



Update on Hypogonadism and Testosterone Replacement Therapy

Learning Objectives

After completing this activity, participants should be better able to:

- Explain the role of testosterone in overall health and the burden of testosterone deficiency
- Recognize the role of hypogonadism in obesity, metabolic syndrome, diabetes, cardiovascular disease, and erectile dysfunction (ED)
- Identify the signs and symptoms of hypogonadism and their complex clinical presentation
- List the options available to treat hypogonadism
- Monitor potential adverse effects of treatment

Introduction

As the etymology of the term *hypogonadism* suggests, this condition centers on underfunctioning gonads—either testes or ovaries. In this section, we focus on hypogonadism, specifically androgen deficiency in men, a condition that involves low serum testosterone levels and low sperm counts. Two components are necessary for a diagnosis of hypogonadism: both signs and/or symptoms of androgen deficiency and a testosterone level that is low or borderline.^{1,2} Low testosterone at any age is defined as hypogonadism, but in older men other specific names have been used, including *andropause*, *androgen decline in aging men (ADAM)*, *late-onset hypogonadism (LOH)*, or *partial androgen deficiency of the aging male (PADAM)*.^{2,3}

The Epidemiology of Hypogonadism: A Common and Undertreated Problem

Although a review of several epidemiologic studies illustrates that agreement on the prevalence of hypogonadism has not been reached, it certainly remains a substantial problem. Results from the Baltimore Longitudinal Study on Aging showed that the prevalence of hypogonadism increases linearly with age, as indicated by the number of participants with total testosterone levels <325 ng/dL.⁴ Using these cut-offs, an incidence of ~20% was estimated for men older than 60 years, 30% for those older than 70 years, and 50% for

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those older than 80 years.⁴ In the Hypogonadism in Males (HIM) study, hypogonadism was defined by a total testosterone of <300 ng/dL, resulting in a prevalence of 39% among the 2162 men aged 45 years or older in a primary care population.⁵ Notably, these men presented to the clinicians' offices for reasons other than clinical symptoms of hypogonadism; therefore, the prevalence number is actually an estimate of hypogonadism in a population of men presenting to clinicians' offices for follow-ups of a variety of chronic illnesses.⁵ In contrast, the crude prevalence of *symptomatic* hypogonadism was estimated to be 5.6% (95% confidence interval [CI], 3.6%-8.6%) among male participants in the Boston Area Community Health (BACH) Survey,⁶ mirroring the results from the 2004 Massachusetts Male Aging Study (MMAS).⁷ In these studies, hypogonadism was defined as low total (<300 ng/dL) and free (<5 ng/dL) testosterone in combination with low libido, ED, osteoporosis or fracture, or 2 or more of the following symptoms: sleep disturbance, depressed mood, lethargy, or diminished physical performance.⁶ These last studies more accurately represent the prevalence of real-world clinical hypogonadism.

Notably, among men with clinically symptomatic hypogonadism, 87.8% are untreated despite access to care.⁸ In 2002, an estimated 4 to 5 million American men had symptomatic hypogonadism; however, only 819,000 received treatment—most between the ages of 46 and 65 years.⁹ Despite the established relationship between age and low testosterone levels, only 13% of patients who received treatment were 65 years of age or older.⁹

Comorbidities Associated With Hypogonadism

An epidemiologic study by Mulligan and colleagues has aptly demonstrated a connection between biochemical hypogonadism (total testosterone <300 ng/dL) and serious comorbidities.⁵ Patients with obesity, type 2 diabetes, hypertension, hyperlipidemia, asthma, chronic obstructive pulmonary disease (COPD), prostate disease, and sleep apnea had a significantly higher likelihood of having hypogonadism than patients without these conditions.^{5,10} The

strongest association was observed between obesity and hypogonadism: a hypogonadism prevalence rate of 52.4 (95% CI, 47.9-56.9) was observed among obese patients, along with a significantly higher risk of having hypogonadism among this population (odds ratio 2.38; 95% CI, 1.93-2.93).⁵

