

Testosterone deficiency: Practical guidelines for diagnosis and treatment

Testosterone can be administered orally, transdermally, or by injection to improve a hypogonadal man's sense of well-being, sexual function, bone density, and muscle strength.

ABSTRACT: Testosterone deficiency in men is a common but often-missed diagnosis. After confirmation of the diagnosis, exclusion of any reversible causes or contraindications to the use of testosterone, replacement therapy may be offered. Methods of replacement include injectable testosterone esters, transdermal testosterone (gels or patches), or oral testosterone in the form of testosterone undecanoate. Men receiving testosterone therapy should be followed according to a standardized monitoring plan; testosterone levels should be assessed 2 to 3 months after therapy is initiated, followed by annual examinations to assess whether symptoms have improved and whether the patient is experiencing adverse events.

Hypogonadism affects approximately 40% of men age 45 or older,¹ although less than 5% of these men are actually diagnosed and treated for the condition. Despite some controversy, testosterone therapy has been established as a safe and effective principal treatment for hypogonadism for nearly 70 years. In the last decade, studies have improved our understanding of hypogonadism and have helped clarify its prevalence and associated comorbid illnesses.¹⁻³

Causes

The principal causes of hypogonadism are testicular failure (primary hypogonadism), pituitary and/or hypothalamic failure (secondary hypogonadism), and age-related dysfunction (generally a combination of primary and secondary hypogonadism).⁴

The most common causes of primary hypogonadism include Klinefelter syndrome, myotonic dystrophy, vanishing testicle syndrome (congenital anorchidism), and radiation-induced or chemotherapy-induced hypogonadism.⁴ Common congenital causes of secondary hypogonadism include Kall-

manns syndrome and idiopathic hypogonadotropic hypogonadism (IHH). Causes of acquired secondary hypogonadism include adult-onset IHH, hematochromatosis, and pituitary tumors, including prolactinomas.⁴

Diagnosis

Confirming a diagnosis of hypogonadism generally involves three components. First, there should be symptoms of androgen deficiency; second, there should be unequivocal biochemical evidence of low testosterone levels; and third, there should be a positive response to testosterone replacement therapy. If all three of these diagnostic components are not present, the practitioner should question the diagnosis and consider discontinuing testosterone therapy.

Symptoms

Symptoms of hypogonadism can include mood changes such as irritability or increased sadness, reduced libido, low energy, fatigue, decreased muscle bulk, decreased muscle strength, mus-

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cle aches, hot flushes, decreased ability to concentrate on tasks, lack of morning erections or less rigid erections, decreased volume of ejaculate, and infertility.⁴

Physical signs of hypogonadism can include a change in body composition with more central body fat, gynecomastia, testicular atrophy (more common with primary hypogonadism), muscular atrophy, osteoporotic fractures, and height loss.⁴

As a comorbid condition, hypogonadism occurs with increased frequency among men with osteoporosis, osteoporotic fractures, type 2 diabetes, metabolic syndrome, and chronic obstructive pulmonary disease (COPD).¹

Table 1 lists some of the specific and less-specific symptoms and signs related to androgen deficiency hypogonadism.⁴ It remains challenging for the physician to detect hypogonadism as many of the symptoms of androgen deficiency are not specific on their own and gain more significance by the company they keep. The less-specific symptoms should prompt investigation for hypogonadism when they occur in concert with specific symptoms.

Testing considerations

Available testosterone tests measure the total amount of the hormone in the serum, the free amount in the serum, or the bioavailable amount, which is a combination of free and loosely albumin-bound testosterone.

While it is a point of some controversy, the author recommends the bioavailable testosterone test as the best for confirming low serum testosterone levels because clinicians have found it enables better distinction of patients who are hypogonadal. Bioavailable testosterone testing is available from a number of laboratories in British Columbia. Although some guidelines suggest first obtaining a total testos-

terone level, sex hormone binding globulin (SHBG) levels can vary widely and lead to erroneous results unless a bioavailable testosterone level is also obtained.^{4,5}

Physicians should be aware that testosterone levels fluctuate even in healthy males. For this reason a eugonadal male will occasionally have a transiently low testosterone level. Repeat testing will generally reveal normal values. Conversely, a hypogonadal male will occasionally have testosterone values in the low-normal range, and repeat testing will then find a low testosterone level and confirm the original clinical impression.⁵⁻⁷

Patients who test low for testosterone should also be tested for luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin levels. Prolactin elevation should prompt consideration of a pituitary tumor. Ferritin levels should be checked in cases of hypogonadotropic hypogonadism to exclude hemochromatosis.^{4,5}

