CME

Hypogonadism in men: Updates and treatments

Gina Ugo-Neff, PA-C; Denise Rizzolo, PhD, PA-C

ABSTRACT

Hypogonadism is a clinical syndrome of testosterone deficiency that presents with nonspecific symptoms of sexual dysfunction, fatigue, and decreased strength or muscle mass. Men with obesity, diabetes, and other comorbidities are at higher risk for hypogonadism. Patients presenting with symptoms should be tested for low testosterone and treated with testosterone replacement. Testosterone therapy carries risks and must be closely monitored. Patients treated for hypogonadism may experience improvement of symptoms and quality of life.

Keywords: hypogonadism, testosterone deficiency, sexual dysfunction, quality of life, treatment, low T

Learning objectives

- Discuss the causes of hypogonadism in adult men.
- Review the pathophysiology of hypogonadism.
- Explain the diagnostic workup of patients presenting with hypogonadism.
- Compare and contrast treatment strategies for patients with hypogonadism.
- Describe common adverse reactions to treatments.

Testosterone deficiency or hypogonadism is defined as "a clinical syndrome that results from failure of the testis to produce physiological concentrations of testosterone."[1] Hypogonadism has been described in the literature by many names: adult-onset hypogonadism, testosterone or androgen deficiency, or late-onset hypogonadism.[2] In the media it is known as *andropause* and *low T*.[2] An estimated 2 to 4 million men in the United States have hypogonadism.[3] Hypogonadism affects one in 10 men over age 60 years and one in three men with diabetes.[4]

Gina Ugo-Neff practices at Uropartners at Rush University in Chicago, Ill. **Denise Rizzolo** is an assistant clinical professor in the Pace Completion Program in the Department of Physician Assistant Studies in New York City and an assessment specialist at the Physician Assistant Education Association. The authors have disclosed no potential conflicts of interest, financial or otherwise.

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Clinicians must know the guidelines for hypogonadism screening and be able to educate patients on treatment and the risks and benefits of each type of testosterone replacement. This article reviews guidelines, diagnosis, and treatment for hypogonadism.

PATHOPHYSIOLOGY

Testosterone is responsible for the development of primary sexual characteristics during puberty, spermatogenesis, regulation of body composition (maintenance of muscle mass and fat distribution), bone health, metabolism, red blood cell production, and aspects of sexual function.[5] The hypothalamic-pituitary axis regulates testosterone production via a negative feedback loop. Gonadatropin-releasing hormone (GnRH) secreted by the hypothalamus travels to the anterior pituitary gland, which in turn secretes luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These hormones, known as gonadotropins, travel to the testicles through the blood, where LH stimulates Leydig cells to produce testosterone and FSH stimulates Sertoli cells to produce sperm.[6] Most testosterone is bound to albumin, which forms a weak bond, or sex hormone-binding globulins (SHBG), which forms a tight bond. The rest circulates as free testosterone, which is unbound to proteins.[7] Only free and weakly bound testosterone is bioavailable or able to bind to the androgen receptors in the tissues. Therefore, free testosterone is important for cell function, such as muscle cell replication.

CAUSES OF HYPOGONADISM

Hypogonadism results from a breakdown or malfunction in the pituitary axis, either from testicular dysfunction

Key points

- Hypogonadism is a clinical syndrome that results from failure of the testis to produce physiologic concentrations of testosterone.
- Diagnosis requires clinical symptoms and two low morning testosterone laboratory values taken on separate days.
- Testosterone replacement can be delivered via transdermal gels, IM or subcutaneous injections, subcutaneous pellet implants, patches, or oral pills.
- Patients on testosterone replacement need close monitoring for abnormal laboratory values and adverse reactions. Adjust the dosage to maintain testosterone at physiologic levels.

(primary hypogonadism) or, in a patient with normally functioning testicles, from problems in the pituitary gland or hypothalamus (secondary hypogonadism).

