypophysitis, Langerhans cell histiocytosis, hemochromatosis, sarcoidosis, infection
- Metastatic lesion
- Trauma (head injury)
- Radiation exposure
- Surgery
- Stalk severance
- Pituitary apoplexy.

See TABLE 1 for a summary of the causes of male hypogonadism.

WHEN IS MRI INDICATED IN EVALUATING SECONDARY HYPOGONADISM?

The yield of pituitary-hypothalamic imaging in older men with secondary hypogonadism is fairly low in the absence of other pituitary hormone abnormalities and deficiencies. There are limited data regarding appropriate criteria for performing hypothalamic-pituitary imaging studies. However, a patient who has multiple anterior pituitary abnormalities on laboratory evaluation should undergo dedicated hypothalamic-pituitary magnetic resonance imaging (MRI).

The Endocrine Society Clinical Practice Guidelines[11] recommend that MRI be performed to exclude a pituitary or hypothalamic tumor or infiltrative disease if the patient has severe secondary hypogonadism (serum testosterone < 150 ng/dL), panhypopituitarism, persistent hyperprolactinemia, or symptoms or signs of tumor mass effect such as headache, visual impairment, or a visual field defect.

WHO SHOULD UNDERGO ASSESSMENT OF TESTOSTERONE STATUS?

Screening for androgen deficiency in the asymptomatic general population is not recommended.[11] The nonspecific nature of many of the signs and symptoms of androgen deficiency makes it difficult to give concrete recommendations as to who should have testosterone levels measured. Clinicians should consider testing if there is evidence of certain clinical disorders that are associated with low testosterone levels (see earlier discussion on the specific causes of primary and secondary hypogonadism).

When a male patient complains of erectile dysfunction, the investigation should include an assessment of serum testosterone. However, if a man who has a constellation of nonspecific symptoms asks for his testosterone level to be assessed (which is common, given the aggressive marketing of testosterone replacement by the pharmaceutical industry), we would recommend a basic evaluation that includes a comprehensive metabolic panel, complete blood count, and TSH level. Further testing should be determined by the history and physical examination. If no obvious explanation has been found for the patient's symptoms at that point, assessment of serum testosterone may be warranted. More often than not the patient's weight and limited physical activity are the driving forces behind the nonspecific symptoms, and counseling a patient on a lifestyle change can provide much benefit if the patient follows through with the physician's recommendations.

Anabolic steroids can result in secondary hypogonadism and testicular atrophy, both of which may persist for years

Men whom we believe should not undergo assessment for testosterone deficiency are those who are acutely ill and hospitalized and those who are severely obese and are complaining of fatigue. Testosterone levels should be assessed only after the acute illness has resolved and, in a severely obese patient with fatigue, only after a thorough evaluation for sleep apnea has been undertaken.

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TREAT THE UNDERLYING CAUSE, IF ONE CAN BE FOUND

If the evaluation of low testosterone leads to the diagnosis of a clear underlying condition that is amenable to treatment, such as prolactin elevation or sleep apnea, then treatment should be directed at the underlying cause, with subsequent monitoring of the patient's symptoms and response in serum testosterone levels. In general, the use of dopamine agonist therapy in the management of hyperprolactinemia and, in cases of panhypopituitarism, of replacement therapy with levothyroxine (Synthroid), hydrocortisone, and possibly growth hormone and desmopressin (DDAVP), fall best under the purview of an endocrinologist. A caveat: serum TSH cannot be used to monitor levothyroxine replacement therapy in cases of secondary hypothyroidism. The clinical picture and serum free T_4 and free T_3 levels are used instead.

In the absence of a correctable (or immediately correctable) cause, testosterone supplementation can be initiated on an individualized basis in select patients who have clinical signs and symptoms of androgen deficiency if the benefits of treatment appear to outweigh the potential risks, and only after a thorough discussion with the patient.[11] The Endocrine Society recommends against offering testosterone therapy to all older men with low testosterone.[11]

Screening for androgen deficiency in the asymptomatic general population is not recommended

INFERTILITY

In men presenting with low serum testosterone, semen analysis is not routine. It is usually reserved for patients presenting with the primary complaint of infertility.