Testosterone levels can be affected by general health status. Acute illness will cause a transient drop in testosterone. To avoid confusion and overdiagnosis of hypogonadism, practitioners should remember that testosterone measurements of men who are sick enough to require hospitalization cannot be relied on for definitive diagnoses. Ideally, the patient should be unstressed and physiologically stable before testing. It is also important to take blood samples for testosterone before 10 a.m. to avoid registering the normal circadian dip in testosterone that occurs in the afternoon.^{4,6}

Screening for hypogonadism in the general population is not indicated.⁴ Case finding in selected circumstances is, however, acceptable, such as when testing for low testosterone is part of the workup for osteoporosis or unexplained anemia.

Table 1. Androgen deficiency symptoms and signs.

Specific symptoms and signs

- Incomplete sexual development, eunuchoidism, aspermia.
- Reduced sexual desire (libido) and activity.
- Fewer spontaneous erections.
- Breast discomfort, gynecomastia.
- Loss of body hair (axillary and pubic)—reduced need to shave.
- Very small or shrinking testes (especially < 5 mL in volume).
- Infertility, low or zero sperm counts.
- Height loss, low-trauma fracture, low bone mineral density.
- Lower muscle bulk and strength.
- Hot flushes, sweats.

Less-specific symptoms and signs

- Decreased energy, motivation, initiative, aggressiveness, self-confidence.
- Feeling sad or blue—depressed mood, dysthymia.
- Poor concentration and memory.
- Sleep disturbance, increased sleepiness.
- Mild anemia (normochromic, normocytic, in the female range).
- Increased body fat, body mass index.
- Diminished physical or work performance.

Adapted from Bhasin S, Cunningham GR, Hayes FJ, et al.⁴

Other useful tests may include assessment for sleep apnea in men with secondary hypogonadism, measurement of fasting blood glucose and lipids, and a DEXA measurement of bone mineral density (BMD) to exclude concomitant osteoporosis.^{4,5}

In men with secondary hypogonadism there is a possibility of pituitary disease. Although imaging of the pituitary gland is not required for most such men, CT or MRI scanning of the pituitary gland should be considered for men who develop secondary hypogonadism before age 50, experience a rapid onset of symptoms, have profound hypogonadism, have elevated prolactin levels, or have visual symptomatology.

Table 2. Adverse events and effects linked to testosterone administration.

Clearly linked effects

- Erythrocytosis.
- Decreased urinary flow rates.
- Acne and oily skin.
- Reduced sperm production and fertility (reversible in the short term).

Uncommon effects less clearly linked

- Gynecomastia.
- Male pattern balding (familial).
- Worsening symptoms of benign prostatic hyperplasia.
- Inducing or worsening of obstructive sleep apnea.
- Fluid retention.
- Growth of pre-existing prostate cancer.
- Growth of breast cancer (theoretical).

Formulation-specific effects

- Alkylated oral tablets: Effects on liver and cholesterol (only applies to alkylated testosterone such as methyltestosterone).
- Injectable testosterone enanthate or cypionate: Fluctuation in mood or libido, pain at injection site, excessive erythrocytosis (especially in older patients).
- Transdermal patches: Skin reactions at application site.
- Transdermal gels: Potential risk of testosterone transfer to partner.

Adapted from Bhasin S, Cunningham GR, Hayes FJ, et al.⁴

Table 3. Monitoring testosterone levels.

- **Injectable testosterone enanthate or cypionate:** Measure serum testosterone levels midway between injections, or at trough. Adjust dose to achieve testosterone levels in mid-normal range.
- **Transdermal patch:** Assess testosterone levels 2 to 12 hours after applying patch. Adjust dose to achieve testosterone levels in mid-normal range.
- **Transdermal gel:** Determine testosterone level any time after patient has been on treatment for at least 1 week. Adjust dose to achieve serum testosterone levels in mid-normal range.
- **Oral testosterone undecanoate:** Check serum testosterone levels 3 to 5 hours after ingestion.