Primary hypogonadism, also called hypergonadotropic hypogonadism, results in low testosterone with above-normal serum LH and FSH concentrations. Causes include genetic conditions such as Klinefelter syndrome, anatomic defects, infection, tumor, injury, iatrogenic causes, and excess alcohol consumption.[5]

Secondary hypogonadism, also called hypogonadotropic hypogonadism, is caused by deficient release of gonadotropins by the pituitary gland, resulting in low testosterone with low to low-normal LH and FSH levels. Causes include hyperprolactinemia (secondary to pituitary adenoma), GnRH deficiency with anosmia (Kallman syndrome), hypothalamic lesions or disorder, and pituitary lesions or disorders.[3] **Table 1** lists common causes of primary and secondary hypogonadism. As men age, total testosterone values decline about 0.8% per year beginning at age 40 years. Free testosterone levels decline about 2% per year and SHBG increases 1.6% per year.[8] Men with comorbidities such as COPD, type 2 diabetes, obesity, dyslipidemia, or hypertension have demonstrated higher prevalence of hypogonadism than healthy men.[9] Men with HIV also have a higher prevalence, with estimates ranging from 20% to 70%.[10] The causes of low testosterone in patients with HIV are related to use of prescription medications, hepatitis C coinfection, loss of lean body mass, poor nutritional status, and use of illicit drugs.[10] Many medications can interfere with testosterone function, especially opioids. Up to 86% of patients on chronic opioids have low testosterone.[11] Opioids directly inhibit GnRH through the mu-opioid receptor, reducing testosterone production via the hypothalamic-pituitary axis.[11] Screen patients for low testosterone if they are on long-term pain management and have hypogonadism symptoms. Both physical and psychologic stressors may reduce testosterone levels temporarily. Clinicians must keep this in mind and not screen patients during acute illness or periods of stress. Testosterone levels typically return to normal in days to weeks after resolution of the stressor.[2]

DIAGNOSIS

Diagnosis of hypogonadism relies on clinical signs and symptoms, confirmed with low total and/or free testosterone levels. Men may report sexual symptoms including erectile dysfunction, decreased libido, and reduced intensity of orgasm and genital sensation.[5] Other symptoms include reduced energy, depressed mood, irritability, decreased muscle mass or strength, and difficulty concentrating.[6] Look for signs of testosterone deficiency, anemia, muscle wasting, reduced bone mass or bone mineral density, absence or regression of secondary sexual characteristics, abdominal adiposity, metabolic syndrome, and oligospermia or azoospermia.[3]

Laboratory testing is essential for making the diagnosis. The guidelines define the threshold for low total testosterone as less than 300 ng/dL or 10.4 nmol/L.[12] In older men, testosterone levels can decrease 15% to 20% over 24 hours.[12] In men under age 50 years, testosterone may drop up to 40% throughout the course of the day. Because of these diurnal variations, measurements must be drawn between 8 a.m. and 10 a.m. The Endocrine Society recommends testing two separate morning total testosterone laboratory values. Measure free testosterone in men whose total testosterone levels are at the lower limit of normal, and in men with conditions predisposing them to lower SHBG (such as diabetes or obesity).[1] Studies demonstrate that men with low free testosterone display sexual and physical symptoms of hypogonadism, regardless of total testosterone concentrations.[1] Therefore, free testosterone values may be valuable to make the diagnosis. The testosterone values must be measured on different days, although the number of days in between tests is not specified. In addition, many commercial insurance companies, including Medicare, require two separate low laboratory values to qualify for coverage of testosterone replacement therapy.[13]

When testing for testosterone, also evaluate LH, which may help establish the cause of hypogonadism.[14] Additional tests such as estradiol and prolactin also may be of value in determining the cause of low testosterone.