Indeed, low testosterone levels are associated with the development of metabolic syndrome, a condition characterized by central obesity, lipid and glucose/insulin dysregulation, and hypertension.¹¹ In 950 men from MMAS followed for 14.4 years, low testosterone levels predicted the development of metabolic syndrome.¹¹ This is important because metabolic syndrome is prognostic for the development of cardiovascular disease.¹² Furthermore, authors of a 2006 study observed an

inversely proportional relationship between testosterone and metabolic syndrome: individuals who presented with more determinants of metabolic syndrome tended to have lower circulating levels of total testosterone ($P < .0001$).¹³

To highlight the significance of hypogonadism, a clinical study from a Veterans Affairs database of 858 men aged older than 40 years with no history of prostate cancer, testicular cancer, or antiandrogen treatment showed that low testosterone levels are associated with an

Even after adjusting for age, medical morbidity, and other clinical covariates, low testosterone levels are associated with increased mortality.

88% increase in mortality from all causes.¹⁴ Even after adjusting for age, medical morbidity, and other clinical covariates, low testosterone levels continued to be associated with increased mortality (hazard ratio, 1.88; 95% CI, 1.34-2.63; $P < .001$), especially of cardiovascular etiology.¹⁴ Since that 2006 publication, another 5 studies have corroborated the original findings. Similar to the original study, a 2007 investigation involving 2314 men found a 25% to 30% higher risk of death from cancer, cardiovascular disease, or all-causes among study participants presenting with the lowest testosterone levels compared with those with the highest levels.¹⁵

Clinical Manifestations

Male hypogonadism involves a complex of signs and symptoms, including increased body mass index (BMI)—with visceral weight gain in particular—low bone mineral density (BMD), irritability, and decreased sexual desire and function (Table 1).^{5,16-19} Reduced energy and increased fatigue are the most common presenting complaints, but unfortunately they are the least specific. Loss of energy is the most profoundly felt symptom of the entire symptom complex, followed by diminished libido, lack of motivation, and irritable mood.²⁰

Hypogonadism is classified as *primary* (caused by testicular dysfunction), *secondary* (caused by hypothalamic or pituitary dysfunction), or *mixed* (etiologies affecting the hypothalamic-pituitary-gonadal axis) (Table 2).^{18,20} Secondary causes of hypogonadism are seen more often clinically.^{10,21}

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Low Testosterone Levels

Under physiologic conditions in men, the hypothalamus produces gonadotropin-releasing hormone (GnRH), which induces the anterior pituitary gland to secrete 2 gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH).²² In turn, these gonadotropins respectively stimulate Leydig cells to produce testosterone and induce Sertoli cells to nurture spermatogenesis. Sperm and testosterone downregulate their own production through a feedback loop that reduces the secretion of hormones by the hypothalamus and pituitary.

Table 1.

Clinical Manifestations of Hypogonadism^{5,17-19,41}

Physical/Metabolic	Psychologic	Sexual
<ul style="list-style-type: none"> ➤ Decreased BMD ➤ Decreased muscle mass and strength ➤ Gynecomastia ➤ Anemia ➤ Frailty ➤ Increased body fat or BMI ➤ Fatigue ➤ Insulin resistance 	<ul style="list-style-type: none"> ➤ Depressed mood ➤ Diminished energy, sense of vitality, or well-being ➤ Impaired cognition and memory 	<ul style="list-style-type: none"> ➤ Diminished libido ➤ ED ➤ Difficulty achieving orgasm ➤ Decreased spontaneous erections

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Table 2.

Classification of Hypogonadism^{10,17,18,21}

Primary	Secondary		Mixed
Testicular causes	Hypothalamic causes	Pituitary causes	Dual HPG axis defects
<ul style="list-style-type: none"> ➤ Klinefelter syndrome ➤ Orchitis ➤ Congenital or acquired anorchia ➤ Autoimmune destruction of testes (older men) ➤ Testicular tumors ➤ Chemotherapy ➤ Trauma 	<ul style="list-style-type: none"> ➤ Kallmann syndrome (congenital absence of GnRH) ➤ Constitutional delay in growth and development ➤ Chronic illnesses such as hypertension, diabetes, hyperlipidemia, sleep apnea, and obesity 	<ul style="list-style-type: none"> ➤ Hypopituitarism ➤ Pituitary tumors 	<ul style="list-style-type: none"> ➤ Hemochromatosis (iron deposits in the pituitary and/or Leydig cells) ➤ Sickle cell disease ➤ Thalassemia ➤ Glucocorticoid treatment ➤ Alcoholism

HPG = hypothalamic-pituitary-gonadal.

