Testosterone Deficiency in Men:
Whom to Evaluate, What to Measure, and How to Treat

Jennifer J. Miranda, MD, and Marc J. Laufgraben, MD, MBA

Whom should a primary care physician evaluate for testosterone deficiency?

Low testosterone levels in men are not uncommon. There is an age-related decline in testosterone levels, falling by about 1% each year.[1] Approximately 1% of healthy young men have total serum testosterone levels below 250 ng/dl and approximately 20% of healthy men over 60 years old have serum testosterone levels below 250 ng/dl.[1] However, despite the frequency of **testosterone deficiency (TD)**, especially in aging men, significant questions remain over whom to evaluate, what to measure and how to treat.

Men with TD commonly experience sexual symptoms such as loss of libido, erectile dysfunction, and decreased volume of ejaculate. More generalized symptoms such as lack of energy, loss of motivation, inability to concentrate, depressed mood, sleep disturbance, and irritability are also frequently seen. Patients may notice loss of muscle strength, muscular aches, hot flushes, and slow beard growth.

Sexual symptoms (low libido and erectile dysfunction) correlate best with low testosterone levels, with generalized symptoms being substantially less specific.[2] Unfortunately, even sexual symptoms have reduced specificity for TD due to the common occurrence of neurovascular causes of erectile dysfunction in aging men, as well as the many physical illnesses and psychosocial stresses that can result in low libido.

Physicians may also suspect TD if they note loss of body hair, very small or "shrinking" testes, height loss, or reduced muscle bulk.[3] TD should also be considered in men with certain clinical disorders where the prevalence of TD is high or for whom therapy may be recommended.[3] Such disorders include sellar mass or radiation to the sellar region; HIV-associated weight loss; end-stage renal disease and maintenance hemodialysis; osteoporosis or low-trauma fracture; moderate to severe COPD; infertility; and treatment with medications that affect testosterone production such as glucocorticoids or opioids.[3] TD is also very common in patients with type 2 diabetes.

It is important to note that self-report case-detection instruments such as the **Androgen Deficiency in Aging Males (ADAM)** questionnaire have poor specificity and are not recommended.[4] Population-based screening in older men is also not recommended.

In summary, primary care physicians should pursue evaluation for TD in men with sexual symptoms or with disorders commonly associated with TD. Evaluation for TD can also be considered in men with more generalized symptoms.

What tests should be measured in men suspected of TD?

The evaluation of men with suspected TD is made confusing by the inherent complexity of testosterone physiology as well as problems with assays to measure testosterone. Testosterone in men is secreted almost solely from the testes. About 40-50% of testosterone is tightly bound to **sex-hormone-binding globulin (SHBG)** and, as a result, is not accessible to receptors in target cells. Approximately 50-60% is loosely bound to albumin and the remaining 1-2% is in the free state.[5] The free testosterone and albumin-bound testosterone are felt to be "bioavailable," i.e. available to act on receptors in target tissues.

Because of alterations in SHBG and albumin (see below), measurements of total testosterone (which includes all free and bound testosterone), may not always accurately reflect the bioavailable component. Nevertheless, most studies of testosterone deficiency rely on measurements of total testosterone and, in general, commercial assays for total testosterone are felt to be much more reliable than assays for free testosterone.[6] Thus, measurement of total testosterone is the screening test of choice for patients with suspected TD. (Routine measurement of free and/or bioavailable testosterone is not recommended.) Testosterone levels demonstrate a circadian rhythm with the peak in the morning (though this circadian may be blunted in older patients).[7] Measurement of total testosterone should always take place in the morning (~8AM).

Although reported ranges for total testosterone are somewhat dependent on the specific lab and assay used, a total testosterone of greater than 320 ng/dl is considered normal.[8] Patients with a morning total testosterone greater than 320 ng/dl will not require further testing. Patients with lower total testosterone levels should have the test repeated in a few weeks to avoid the possibility of temporary low testosterone due to stress or illness. It has been reported that 30% of men may have a normal testosterone on repeat measurement.[3]

Men with total testosterone less than 200 ng/dl on more than one occasion have testosterone deficiency. Unfortunately, total testosterone levels in the range from 200-320 ng/dl are equivocal.[8] Such patients should have assessment of free or bioavailable testosterone. The gold standard for measurement of free testosterone is equilibrium dialysis, but this methodology is expensive and not widely available.[5] Fortunately, calculated free testosterone (using total testosterone, albumin, and SHBG) provides values nearly identical to free testosterone by equilibrium dialysis.[5]

Other than patients with equivocal (200-320 ng/dl) total testosterone levels, only patients suspected of harboring altered levels of SHBG should be screened with (calculated) free or bioavailable testosterone. SHBG levels can be altered in a number of circumstances including aging, obesity, diabetes, thyroid disease, and HIV.