Adapted from Bhasin S, Cunningham GR, Hayes FJ, et al.⁴

All men diagnosed with hypogonadism should be given a complete physical examination with special attention to the testicles, prostate, and breasts.^{4,5}

Treatment

Studies have shown that testosterone replacement therapy for hypogonadal men improves their sense of well-being, sexual function, mood, libido, bone density, muscle bulk, and muscle strength. It also may decrease visceral and peripheral body fat and can reduce insulin resistance and blood sugar.^{4,5,8}

Treatment of hypogonadism can be provided through injectable testosterone esters, transdermal testosterone (gels or patches), or oral testosterone in the form of testosterone undecanoate. All of these delivery modes are acceptable in appropriate doses and allow patients the benefit of having a variety of options to choose from. It may be necessary for practitioners to adjust the dose to suit a patient's physiology, and switching to another delivery mode may be necessary if blood levels are not appropriate or if side effects such as polycythemia should occur.^{4,5}

Some common delivery modes and recommended regimens for testosterone replacement therapy are as follows:

- **Injection:** 75 to 100 mg of testosterone enanthate or cypionate administered weekly, or 150 to 200 mg administered every other week.
- **Patch:** One or two 5 mg testosterone patches applied nightly on the skin of the back, thigh, or upper arm—away from pressure areas.
- **Gel:** 5 to 10 g of testosterone gel applied daily.
- **Tablet:** 80 mg of testosterone undecanoate taken orally twice a day with meals.⁴

Table 2 lists some potential adverse effects of testosterone treat-

ment.⁴ It is very uncommon to see a deterioration in mood with aggressiveness or anger as an outcome of testosterone treatment. Generally, this symptom complex is more often associated with hypogonadism, and mood in fact improves with restoration of the eugonadal state.⁹ In patients with severe heart failure or liver disease, or occasionally among very elderly patients, testosterone treatment may result in mild fluid retention that requires dose adjustments or diuretic therapy.^{4,5}

Monitoring

Men receiving testosterone therapy should be followed according to a standardized monitoring plan^{4,5} to ensure any potential side effects are detected early. Before initiating treatment, the practitioner should perform a digital rectal examination (DRE) and check the PSA level. This should be done again at 3 months, and then in accordance with guidelines for prostate cancer screening, depending on the age and ethnicity of the patient. Testosterone levels should be assessed 2 to 3 months after therapy is initiated, as described in **Table 3**. The goal is to raise serum testosterone levels to the mid-normal range. As well as assessing prostate health and testosterone levels, the practitioner should do the following:

- Evaluate the patient 3 months after treatment begins, and follow up with annual examinations to assess whether symptoms have improved and whether the patient is experiencing any adverse events.
- Obtain a baseline hematocrit value, check at 3 months, and then check annually. If hematocrit is greater than 52%, stop therapy until it decreases to a safe level and re-evaluate the patient for hypoxia and sleep apnea. If erythrocytosis develops with intramuscular (IM) therapy,

three options exist: the dose can be reduced; the dose interval can be contracted with a lower dose per injection but a similar overall total dose per month; or a non-IM delivery mode can be used. Erythrocytosis is much less common with transdermal formulations, and extremely rare with oral testosterone undecanoate.

- Measure bone mineral density (BMD) of the lumbar spine or femoral neck (or both) after 1 to 2 years of testosterone therapy in hypogonadal men with osteoporosis or low-trauma fracture, consistent with regional standard of care.
- Request a urologic consultation in the following cases:
 - Verified serum PSA concentration greater than 4.0 µg/L.
 - Increase in serum PSA concentration greater than 1.4 µg/L within any 12-month period of testosterone treatment.
 - PSA velocity greater than 0.4 µg/L/year, using the PSA level after 6 months of testosterone administration as a reference (only applicable if PSA data are available for at least 2 years).
 - Prostatic abnormality is detected on DRE.
 - AUA/IPSS (International Prostate Symptom Score) greater than 19.
- Evaluate formulation-specific adverse effects at each visit:
 - Intramuscular injections of testosterone enanthate and cypionate: Ask about fluctuations in mood or libido.
 - Testosterone patches: Look for skin reaction at the application site.
 - Testosterone gels: Advise patients to cover the application sites with a shirt and to wash the skin with soap and water before having skin-to-skin contact because testosterone gel leaves a residue on the skin that can be transferred to a woman or

child who comes in close contact. Serum testosterone levels are maintained when the site is washed 6 hours after applying the gel.

Cautions and considerations

Special considerations are necessary for testosterone treatment in patients with certain diseases. It is generally recommended that men with prostate cancer not be treated with androgens

for fear of accelerating tumor growth.⁴ However, opinions vary on treatment for men who are clearly hypogonadal and who have been successfully treated for prostate cancer in the past.^{4,5} It is the author's opinion that a year or two after successful surgical treatment for prostate cancer and in consultation with the patient's urologist or oncologist, testosterone treatment can be provided for carefully selected patients under medical supervision and with informed consent.¹⁰

There are currently no definitive studies suggesting that risk of prostate cancer is increased in hypogonadal men rendered eugonadal. Large, randomized, placebo-controlled studies in this area would be welcomed to definitely determine if any risk exists.