If an endocrine disorder such as prolactin elevation or hypothyroidism is the suspected cause of infertility, the patient should be referred to an endocrinologist for further evaluation and management. Treatment of male infertility should be directed at the underlying cause, but often requires exogenous human chorionic gonadotropin, FSH, GnRH (via a pulsatile pump), and possibly sperm harvesting from the testis with subsequent in vitro fertilization with intracytoplasmic sperm injection. It is critical that the partner be included in the evaluation of infertility.

These patients should be referred to a urologic or fertility center specializing in the diagnosis and treatment of infertility. For further information regarding male infertility, patients can be directed to www.fertilitylifelines.com.

CASE CONCLUDED

The patient's low serum testosterone was confirmed on subsequent measurements at 8 AM, with levels of 128 and 182 ng/dL (reference range 249–836). Other laboratory values:

- LH 1.4 mIU/mL (reference range 1.2–8.6)
- FSH 2.7 mIU/mL (1.3–9.9 mIU/mL)

(Both of these values are inappropriately normal in the setting of the low testosterone.)

- TSH 248 µIU/mL (0.4–5.5)
- Prolactin 24.6 ng/mL (1.6–18.8).

The patient was started on levothyroxine replacement therapy and after 3 months was noted to be euthyroid (TSH 1.8 µIU/mL) and to have a normal serum prolactin level. Testosterone levels (8 AM) at this time were 350 ng/dL and 420 ng/dL.

Therefore, the cause of this patient's hypogonadism was severe hypothyroidism and associated mild hyperprolactinemia. This case shows that a thorough evaluation is warranted before initiating testosterone therapy.

REFERENCES

1. **Pitteloud N, Dwyer AA, DeCruz S, et al**. Inhibition of luteinizing hormone secretion by testosterone in men requires aromatization for its pituitary but not its hypo-thalamic effects: evidence from the tandem study of normal and gonadotropin-releasing hormone-deficient men. J Clin Endocrinol Metab 2008; 93:784–791.
2. **Hayes FJ, DeCruz S, Seminara SB, Boepple PA, Crowley WF Jr**. Differential regulation of gonadotropin secretion by testosterone in the human male: absence of a negative feedback effect of testosterone on follicle-stimulating hormone secretion. J Clin Endocrinol Metab 2001; 86:53–58.
3. **Hayes FJ, Pitteloud N, DeCruz S, Crowley WF Jr, Boepple PA**. Importance of inhibin B in the regulation of FSH secretion in the human male. J Clin Endocrinol Metab 2001; 86:5541–5546.
4. **Pitteloud N, Dwyer AA, DeCruz S, et al**. The relative role of gonadal sex steroids and gonadotropin-releasing hormone pulse frequency in the regulation of follicle-stimulating hormone secretion in men. J Clin Endocrinol Metab 2008; 93:2686–2692.
5. **Cooke RR, McIntosh JE, McIntosh RP**. Circadian variation in serum free and non-SHBG-bound testosterone in normal men: measurements, and simulation using a mass action model. Clin Endocrinol (Oxf) 1993; 39:163–171.