The next step in the evaluation of hypogonadal men should be measurement of **lutenizing hormone (LH)** and **follicle-stimulating hormone (FSH)**. In the setting of low total testosterone, an elevated LH and FSH indicate primary testicular failure. In men with primary

testicular failure, karyotype testing to exclude Klinefelter's Syndrome should be considered.

Patients with low or normal LH and FSH in the setting of low testosterone have a pituitary and/or hypothalamic cause of hypogonadism (hypogonadotrophic hypogonadism). The optimal evaluation of such patients has not been determined. At minimum, a serum prolactin level (to exclude hyperprolactinemia) and iron saturation (to exclude hemochromatosis) should be performed. Patients with total testosterone levels less than 150 ng/dl have enhanced likelihood of abnormalities on pituitary MRI and pituitary function testing, and should be strongly considered for such evaluations.[9] Whether all other patients with hypogonadotrophic hypogonadism should undergo further testing of pituitary function is debated, but certainly should be considered if signs or symptoms of hypopituitarism are present. Similarly, any patient with hypogonadotrophic hypogonadism with signs or symptoms suggestive of mass effect from pituitary tumor (headache or visual deficits) should undergo pituitary MRI.

Because of the risk of bone loss, all men with testosterone deficiency should be considered for bone densitometry.

How should patients with testosterone deficiency be treated and monitored?

Treatment for testosterone deficiency can be offered to symptomatic men with low testosterone levels with the goal of maintaining secondary sex characteristics and improving sexual function, sense of well-being, and bone mineral density,[3] provided that no contraindications to treatment exist. Testosterone therapy is not recommended for men with prostate or breast cancer, hematocrit above 50%, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms, or severe heart failure.[2] A **digital rectal exam (DRE)** as well as serum PSA measurement should be performed prior to the initiation of testosterone therapy. Men with palpable prostate abnormalities or a PSA > 4 ng/dl (or PSA > 3 in high-risk patients) should have further urologic evaluation before testosterone is considered.[3] Testosterone replacement is not the appropriate treatment for men with TD desiring fertility; such patients should be referred to endocrinologists or urologists for specialized evaluation and treatment.

Testosterone replacement is usually given by transdermal gel or patch, or by **intramuscular (IM)** injection. Testosterone gels are applied to nonscrotal skin once daily and are preferred by most patients. They are convenient, easily titratable and maintain steady day-to-day testosterone levels. However, gels are more expensive than other testosterone treatments. There is also the risk of potential transfer of testosterone to a sexual partner or child by direct skin-to-skin contact.

Because of the risk of bone loss, all men with testosterone deficiency should be considered for bone densitometry.

Testosterone patches are applied nightly to the hairless skin of the upper back, arm, or thigh; nightly application provides the closest approximation of the normal circadian rhythm of testosterone. Skin irritation and rash at the site of patch application is not rare; a low-dose triamcinolone cream applied prior to patch placement can reduce skin irritation without affecting testosterone absorption.[9]

IM testosterone was the major mode of testosterone treatment prior to the introduction of patches and gels. Intramuscular injections of testosterone enanthate or cypionate may be administered weekly (75-100 mg) or, more commonly, every 2 weeks (150-200 mg). With this formulation, the testosterone level peaks within a few days of administration and then slowly decline over the following 2 weeks. Its major drawback—in addition to the need for injection—is that men may develop fluctuating symptoms associated with the peaks (breast tenderness, hyperactivity) and valleys (fatigue, depression) of testosterone. Nevertheless, IM testosterone remains a common treatment for hypogonadism, particularly when cost is a factor or when men cannot achieve adequate serum levels with gels or patches.

Buccal tablets and implanted pellets are also available for testosterone therapy, but these are rarely used in routine practice. It should be noted emphatically that oral testosterone preparations are not approved for the treatment of testosterone deficiency in the United States and should not be used "off-label": they can cause serious liver toxicity.

The goal of replacement is to raise serum testosterone levels into the mid-normal range for healthy young men, roughly 400-700 ng/dl. In patients using gels, testosterone levels may be measured at any time of day. Patients using patches should have testosterone levels measured 3 to 12 hours after patch application.[3] Patients on IM testosterone should have testosterone levels checked at the midpoint between injections. Patients with levels above or below 400-700 ng/dl will require adjustments in their therapy.[3] Assessment of testosterone levels generally occurs after 3 months of treatment, but may occur as soon as 1-2 weeks after initiation of therapy in patients using gels.