Circadian rhythm has an effect on total testosterone levels in younger men, causing a diurnal pattern wherein the androgen levels peak in the morning. The diurnal patterns of total testosterone wane in older adults (although the age cut-off has not been defined); however, free and bioavailable levels maintain the rhythm.²³ Hence, the guidelines issued by the International Society for the Study of the Aging Male (ISSAM) and the European Association of Urology (EAU) propose obtaining serum samples for testosterone between 7:00 AM and 11:00 AM.¹

Two aspects are considered in diagnosing hypogonadism: signs or symptoms and a testosterone level that is low or borderline.

A threshold level of testosterone below which an individual's level is considered "low" has not been agreed upon. A recent rigorously conducted study of 3 geographically distinct cohorts found that men in the 2.5th percentile had total testosterone levels of ≤ 348.3 ng/dL (12.1 nmol/L) and free testosterone levels of ≤ 70.0 pg/mL (243 pmol/L).²⁴ An international consensus group created a widely used algorithm, which states that a total testosterone level below 230 ng/dL deserves replacement, while levels between 230 and 350 ng/dL are equivocal.²⁵ The American Association of Clinical Endocrinologists

(AACE) recommends that men with clinical symptoms of hypogonadism and testosterone levels of 200 ng/dL or below should definitely be considered for testosterone replacement therapy (TRT).¹⁸ The Endocrine Society guidelines postulate that a total testosterone level of <200 ng/dL is diagnostic of hypogonadism, while 200-320 ng/dL is equivocal.²⁶ For equivocal results, free testosterone or bioavailable testosterone measurements can help differentiate eugonadism from hypogonadism. Equilibrium dialysis free testosterone levels of <6.5 ng/dL (<50 pg/mL) are considered outside of normal limits.²⁶ Meanwhile, for research studies involving hypogonadism, the US Food and Drug Administration defines hypogonadism as total testosterone levels of ≤ 300 ng/dL.

Testosterone Replacement Therapy

Benefits of Testosterone Replacement Therapy

The benefits of TRT can include restoring libido and erectile function, increasing energy levels, and improving mood.²⁷ TRT can improve body composition by decreasing fat mass, increasing lean body mass, potentially increasing muscle strength, and stabilizing or increasing BMD, as well as reducing bone fractures.^{27,28}

One study evaluated long-term effects of TRT in 371 hypogonadal men for up to 12 months.²⁹ In this study, significant improvements in lean body mass, fat mass, sexual desire, and sexual performance were noted—beginning a few months after the start of treatment for the sexual effects and several months later for the effects on mass. Furthermore, improved glycemic control has been noted among hypogonadal men treated with TRT. A double-blind, placebo-controlled study of 24 men noted improved fasting insulin sensitivity, reduced glycated hemoglobin (A1C) ($-0.37 \pm 0.17\%$; $P = .03$), reduced fasting blood glucose (-1.58 ± 0.68 mmol/L; $P = .03$), and reduced waist circumference (-1.63 ± 0.71 cm; $P = .03$).³⁰ Among the 220 hypogonadal men with diabetes and/or metabolic syndrome observed in the testosterone replacement in hypogonadal men with either metabolic syndrome or type 2 diabetes (TIMES2) study, TRT improved insulin resistance in all patients by 15.2% at 6 months ($P = .018$) and 16.4% at 12 months ($P = .006$), glycemic control in those with type 2 diabetes (A1C: treatment difference, -0.446% ; $P = .035$), and total and low-density lipoprotein (LDL) cholesterol, lipoprotein-a, body composition, libido, and sexual function in select patient groups.³¹ TRT positively affected all metabolic syndrome parameters considered in another 12-month study, causing declines in blood pressure, waist circumference, plasma cholesterol and LDL, and an increase in plasma high-density lipoprotein (HDL).³²

In the TIMES2 study, TRT improved insulin resistance in all patients.