TREATMENT

Testosterone replacement therapy has been shown to improve symptoms of low libido, lean body mass, and sexual function as well as to maintain bone strength.[15] Therapy comes in several different forms: gels, injections, pellet insertions, patches, and oral pills. Work with patients to find the type of treatment that fits best with the patient and his lifestyle. Because many of these treatments are expensive, insurance coverage also is a factor. All formulations of testosterone replacement therapy have demonstrated increases in testosterone levels in men with

TABLE 1. Causes of hypogonadism[5,6]

Primary
- Klinefelter syndrome
- Cryptorchidism
- Undescended testicles
- Varicocele
- Toxins such as heavy metals or alcohol
- Testicular trauma such as radiation or chemotherapy
- Chronic renal failure
- HIV/AIDS
- Hemochromatosis
- Infections such as mumps orchitis
- Drugs such as opioids, spironolactone, corticosteroids, ketoconazole, anticonvulsants, and immunosuppressants

Secondary
- Pituitary disease
- Head or pituitary trauma
- Space-occupying lesions of the pituitary or hypothalamus
- Diabetes
- Obesity
- Neoplasm
- Chronic systemic illness such as chronic obstructive pulmonary disease
- Prader-Willi syndrome
- Kallman syndrome
- Drugs

hypogonadism. Formulations may change throughout treatment based on patient preferences, adverse reactions, and patient response. Educate patients about the frequent monitoring required to establish a steady dose, and the regular laboratory checks that are needed throughout treatment (**Table 2**).[14]

INJECTIONS

Injectable forms of testosterone have been used since 1937. Testosterone propionate was the first on the market, but its half-life was short, only 1 to 2 days.[16] The three main formulations now on the market are testosterone cypionate (TC), testosterone enanthate, and testosterone undecanoate.

TC normally is given IM every 2 weeks. It comes in 100 mg/mL and 200 mg/mL solutions. The half-life is 8 days. Peak levels are achieved within 24 hours and last 3 to 5 days.[17] TC is suspended in cottonseed oil, and is contraindicated in patients with sensitivity to testosterone synthesized from soy.[18]

Testosterone enanthate has similar pharmacokinetics as TC, with a half-life of 7 to 9 days, but is suspended in sesame seed oil.[19] In both TC and testosterone enanthate, concentrations peak 1 to 2 days after injection and wane over 2 weeks. Benefits of IM injections are that they can be performed at home, with convenient dosing and effective normalization of testosterone levels. Risks of injections include bleeding and discomfort. Though standard application is IM, multiple studies have demonstrated subcutaneous injections to be as effective at increasing and maintaining testosterone levels.[20] Research also demonstrates that patients prefer and tolerate subcutaneous injections over IM injections. Patients report lower preinjection anxiety and postinjection pain.[21] Subcutaneous injections are given once weekly with a 27- to 28-gauge needle. A subcutaneous autoinjector of testosterone enanthate is now available in 50 mg, 75 mg, and 100 mg strengths.[22]

Testosterone undecanoate is a long-acting injectable testosterone formulation. After the first injection, this offers the convenience of injections being given once every 10 to 12 weeks. However, these injections must be given by a trained healthcare professional because of the risk of pulmonary oil microembolism and anaphylaxis.[23] Although this adverse reaction is rare, the compound is only available through a Risk Evaluation and Mitigation Strategy program and cannot be injected at home.[23]

TOPICAL GELS

Transdermal gels became available in 2003, with androgel 1% (a testosterone gel) being the first on the market in the United States. Multiple formulations followed with similar carrier systems.[18] Gels or foams come in metered-dose pumps, packets, or tubes in various concentrations. All formulations are generic. The benefits of gels are high efficacy of testosterone normalization, effective treatment of hypogonadal symptoms, ease of application, and consistent testosterone levels.[15,18] Disadvantages associated with transdermal gels include skin irritation and risk of skin-to-skin transference to others. Explain to patients using gels that they must apply the gel daily using gloves or wash their hands well after application.