Testosterone and cardiovascular events

A recent study in the *New England Journal of Medicine* questioned the cardiovascular safety of testosterone therapy in aging men.¹¹ The study was designed to assess whether testosterone replacement increased muscle strength for frail elderly men. Although the results supported this hypothesis, they also suggested an increased rate of cardiovascular events in the subject

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group, and as a result the study was ended early.¹¹

It is important to note that the results of this study do not indicate a causal relationship between testosterone treatment and heart disease. The study was not designed to assess the risk of cardiovascular disease related to testosterone and, more importantly, there was a randomization failure with respect to the risk for adverse cardiovascular events. More patients in the testosterone treatment arm of the study had hypertension or dyslipidemia, thereby predisposing them to cardiovascular disease and biasing the study outcome.¹¹

Meta-analyses exploring a possible connection between testosterone use and adverse coronary events have

found no evidence of such a connection.¹² Testosterone therapy in hypogonadal men has been shown to decrease angina,¹³ and testosterone deficiency is a marker for increased mortality in men with known coronary artery disease.¹⁴

have shown testosterone replacement therapy increases bone mineral density in hypogonadal men.¹⁶⁻¹⁸ However, larger long-term studies are needed to assess whether fracture rates are lower in osteoporotic hypogonadal men treated with testosterone.

When healthy men are given replacement doses of testosterone, approximately two-thirds of them are rendered azoospermic. In short-term studies this outcome is completely reversible.

A multicentre study sponsored by the National Institutes of Health is presently under way in the United States to clarify the long-term cardiovascular effects of testosterone therapy in men. In the interim, a significantly hypogonadal man who has heart disease or is at risk for heart disease should not be refused testosterone therapy on the basis of cardiovascular risk. It would be prudent, however, to monitor the man and to ensure his cholesterol levels are not adversely affected by the introduction of testosterone.

Testosterone and osteoporosis

Hypogonadism is a well-established cause of osteoporosis in men and women. Androgen deprivation in men increases the risk of osteoporosis and osteoporotic fractures.¹⁵ Several trials

Testosterone and infertility

When healthy men are given replacement doses of testosterone, approximately two-thirds of them are rendered azoospermic. In short-term studies this outcome is completely reversible. In hypogonadal men given testosterone, any residual sperm production present at the time of diagnosis will be further suppressed, and it is important that patients be informed about this side effect. For patients who wish to retain their fertility, androgen replacement can be deferred until their family is completed, or they may be offered alternative therapies.⁴

For men with primary hypogonadism, the spermatogenic defect is not usually treatable. Men with secondary hypogonadism can usually be rendered fertile by either gonadotropin therapy or occasionally clomiphene citrate.

Androgen abuse by athletes

Misuse of androgens by competitive and recreational athletes is quite common, and physicians should be alert to this. Both testosterone esters and synthetic testosterone are used.

Red flags for androgen abuse among men include small testes, low sperm count, high hematocrit and hemoglobin values, low serum SHBG, and undetectable LH and FSH concentrations. Alkylated testosterone compounds may also elevate liver function test results and dramatically lower HDL cholesterol, while recent use of injectable testosterone can increase creatine phosphokinase (CPK) levels.

Summary

Approximately 40% of men age 45 or older are affected by hypogonadism, although less than 5% are diagnosed and treated for this condition.

Symptoms of hypogonadism can include mood changes, reduced libido, low energy, decreased muscle bulk and strength, hot flushes, decreased ability to concentrate, lack of morning erections, decreased volume of ejaculate, and infertility.

To confirm a diagnosis of hypogonadism physicians should look for:

- Symptoms of androgen deficiency.
- Unequivocal biochemical evidence of low testosterone levels.
- A positive response to testosterone replacement therapy.

The principal treatment for hypogonadism is testosterone replacement therapy, which can be delivered by injection, transdermally, or orally. Testosterone replacement therapy for hypogonadal men has been shown to improve sense of well-being, sexual function, mood, libido, bone density, and muscle bulk and strength. It also may decrease visceral and peripheral body fat and can reduce insulin resistance and blood sugar.

It is generally recommended that men with existing prostate cancer not be treated with androgens to avoid the possibility of accelerating tumor growth.

Hypogonadal men given testosterone will experience further suppression of sperm production. Patients who wish to retain their fertility should be informed about this side effect.

Competing interests

Dr Bebb has received fees for speaking and/or consulting for Solvay, Abbott, and Organon.

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