Testosterone Replacement Therapy and Prostate Cancer

In a multinational physician survey, the most common physician concern affecting the prescribing of TRT was a presumed risk of inducing prostate cancer (63%).³³ This relationship between testosterone and prostate cancer derived from a 1941 study, in which Huggins and Hodges showed that the metastasis of prostate cancer to bone was dependent on the presence of androgens. An enhanced rate of tumor growth was observed with testosterone administration, and this observation led to the authors being awarded a Nobel Prize in medicine; however, some feel that only 1 patient had valid data.³⁴

Since then, many studies have been conducted to assess the potential connection between serum testosterone levels and prostate cancer risk. Evidence from a pooled analysis by the Endogenous Hormones and Prostate Cancer Collaborative Group was contrary to the conclusions of Huggins and Hodges. The analysis of 18 prospective studies with 3886 men with cancer and 6438 controls produced no evidence of an association between prostate cancer and any endogenous sex steroid, especially testosterone.³⁵ In fact, low sex hormone-binding globulin (SHBG) concentrations (which has been directly correlated to testosterone levels) were associated with an increased risk for prostate cancer.³⁵

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A systematic review of the literature considered 44 articles regarding prostate cancer risk in individuals taking TRT for hypogonadism.³⁶ Eleven randomized, placebo-controlled studies that made direct comparisons of the incidence of new prostate cancer in hypogonadal men receiving TRT to that of hypogonadal men not receiving TRT were included, along with another 29 non-placebo-controlled studies of men with no history of prostate cancer and 4 non-placebo-controlled reports of TRT in hypogonadal men after prostate cancer treatment.³⁶ No evidence was found linking TRT to increases in prostate cancer risk in hypogonadal men. Moreover, within the study population receiving treatment, there was no increase in the incidence of new prostate cancer, no progression of high-grade prostate intraepithelial neoplasia (PIN) to frank prostate cancer, and no increased risk of recurrence or metastasis for up to 12 years of TRT following curative prostate cancer treatment. It is also interesting to note that a 2001 study of 156 patients reported a significant association between low serum testosterone levels and high-grade prostate cancer ($P < .01$).³⁷ In this study, men with low testosterone levels had higher mean Gleason scores (7.4 vs 6.2) and lower prostate-specific antigen (PSA) levels (25.3 vs 31.9 ng/mL).³⁷ This and other studies strongly suggest that when men with low testosterone develop prostate cancer, they experience a more aggressive disease.^{37,38}

Potential Adverse Effects of Testosterone Replacement Therapy

Testosterone formulations most commonly include injectable, implantable, and topical agents (Table 3).¹⁹ Not all men are able to absorb the available topical formulations, and the injectable form may not be appropriate to prescribe for men with depression because of large fluctuations in testosterone levels from supraphysiologic levels to subnormal concentrations with concomitant mood swings (Table 4).¹⁹ Buccal forms are rarely used and oral formulations of testosterone are not used in the United States because of potential liver toxicity.¹⁹ Infections or expulsions are possible consequences of using the implant formulations¹⁹; expulsions can be avoided, however, by insertion in a “v” shape and anchoring with a stitch. Skin-to-skin transference is a risk of topical forms of testosterone; hand washing after application and

Table 3.

Testosterone Formulations^{19,42}

Formulation	Dosage
Injectable (IM)	
Testosterone cypionate/enanthate TU (in development in the United States)	150-200 mg every 2 wk
Implants	
Testosterone pellets	150-450 mg (3-6 pellets) every 3-6 mo
Topical	
Topical gel	5-10 g daily (depending on the formulation)
Transdermal patch system	1-2 patches, designed to deliver 5-10 mg daily
Topical solution	60 mg daily (30 mg per axilla)
Buccal	
Buccal system	30 mg every 12 hr, anchored to the gum above an incisor

IM = intramuscular; TU = testosterone undecanoate.