Androderm, the only testosterone transdermal patch on the US market, is an effective delivery system, but has a high incidence of skin irritation that causes many patients to discontinue treatment.[24]

BUCCAL AND NASAL PREPARATIONS

Buccal and nasal preparations are available, but have limited use due to common adverse reactions. The only available buccal form of testosterone is a 30-mg tablet applied to the gums twice daily; the tablet is effective in maintaining testosterone levels, and the most common adverse reactions are gingivitis, gum irritation, and taste disturbance.[25,26]

A nasal gel delivering 5.5 mg of testosterone per pump can be self-administered into the nostrils three times daily. The recommended dose is 33 mg daily (6 pumps).[16] Its half-life is variable, between 10 and 100 minutes. About 40 minutes after administration, testosterone levels return to normal.[27] This quick onset, shorter half-life, and longer troughs between peaks of testosterone may mimic the circadian pattern of testosterone release. Therefore, the nasal gel may preserve aspects of the hypothalamic-pituitary gonadal function, such as continued release of gonadotropins and production of endogenous testosterone. The

longer troughs between peaks reduce exposure of exogenous testosterone and may help limit adverse reactions to testosterone replacement therapy such as hematocrit overproduction, and preserve the production of sperm and fertility.[28] Adverse reactions to the nasal gel include nasopharyngitis, rhinorrhea, parosmia, headache, and nasal discomfort.[29]

SUBCUTANEOUS PELLETS

Subcutaneous testosterone pellets were the first effective testosterone replacement developed in the 1940s, but were not approved by the FDA until 1972.[16] The one brand available now contains 75 mg of testosterone in each pellet; a pellet is inserted into the fat of the buttocks, lower abdomen, or thigh every 3 to 6 months. This procedure is performed in the clinician's office or hospital using sterile technique and takes about 15 minutes. The number of pellets varies by patient and can range from 6 to 12. Men with a BMI greater than 25 require 10 to 12 pellets; those whose BMI is less than 25 require 6 to 9 pellets.[30] Testosterone concentration peaks within 2 weeks, with a slow decline over 3 to 4 months, but levels remain above 300 ng/dL for the 3 to 4 months.[31] Risks of pellet insertion include pain, bleeding, infection, and pellet extrusion.

TABLE 2. Testosterone treatments[17,20,21]

Testosterone formulation	Initial dosing	Dose frequency	Pharmacokinetics	Adverse reactions	Serum testosterone monitoring
IM testosterone cypionate	100 mg/mL 200 mg/mL	1-2 weeks	Supratherapeutic testosterone levels 4-8 days after injection	Pain and inflammation at injection site	1 week after dose and trough level
IM testosterone enanthate	200 mg/mL	1-2 weeks	Supratherapeutic testosterone levels 36-48 hours	Pain and inflammation at injection site	1 week after dose and trough level
IM testosterone undecanoate	750 mg once, 750 mg 4 weeks, 750 mg every 10 weeks	10 weeks	Serum testosterone peaks by day 7, testosterone declines over 10 weeks	Pain and inflammation at injection site, POME/anaphylaxis	Trough level
Subcutaneous testosterone cypionate	100 mg/mL or 50 mg/mL	1 week or twice weekly	Testosterone levels peak in 24 hours	Pain and inflammation at injection site	Trough level
Subcutaneous testosterone enanthate	75 mg/mL	Once per week	Peaks in about 6 hours, declines over 1 week	Pain and inflammation at injection site	Trough level
Gel 1.62% (Androgel)	50 mg or 2 pumps applied to shoulders, upper arms daily in morning	Daily	Peaks in 16-22 hours and absorbed continuously over 24 hours	Application site skin irritation, acne	2-4 weeks after application
Gel 2% (Axiron)	60 mg (2 pumps) applied under arm	Daily	Peaks in 2-4 hours	Application site skin irritation	2-4 weeks after application
Gel 1% (Testim)	50 mg/5 g (1 tube) applied to shoulders, upper	Daily	Peaks in 2-4 hours	Application site skin irritation	2-4 weeks
Gel 2% (Fortesta)	10 mg/0.5 g applied to inner thigh	Daily	Peaks in 2-4 hours	Application site skin irritation	2-4 weeks
Transdermal patch (Androderm)	4 mg/day	Daily	Peaks in 8 hours	Skin blistering, pruritus, skin irritation	2 weeks
Buccal (Striant)	30 mg applied to gums	Applied every 12 hours	Peaks in 10-12 hours	Gum irritation, gingivitis	2 weeks after dose
Nasal (Natesto)	33 mg/day 1 actuation in each nostril	Three times daily	Peaks in 40 minutes	Nasal irritation, rhinorrhea, nose bleeds, nasal discomfort	2 weeks
Testosterone pellets (Testopel)	75 mg/pellet 6-12 pellets	Inserted every 3-6 months	Peaks within 2 weeks	Insertion site pain, bleeding, infection, pellet extrusion	1-month peak level, and 10-12 weeks post insertion