In addition to being assessed for appropriate testosterone levels, patients require monitoring for potential adverse effects. A major concern is the potential for unmasking occult prostate cancer with testosterone replacement. Both DRE and PSA should be repeated at 3 to 6 months, and then in accordance with evidence-based guidelines for prostate cancer screening. If there is an increase in PSA > 1.4 ng/ml within a 12-month period of therapy, detection of a prostatic abnormality on DRE, or an AUA/IPSS > 19, then urologic consultation should be obtained. For those men who have sequential PSA measurements for a period more that 2 years, PSA velocity should be used for identification of men at higher risk for prostate cancer. If after 6 months of testosterone therapy the PSA velocity is > 0.4 ng/ml per year, then urological consultation is recommended. Men younger than age 40 are at low risk for the development of prostate cancer, and screening may not be necessary.[3]

Erythrocytosis, or hematocrit > 54%, can occur in testosterone replacement due to the stimulating effect of testosterone on erythropoiesis. Hematocrit should be checked prior to initiation of therapy, at 3 to 6 months, and then annually. Erythrocytosis results in increased blood viscosity, which increases the risk for vascular

events including stroke and myocardial infarction.[5] Transdermal testosterone is less likely to cause erythrocytosis than IM testosterone. If a patient is found to have erythrocytosis from testosterone replacement, reduction of dose, change in method of delivery, cessation of therapy or even phlebotomy may be indicated.

Development or exacerbation of sleep apnea may occur in patients otherwise at risk of this disorder. Gynecomastia may occur due to aromatization of testosterone to estradiol in peripheral fat tissue,[5] but is usually reversible if therapy is discontinued. Bone mineral density should be repeated after 1 to 2 years of testosterone therapy in hypogonadal men with osteoporosis or low trauma fracture.[3]

The effects of testosterone replacement on cardiovascular health have not been determined. Recently, a trial of testosterone supplementation in older men with limited mobility was terminated early due to an increased occurrence of adverse cardiovascular events in the treatment group.[10] These results may have been due to chance. Still, the outcome should sound a note of caution.

It is important to recognize that recommendations regarding testosterone therapy are primarily based on short-term studies. The risks and benefits of long-term testosterone treatment are, unfortunately, unknown.

References

1. Kazi M, Geraci SA, Koch CA. Considerations for the diagnosis and treatment of testosterone deficiency in elderly men. *Am J Med* 2007; 120:835-40.
2. Wu FCW, Tajar A, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med* 2010;363:123-35.
3. Bhasin S, Cunningham G, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95: 2536-59.
4. Wang C, Nieschlag E, et al. Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. *J Andrology* 2009;30:1-9.
5. Tung D, Cunnigham G. Androgen deficiency in men. *The Endocrinologist* 2007;17: 101-15.
6. Wheeler MJ, Barnes SC. Measurement of testosterone in the diagnosis of hypogonadism in the ageing male. *Clin Endocrinol* 2008;69:515-25.
7. Nolten, W. Androgen deficiency in the aging male: when to evaluate and when to treat. *Current Urology Reports* 2000;1:313-9.
8. Rosner W, Auchus R, et al. Utility, limitations and pitfalls in measuring testosterone: An Endocrine Society position statement. *J Clin Endocrinol Metab* 2007;92:405-13.
9. Miner M, Sadovsky R. Evolving issues in male hypogonadism: Evaluation, management, and related comorbidities. *Cleve Clinic J Med* 2007;74:S38-S46.
10. Basaria S, Coviello AD, et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010;363:109-22.

Jennifer J. Miranda, MD, is Clinical Fellow, Division of Endocrinology, Alpert Medical School of Brown University.

Marc J. Laufgraben, MD, MBA, is Clinical Associate Professor of Medicine, Division of Endocrinology, Alpert Medical School of Brown University, and Clinical Director of Hallett Center for Diabetes and Endocrinology.

Disclosure of Financial Interests

The author and/or spouse/significant other has no financial interests to disclose.

Correspondence

Marc J. Laufgraben, MD, MBA
Hallett Center for Diabetes and Endocrinology
900 Warren Avenue
East Providence, RI 02914
Phone: (401) 444-6304
e-mail: mlaufgraben@lifespan.org