Table 4.**Testosterone Formulation-Specific Adverse Effects¹⁹**

Formulation	Adverse Effects
Injectable (IM)	
Testosterone cypionate/enanthate	<ul style="list-style-type: none"> ➤ Mood fluctuations or changes in libido ➤ Pain at injection site ➤ Erythrocytosis
TU (in development in the United States)	<ul style="list-style-type: none"> ➤ Pain at injection site
Implants	
Testosterone pellets	<ul style="list-style-type: none"> ➤ Infections or expulsion
Topical	
Topical gel and solution	<ul style="list-style-type: none"> ➤ Skin-to-skin transference ➤ Skin irritation
Patch system	<ul style="list-style-type: none"> ➤ Skin irritation
Buccal	
Buccal system	<ul style="list-style-type: none"> ➤ Alterations in taste and irritation of gums and oral mucosa

among patients given testosterone in gel or patch formulations.¹⁹ Regardless of the type of TRT given, because of the risk of polycythemia, patients should be monitored for changes in hematocrit levels, and therapy should be halted or doses reduced if the hematocrit exceeds 54%.^{17,19} Liver function abnormalities are rarely encountered in patients taking TRT with any of the currently available formulations; cases of liver function abnormalities were seen initially, primarily in men using oral methyltestosterone therapy.¹⁹ In older men, lower extremity edema can be a consequence of injectable formulations of testosterone, especially when supraphysiologic doses are used or if the men have early congestive heart failure and partial renal insufficiency.⁴⁰

Initiation of Testosterone Replacement Therapy and Monitoring: Guideline Recommendations

Overall, the goals of TRT are to treat the signs and symptoms of hypogonadism, to achieve and maintain eugonadal serum testosterone levels, and to individualize the therapy to meet each specific patient's needs, taking into account contributing factors such as age.⁴⁰ In order to achieve these goals, titration may be required, as well as multiple consultations with the patient to monitor and encourage regimen adherence. Missing even a few doses of testosterone gel per month, for example, can lead to subtherapeutic levels.⁵

avoidance of contact with children is essential to avoid this adverse effect.¹⁹ Patches can cause dermatitis, as can the buccal form; the latter has also been associated with bad breath.¹⁹

The general potential risks associated with TRT include acne and gynecomastia (Table 5).^{2,39} Gynecomastia is rarely seen with the newer forms of TRT in which the levels reached are not supra-physiologic^{2,19}; more cases of gynecomastia are seen in men who present with hypogonadism due to a reversal of the testosterone/estradiol ratio. In these cases, patients can be prescribed an aromatase inhibitor if the gynecomastia does not resolve with standard TRT. Care should be taken in men with sleep apnea, as supraphysiologic levels of testosterone may aggravate the condition.² Both gynecomastia and aggravation of sleep apnea are infrequently seen in the clinic

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Table 5.

Risks Associated With Testosterone Replacement Therapy²

Risk	Comment
Oily skin, acne, skin reactions	Skin irritation more common with nonscrotal patches and some gels
Breast enlargement or tenderness	Often transient and abates with continued treatment
Sleep apnea	Rare when levels of testosterone are not supraphysiologic
Polycythemia	Uncommon, but associated with age, sleep apnea, smoking history, and COPD
Liver function abnormalities or tumors	Rare with injectable esters and transdermal formulations
Lower extremity edema and other cardiovascular manifestations	In older men with early heart failure and/or renal insufficiency, due to salt and water retention, especially with supraphysiologic levels of testosterone
Symptomatic BPH and prostate cancer	Modest and inconsistent increases in prostate volume

BPH = benign prostatic hyperplasia.