ORAL TESTOSTERONE

Testosterone undecanoate is the newest approved testosterone formulation in the United States, and the first oral testosterone approved since the 1960s. The medication is taken twice daily with food and comes in 158 mg, 198 mg, and 237 mg strengths. The recommended starting dose is 237 mg twice daily and may be titrated with the 158 mg and 198 mg doses. Common adverse reactions include headache, hematocrit increase, BP increase, burping, and decreased high-density lipoprotein cholesterol.[32]

SAFETY CONCERNS

Safety, particularly cardiovascular (CV) and prostate health risks, remains a concern for men on testosterone replacement therapy. Testosterone replacement therapy is contraindicated in men with breast cancer, metastatic prostate cancer, unevaluated prostate nodule or induration, unevaluated prostate-specific antigen (PSA) greater than 4 ng/mL, and uncontrolled heart failure. Warn men who would like to remain fertile of the possibility of infertility and reduced sperm counts with use of testosterone replacement.[14] All men considering testosterone replacement therapy should be educated on the risks so that they can make an informed decision.

CV risk Multiple studies have reported an increase in CV events in men on testosterone replacement therapy.[33-35] Many of these studies had limitations of short follow-up (less than 3 years), inconsistent dosing measurements, and dissimilar end points. Despite these limitations, the FDA issued a safety notification regarding the misuse of testosterone-containing products because of potential CV and thromboembolic risk.[36] However, the most recent meta-analysis on CV risk and testosterone replacement therapy did not confirm these results, and suggested a neutral effect when all events and testosterone preparations were considered.[37] Although the current literature does not provide clear evidence for or against testosterone replacement therapy in men with a history of CV disease, experts recommend withholding testosterone replacement therapy for 3 to 6 months after a cardiac event.[14] Further long-term studies are needed for conclusive evidence of causality.

Prostate risk Testosterone supplementation has long been thought to contribute to prostate growth and prostate cancer risk. After all, testosterone plays a role in prostate cell stimulation, and androgen deprivation has been the primary treatment for prostate cancer for many years. Despite these facts, evidence suggests that testosterone replacement therapy does not support an increased risk.[37] A recent meta-analysis of prostate risk demonstrates a short-term increase in PSA and prostate volume, despite no increased risk of prostate cancer or prostate-related events in patients on testosterone replacement therapy.[37] Though no strong evidence suggests a causal link for testosterone administration, both the American Urologic Association (AUA) and Endocrine Society guidelines recommend PSA monitoring in patients on testosterone replacement therapy.[1,14] Tell patients about the absence of evidence linking testosterone replacement therapy to the development of prostate cancer, and use shared decision-making.[14]

Erythrocytosis The most frequently reported adverse reaction to testosterone replacement therapy is erythrocytosis, an abnormal elevation of hemoglobin (greater than 18.5 g/dL) or hematocrit (greater than 52%).[1,38] Elevations in these values have potentially been linked to increases in CV events and venous thromboembolism (VTE).[38] However, no studies to date have demonstrated a link between testosterone replacement therapy-induced erythrocytosis and CV events or VTE.[38] Short-acting testosterone injections (TC and testosterone enanthate) demonstrate a 40% increase in erythrocytosis, compared with gels and pellets.[39] Despite this fact, warn patients about the risk of erythrocytosis, and monitor their hemoglobin and hematocrit levels. Suspend testosterone replacement therapy or phlebotomy treatment if hematocrit rises to 54% or above. Testosterone replacement therapy may be resumed at a lower dose once the patient's hematocrit levels return to normal.[9]

