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Evolving issues in male hypogonadism: Evaluation, management, and related comorbidities

ABSTRACT

Hypogonadism in men has a complex and varied pathogenesis. In addition to multiple established causes of the disease, low testosterone levels are associated with various comorbidities, including metabolic syndrome and type 2 diabetes. Symptoms associated with hypogonadism include reduced sex drive, fatigue, and mood disturbances, but accurate diagnosis requires biochemical testing. Total testosterone is considered the appropriate testosterone measurement in most situations in primary care, although free testosterone is a more accurate marker and is indicated in some situations. Testosterone replacement therapy is a valid treatment option for men with testosterone deficiency accompanied by symptoms of hypogonadism. The goals of therapy are to restore physiologic testosterone levels and alleviate symptoms. A potential association of testosterone replacement therapy with prostate cancer is the biggest safety concern, so patient monitoring should include regular digital rectal examination and prostate-specific antigen tests.

DEFINITION OF THE CONDITION

Hypogonadism in men is classified as primary (testicular failure), secondary (insufficient testicular stimulation by pituitary gonadotropins), or mixed. Regardless of age or disease etiology, men with a total testosterone level less than approximately 300 ng/dL often develop signs and symptoms associated with classic hypogonadism, which can have consequences for their long-term health.[1,2] Notably, there is some variation in what is considered the threshold total testosterone level for indicating hypogonadism, with the Endocrine Society and the American Association of Clinical Endocrinologists (AACE) recognizing 200 ng/dL as the threshold and the US Food and Drug Administration (FDA) recognizing 300 ng/dL.[1,2]

PREVALENCE AND SOCIAL IMPLICATIONS

Declines in total testosterone with advancing age have been documented in longitudinal studies.[3–5] As men age, serum testosterone declines by about 1% to 2% a year after age 30.

As noted in a 2003 report from the Institute of Medicine,[6] a simultaneous age-associated increase in sex hormone-binding globulin (SHBG) results in an even lower concentration of free testosterone, eventually culminating in a condition that some have called ADAM (androgen deficiency in aging males), andropause, late-onset hypogonadism, or EDAM (endocrine decline in aging males). The term "andropause" is a misnomer in that true andropause exists only in men who have lost all testicular function, which occurs only after disease, accident, or castration.

Published estimates of the frequency with which testosterone concentrations reach levels that can be interpreted as hypogonadal (ie, two standard deviations below the mean for young men) vary from 30% to 40% in men older than 65 years to as high as 70% in men 80 years of age or older.[4,7,8] However, not all men with a low testosterone level should be treated for the condition. As with many other medical conditions, therapy for hypogonadism is often initiated to resolve bothersome symptoms or to reduce risks posed by the condition. Notably, asymptomatic men with low testosterone levels are at increased risk for certain other conditions, as outlined below.

Associated comorbidities

Low serum testosterone levels are associated with several comorbid conditions, including metabolic syndrome, diabetes mellitus, dyslipidemia, and erectile dysfunction.

Metabolic syndrome. Observational data summarized in the 2003 Institute of Medicine report support an association between hypogonadism and several

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components of metabolic syndrome.[6] For example, low levels of testosterone are inversely associated with concentrations of insulin, glucose, and triglycerides, and positively associated with levels of high-density lipoprotein (HDL) cholesterol.[9] A series of data analyses from the Kuopio Ischemic Heart Disease Risk Factor Study, conducted in Finland, shows that nondiabetic men were nearly four times more likely to develop metabolic syndrome if they were hypogonadal.[9]

Other recent studies have confirmed that hypogonadism predisposes men to insulin resistance, obesity, abnormal lipid profiles, and borderline or overt hypertension.[10] In 2005, a systematic review concluded that the evidence linking hypogonadism and metabolic syndrome is strong enough that the definition of metabolic syndrome in men may be expanded in the future to include hypogonadism as a diagnostic parameter.[10]

Diabetes. Dhindsa et al found that one third of men with type 2 diabetes referred to their diabetes center were hypogonadal, and that levels of luteinizing hormone and follicle-stimulating hormone were lower in the hypogonadal men than in those with normal levels of free testosterone.[11]

Hypogonadism also predicts the subsequent development of diabetes and metabolic syndrome in middle-aged men, and has been proposed to be involved in the pathogenesis of these diseases.[12] Stellato et al demonstrated that lower levels of free testosterone and SHBG predicted incident type 2 diabetes in middle-aged men.[13] A 2006 meta-analysis by Ding et al confirmed that testosterone levels were significantly lower in men with type 2 diabetes than in controls, and that higher baseline levels of testosterone and SHBG significantly reduced the risk of type 2 diabetes in men.[14]

Dyslipidemia. Although there have been no long-term studies of cardiovascular morbidity and mortality among recipients of testosterone replacement therapy, total testosterone levels are positively correlated with HDL cholesterol levels and negatively correlated with triglycerides in men with and without diabetes.[15] Moreover, Zmuda et al confirmed that reductions in testosterone levels were associated with unfavorable changes in triglycerides and HDL cholesterol among male participants in the Multiple Risk Factor Intervention Trial.[3]