A prostate health assessment is recommended before initiation of TRT. The assessment should include a digital rectal examination (DRE) checking for nodules, indurations or asymmetry of the prostate, and baseline measurement of PSA, hematocrit, and hemoglobin levels.² The history should include inquiries about sleep apnea or voiding difficulties.² If the serum or plasma PSA concentration is >4.0 ng/mL, a urologist should be consulted.^{17,19} Testosterone replacement is then initiated, and after the new PSA baseline is established in 3 to 6 months, PSA levels should be measured annually. A consultation with a urologist is recommended if an increase in PSA concentration greater than 1.4 ng/mL within any 12-month period of testosterone treatment is observed.¹⁹ Apart from a change in PSA, other situations requiring the referral to a urologist include the detection of a prostate abnormality during a DRE or a patient-reported American Urological Association (AUA) prostate symptom score of >19.¹⁹

The efficacy of treatment should be assessed after 1 to 2 months of therapy and the dosage should be adjusted for those with a suboptimal response. Thereafter, a full evaluation at 4 to 6 months from the start of therapy should be conducted, and then annually to assess the symptom response and the development of adverse effects; this should include a yearly PSA measurement and assessment of hematocrit and hemoglobin levels.^{17,19} Another DRE is performed at 3 to 6 months and then yearly, along with the biochemical measurements.¹⁹ BMD measurements are recommended after 1 to 2 years of therapy in men with osteoporosis.¹⁹ Correction of any anemia may be done periodically every 6 to 12 months, as needed.

CASE: A 48-Year-Old Man With Low Testosterone



Presentation

A 48-year-old man presents with ED, fatigue, low mood, and distress in his marital relationship, with an otherwise unremarkable medical history. Physical examination reveals:

- Weight: 220 lb
- Height: 5 ft 6 in
- Waist circumference: 41 in
- Blood pressure: 140/90 mm Hg
- Genital examination: normal
- DRE: normal

Clinical Decision Point

What would be your next step?

- Refer to marital counseling
- Refer to psychiatrist
- Order laboratory tests including testosterone
- Prescribe phosphodiesterase type 5 (PDE5) inhibitor
- Prescribe testosterone

Comment

Your patient's presentation includes several factors that have been significantly correlated to an increased risk for hypogonadism: high blood pressure, large waist circumference (>40 in), and visceral obesity, suggestive of the presence of metabolic syndrome. Individuals with any 3 of the following—triglycerides ≥ 150 mg/dL, HDL cholesterol < 40 mg/dL, fasting glucose ≥ 110 mg/dL, systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg or on antihypertensive medication, and BMI > 28.8 kg/m² or waist circumference of 102 cm—are considered to have metabolic syndrome, putting them at significantly higher risk for coronary heart disease (3.7-fold) and type 2 diabetes (24.5-fold; $P < .0001$).¹² The presence of ED is a sign of poor vascular health, and until proven otherwise, the patient is considered to have hypogonadism, so laboratory tests including testosterone levels should be ordered. The first test of testosterone levels must be validated by another test, and prostate health needs to be evaluated before TRT can be prescribed. In addition, the patient will be instructed to exercise and eat a Mediterranean-style diet, as the first recommendations to the patient should involve lifestyle modification.

Laboratory Results

- Morning total testosterone: 160 ng/dL
- LH: low-normal, 2 IU/L (2-9 IU/L)
- Prolactin: normal
- Thyroid functions: normal
- Liver and kidney functions: normal
- LDL: 160 mg/dL
- Fasting glucose: 105 mg/dL
- Complete blood count (CBC): normal

Clinical Decision Point

What would be your next step?

- Prescribe testosterone
- Prescribe PDE5 inhibitor
- Prescribe testosterone + PDE5 inhibitor
- Initiate weight loss program
- Prescribe statin and oral hypoglycemic

Comment

All the above options are appropriate to consider, with the exception of prescribing the oral hypoglycemic agent and statin, considering his current respective levels. Of clinical relevance, waist circumference can be a more telling factor regarding cardiovascular health than BMI. In particular, because of the presence of significant risk factors for having a cardiovascular event, weight reduction is of key importance. Weight loss programs more effectively reduce signs of metabolic syndrome in hypogonadal men when coupled with testosterone repletion,⁴³ and the patient has 4 of the 5 components of metabolic syndrome. TRT can be prescribed after prostate health is assessed. Furthermore, because this particular patient's testosterone levels are so low, a PDE5 inhibitor may not be effective, so the clinician might wait 1 to 2 months after the initiation of TRT to add a PDE5 inhibitor.