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6. **Diver MJ, Imtiaz KE, Ahmad AM, Vora JP, Fraser WD**. Diurnal rhythms of serum total, free and bioavailable testosterone and of SHBG in middle-aged men compared with those in young men. Clin Endocrinol (Oxf) 2003; 58:710–717.
7. **Clair P, Claustrat B, Jordan D, Dechaud H, Sassolas G**. Daily variations of plasma sex hormone-binding globulin binding capacity, testosterone and luteinizing hormone concentrations in healthy rested adult males. Horm Res 1985; 21:220–223.
8. **Woolf PD, Hamill RW, McDonald JV, Lee LA, Kelly M**. Transient hypogonadotropic hypogonadism caused by critical illness. J Clin Endocrinol Metab 1985; 60:444–450.
9. **Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H**. Position statement: utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. J Clin Endocrinol Metab 2007; 92:405–413.
10. **Rosner W, Vesper H; Endocrine Society; American Association for Clinical Chemistry; American Association of Clinical Endocrinologists; et al**. Toward excellence in testosterone testing: a consensus statement. J Clin Endocrinol Metab 2010; 95:4542–4548.
11. **Bhasin S, Cunningham GR, Hayes FJ, et al; Task Force, Endocrine Society**. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010; 95:2536–2559.
12. **Wu FC, Tajar A, Beynon JM, et al; EMAS Group**. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010; 363:123–135.
13. **Farrer JH, Sikka SC, Xie HW, Constantinide D, Rajfer J**. Impaired testosterone biosynthesis in cryptorchidism. Fertil Steril 1985; 44:125–132.
14. **Sikka SC, Swerdloff RS, Rajfer J**. In vitro inhibition of testosterone biosynthesis by ketoconazole. Endocrinology 1985; 116:1920–1925.
15. **Pallais JC, Au M, Pitteloud N, Seminara S, Crowley WF Jr**. Kallmann syndrome. In: Pagon RA, Bird TD, Dolan CR, Stephens K, Adam MP, eds. GeneReviews™ (Internet). Seattle, WA: University of Washington; 1993.
16. **Chevrier L, Guimiot F, de Roux N**. GnRH receptor mutations in isolated gonadotropic deficiency. Mol Cell Endocrinol 2011; 346:21–28.
17. **Romero CJ, Pine-Twaddell E, Radovick S**. Novel mutations associated with combined pituitary hormone deficiency. J Mol Endocrinol 2011; 46:R93–R102.
18. **Colameco S, Coren JS, Ciervo CA**. Continuous opioid treatment for chronic noncancer pain: a time for moderation in prescribing. Postgrad Med 2009; 121:61–66.
19. **Fraser LA, Morrison D, Morley-Forster P, et al**. Oral opioids for chronic non-cancer pain: higher prevalence of hypogonadism in men than in women. Exp Clin Endocrinol Diabetes 2009; 117:38–43.
20. **Morrison D, Capewell S, Reynolds SP, et al**. Testosterone levels during systemic and inhaled corticosteroid therapy. Respir Med 1994; 88:659–663.
21. **Mah PM, Wittert GA**. Obesity and testicular function. Mol Cell Endocrinol 2010; 316:180–186.
22. **Grossmann M**. Low testosterone in men with type 2 diabetes: significance and treatment. J Clin Endocrinol Metab 2011; 96:2341–2353.
23. **Gascón F, Valle M, Martos R, et al**. Sex hormone-binding globulin as a marker for hyperinsulinemia and/or insulin resistance in obese children. Eur J Endocrinol 2000; 143:85–89.
24. **Dhindsa S, Miller MG, McWhirter CL, et al**. Testosterone concentrations in diabetic and nondiabetic obese men. Diabetes Care 2010; 33:1186–1192.
25. **Grossmann M, Gianatti EJ, Zajac JD**. Testosterone and type 2 diabetes. Curr Opin Endocrinol Diabetes Obes 2010; 17:247–256.
26. **Andersson B, Mårin P, Lissner L, Vermeulen A, Björntorp P**. Testosterone concentrations in women and men with NIDDM. Diabetes Care 1994; 17:405–411.