ALTERNATIVE THERAPIES

Not all men are good candidates for testosterone replacement therapy. Those wishing to preserve fertility and those concerned with the risks of testosterone replacement therapy may consider one of the following alternative options:

Selective estrogen receptor modulator Clomiphene citrate is not FDA-approved for use in men or in patients with hypogonadism, but has been widely researched and used off-label. This drug blocks the estrogen receptor in the hypothalamus and pituitary gland, increasing FSH and LH. Gonadotropins stimulate the testes to increase production of testosterone and sperm.[40] Clomiphene citrate comes in 50-mg tablets and is taken every other day.[41] The drug maintains sperm production through its actions on FSH, in contrast to testosterone replacement therapy.[42] Long-term studies have demonstrated that it is an effective treatment for maintaining testosterone levels in men with hypogonadotropic hypogonadism and an intact hypothalamic pituitary axis.[40] Advantages of clomiphene citrate include preservation of fertility, effective long-term maintenance of testosterone levels, and low risk of polycythemia compared with men on testosterone replacement therapy.[43] Clomiphene citrate also is less expensive than testosterone replacement.[41] Although clomiphene citrate increases testosterone levels, data on its improvement of hypogonadal symptoms are conflicting.[44]

Other alternatives include human chorionic gonadotropin (HCG) and aromatase inhibitors, which are beyond the scope of this article. Patients requiring these medications should be referred to a specialist.

LIFESTYLE CHANGES

Obesity is linked to a decrease in both free and total testosterone, and is the strongest risk factor associated with low testosterone levels in middle-aged and older men.[45] Obese men have more adipose tissue, which upregulates aromatase activity. The aromatase enzyme converts testosterone to estradiol, reducing testosterone levels and increasing estradiol.[46] Weight loss has demonstrated significant increases in total testosterone in obese men. Longitudinal data have reported that a 5% weight loss was associated with an increase in total testosterone by almost 60 ng/dL.[47] Therefore, encourage weight loss as first-line treatment in these patients.[48]

FOLLOW-UP AFTER TREATMENT INITIATION

Patients receiving any treatment for low testosterone should have total testosterone levels checked as follows:

- Patients on injection therapies should have a trough level (the lowest level before injection) and midcycle level measured in the first 2 months. Dosages may be adjusted to avoid very high peaks and very low troughs.
- Patients on transdermal gels should have levels checked after 2 to 4 weeks of daily application. Remind patients to apply the gel each morning, because levels decline throughout the day.[49]
- Patients on clomiphene citrate should not be checked earlier than 4 weeks.[14]
- Patients who have had pellet placement should be tested 4 weeks after insertion and again at 10 to 12 weeks post insertion to determine when the next administration should occur.[14]

After therapeutic levels are determined, all patients should have total testosterone level, PSA level, and a complete blood cell count every 6 to 12 months. In addition, regularly evaluate symptoms and adverse reactions such as acne, mild fluid retention, breast enlargement, decreased testicular size, and worsening of sleep apnea.[3] Consider discontinuing therapy if patients do not report symptom improvement with normalization of testosterone levels after 3 to 6 months.[14]

CONCLUSION

Hypogonadism often goes undiagnosed and untreated. Men with signs and symptoms of low testosterone should be screened and treated appropriately, using the medication and formulation best for the patient and his lifestyle. Patients should be made aware of risks associated with testosterone therapy, as well as the required follow-up visits and testing once on the medication. Lifestyle modification should always be offered as first-line therapy or in conjunction with any treatment. **JAAPA**

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