Waist circumference can be a more telling factor regarding cardiovascular health than BMI.

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Frequently Asked Questions About Hypogonadism

Q. What is the difference between free testosterone and total testosterone?

A. Testosterone circulates in the body in 3 forms; a small percentage (~1%-2%) is free and the rest is weakly bound to albumin (30%-35%) or strongly bound to SHBG (60%-65%). *Total testosterone* includes all 3 forms found in the serum. *Bioavailable testosterone* is the free testosterone plus the portion that is weakly bound to albumin; these fractions are also the basis of the calculated free testosterone. *Free testosterone* is the small amount that is unbound, and this form is biologically active. Under certain conditions, altered levels of SHBG can affect the free testosterone levels. Indeed, with age, the production of SHBG increases and binds to more testosterone, making less androgen available to the body.¹ Furthermore, some chronic diseases or drug treatments can affect SHBG levels, making free testosterone a more reliable indicator of biochemical hypogonadism.

Q. Should the testosterone level drawing times be shifted for patients who work nights or rotating shifts?

A. Perhaps the circadian rhythms of individuals who routinely work during the night and sleep during the day are different, but no studies have assessed whether testosterone measurements should be drawn in the evening instead of the morning for these individuals. In this population, it may be best to measure testosterone in the morning as well as in the evening. Men who have significantly low testosterone often have blunted circadian rhythms, so the time of day of testosterone draw is difficult to interpret. Results from a 2008 study suggest that it is not critical to draw total testosterone levels in the morning in men aged ≥ 45 years.²

Q. Is there any age at which PSA levels are no longer reliable?

A. Recommendations for the general detection of prostate cancer in an individual who does not take testosterone repletion suggest that past the age of 75 years, there is less benefit to PSA screenings. However, a patient taking TRT needs to be monitored indefinitely because the treatment is contraindicated in the presence of prostate cancer, which may occur at any age, and is more common in older men.

Q. How do you manage patients who are uncomfortable with DREs?

A. Although some organizations, such as the American Cancer Society, support optional inclusion of DREs during a physical examination,³ DREs remain a recommended element of other relevant guidelines.⁴⁻⁶ Often men may feel more comfortable being examined by a male practitioner, so if the practitioner is a

woman, offer to have a male clinician complete the examination. Also, encouraging the patient to relax ameliorates the examination. If the patient refuses to have a DRE, then document the refusal in detail.

Q. How does chronic opioid use affect testosterone levels?

A. A number of studies have shown that chronic pain medications, especially opioids, are associated with low testosterone levels. Indeed, many patients on chronic opioid therapy are referred from pain clinics with dramatically low testosterone levels. In addition to being fatigued because of pain, these patients are lethargic because of low testosterone levels, dramatically affecting their quality of life. This population of patients benefits from TRT.

Q. Do you treat men after radical prostatectomy who have a low testosterone level with testosterone repletion?

A. ED and reduced libido are common adverse effects of radical prostatectomy.⁷ According to the majority in the Sexual Medicine Society of North America, patients with low testosterone, clinical signs of hypogonadism, and 2 PSA readings of $<.01$ (ie, negligible) might be managed with TRT with a low risk of cancer recurrence, but the decision to initiate TRT in these patients should be made on a case-by-case basis. The patient has to be warned that this is a controversial area.

Q. With female hormone replacements, there is a risk of blood clots. Is this also the case with testosterone?

A. Contraceptives for childbearing-age women and estrogen replacement therapy for postmenopausal women are associated with an increased risk for blood clots (especially in smokers), along with the associated morbidity and potential mortality. In contrast, blood clotting has not been observed to be a significant risk with TRT.

Q. If TRT is successful, is it then continued throughout a patient's life?

A. Patients with low testosterone due to primary testicular failure will need ongoing treatment. Secondary hypogonadism has various causes, some of which can be resolved. For example, with treatment of obesity and sleep apnea, testosterone levels can rise, allowing discontinuation of TRT, with appropriate follow-up of testosterone levels.

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