27. **Santamaria JD, Prior JC, Fleetham JA**. Reversible reproductive dysfunction in men with obstructive sleep apnoea. Clin Endocrinol (Oxf) 1988; 28:461–470.
28. **Grunstein RR, Handelsman DJ, Lawrence SJ, Blackwell C, Caterson ID, Sullivan CE**. Neuroendocrine dysfunction in sleep apnea: reversal by continuous positive airways pressure therapy. J Clin Endocrinol Metab 1989; 68:352–358.
29. **Matsumoto AM, Sandblom RE, Schoene RB, et al**. Testosterone replacement in hypogonadal men: effects on obstructive sleep apnoea, respiratory drives, and sleep. Clin Endocrinol (Oxf) 1985; 22:713–721.
30. **Bremner WJ, Vitiello MV, Prinz PN**. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. J Clin Endocrinol Metab 1983; 56:1278–1281.
31. **McDermott JH, Walsh CH**. Hypogonadism in hereditary hemochromatosis. J Clin Endocrinol Metab 2005; 90:2451–2455.
32. **Kelly TM, Edwards CQ, Meikle AW, Kushner JP**. Hypogonadism in hemochromatosis: reversal with iron depletion. Ann Intern Med 1984; 101:629–632.
33. **Milenkovic L, D'Angelo G, Kelly PA, Weiner RI**. Inhibition of gonadotropin hormone-releasing hormone release by prolactin from GT1 neuronal cell lines through prolactin receptors. Proc Natl Acad Sci U S A 1994; 91:1244–1247.
34. **Valensi P, Coussieu C, Kemeny JL, Attali JR, Amouroux J, Sebaoun J**. Endocrine investigations in two cases of feminizing Leydig cell tumour. Acta Endocrinol (Copenh) 1987; 115:365–372.
35. **Young S, Gooneratne S, Straus FH 2nd, Zeller WP, Bulun SE, Rosenthal IM**. Feminizing Sertoli cell tumors in boys with Peutz-Jeghers syndrome. Am J Surg Pathol 1995;19:50–58.
36. **Zayed A, Stock JL, Liepman MK, Wollin M, Longcope C**. Feminization as a result of both peripheral conversion of androgens and direct estrogen production from an adrenocortical carcinoma. J Endocrinol Invest 1994; 17:275–278.
37. **Russ MJ, Ackerman SH, Barakat R, Levy B**. Hypogonadotropic hypogonadism and delayed puberty in a man with anorexia nervosa. Psychosomatics 1986; 27:737–739.
38. **Rigotti NA, Neer RM, Jameson L**. Osteopenia and bone fractures in a man with anorexia nervosa and hypogonadism. JAMA 1986; 256:385–388.
39. **Cohan GR**. HIV-associated hypogonadism. AIDS Read 2006; 16:341–345, 348, 352–354.
40. **Handelsman DJ, Strasser S, McDonald JA, Conway AJ, McCaughan GW**. Hypothalamic-pituitary-testicular function in end-stage nonalcoholic liver disease before and after liver transplantation. Clin Endocrinol (Oxf) 1995; 43:331–337.
41. **Lim VS, Fang VS**. Gonadal dysfunction in uremic men. A study of the hypothalamo-pituitary-testicular axis before and after renal transplantation. Am J Med 1975; 58:655–662.
42. **Handelsman DJ, Dong Q**. Hypothalamo-pituitary gonadal axis in chronic renal failure. Endocrinol Metab Clin North Am 1993; 22:145–161.
43. **Handelsman DJ, Spaliviero JA, Turtle JR**. Hypothalamic-pituitary function in experimental uremic hypogonadism. Endocrinology 1985; 117:1984–1995.
44. **Tengstrand B, Carlström K, Hafström I**. Bioavailable testosterone in men with rheumatoid arthritis-high frequency of hypogonadism. Rheumatology (Oxford) 2002; 41:285–289.
45. **Tengstrand B, Carlström K, Hafström I**. Gonadal hormones in men with rheumatoid arthritis--from onset through 2 years. J Rheumatol 2009; 36:887–892.
46. **Emanuele MA, Emanuele NV**. Alcohol's effects on male reproduction. Alcohol Health Res World 1998; 22:195–201.
47. **Meikle AW**. The interrelationships between thyroid dysfunction and hypogonadism in men and boys. Thyroid 2004; 14(suppl 1):S17–S25.
48. **Vagenakis AG, Dole K, Braverman LE**. Pituitary enlargement, pituitary failure, and primary hypothyroidism. Ann Intern Med 1976; 85:195–198.

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