Erectile dysfunction. Low serum testosterone can manifest as diminished sexual desire. Recent studies support the long-held belief that adequate testosterone concentrations are important for sexual function, and that reduced testosterone levels are associated with reduced sexual health, specifically in terms of libido.[16,17] Although the exact level of testosterone required for adequate sexual function is unknown, treatment with testosterone replacement alone has been shown to improve sexual desire and function in hypogonadal men.[18–20]

In men with erectile dysfunction who are treated with testosterone replacement and the phosphodiesterase type 5 (PDE-5) inhibitor sildenafil, testosterone levels have been shown to correlate with penile arterial blood flow.[21] Similarly, testosterone therapy given in combination with PDE-5 inhibitors in short-term studies improved sexual function in androgen-deficient men (total testosterone < 400 ng/dL) who had suboptimal response to PDE-5 inhibitor therapy alone, yielding greater potency, erectile function, orgasmic function, and overall satisfaction.[22,23] There is uncertainty, however, whether the effect of this combination therapy can be sustained beyond 3 months, as well as over the exact role that testosterone replacement might have in salvaging PDE-5 inhibitor therapy failures.

In an analysis of men aged 50 years or older being treated for erectile dysfunction, nearly one fifth (18.7%) of the 2,823 subjects who had testosterone checked were found to have low testosterone levels (< 280 ng/dL).[24] The authors therefore concluded that routine screening for testosterone deficiency may be warranted in the work-up for erectile dysfunction.[24]

PATHOGENESIS

Hypogonadism has a complex and varied pathogenesis.[25] In addition to multiple established causes, low testosterone levels are associated with stress, aging, disease, and medications that have antiandrogen effects.[5,8,26] Many medical disorders are associated with low testosterone as well:

- Acute severe illness
- Chronic illnesses, including diabetes, cardiovascular disease, hypertension, hereditary hemochromatosis, and human immunodeficiency virus infection
- Lifestyle habits, including alcohol and tobacco use
- Malnutrition or obesity.

Because the underlying cause may be multifactorial and complex, a definitive etiologic diagnosis is not always attainable.[27] However, hypogonadism is thought to be either primary (ie, testicular) or secondary (ie, pituitary or hypothalamic) in etiology.

The most common congenital cause of hypogonadism is Klinefelter syndrome, a primary testicular disorder that results in small, undeveloped testes and elevated serum gonadotropin levels.

Most cases of hypogonadism in men aged 30 to 50 years have a combination of primary and secondary

TABLE 1
Questions used as part of the Saint Louis University ADAM questionnaire

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased "enjoyment of life"?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noted a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

A positive questionnaire result is defined as a "yes" response to questions 1 or 7 or to any three other questions.

ADAM = androgen deficiency in aging males

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causes. A gradual increase in serum concentrations of luteinizing hormone indicates a degree of primary hypogonadism.

PRESENTING SYMPTOMS

The diagnosis of hypogonadism in men is based on a combination of clinical signs and symptoms and laboratory tests.[28]

The most commonly noted symptoms include rather vague complaints such as lack of energy, loss of motivation, cantankerous mood, inability to concentrate, and sexual symptoms such as loss of desire, sexual dysfunction, erectile difficulties, impotence, and decreased ejaculate volume. Less commonly reported symptoms include hot flushes, slow beard growth, and muscular aches.

Symptoms may be elicited through use of a questionnaire, such as the ADAM **(Table 1)** or EDAM questionnaires.[29] However, the usefulness of symptom-based screening questionnaires may be limited by considerable variation in symptoms among different men. Kelleher et al noted that among a mixed population of men with primary, secondary, and mixed hypogonadism, the threshold for symptoms of androgen deficiency was highly reproducible in individual men but varied widely among different men.[30]

Symptoms depend on the patient's age at the time that hypogonadism develops. The symptoms mentioned above are manifestations of hypogonadism in postpubertal men, whereas small testes, reduced muscle mass, gynecomastia, a high-pitched voice, and scant pubic and axillary hair predominate in prepubertal boys with hypogonadism, which often goes unrecognized unless accompanied by short stature or endocrine abnormalities.

DIFFERENTIAL DIAGNOSIS

Table 2 outlines symptoms and signs that call for the inclusion of hypogonadism in the differential diagnosis, along with other possible diagnoses.

EVALUATION

Because of the vague nature of the symptoms of hypogonadism, corroborating symptom-based impressions with actual biochemical assessment is important when making the diagnosis. Biochemical assessments for suspected hypogonadism include measures of total testosterone, free testosterone, SHBG, follicle-stimulating hormone, and luteinizing hormone.

Start by checking testosterone

Measurement of serum total testosterone levels is the most simple means of screening for hypogonadism and monitoring therapy. Total testosterone is considered the appropriate testosterone measurement in most situations in the primary care setting by most expert groups. Because of the circadian rhythm of plasma testosterone levels, which leads to higher levels in the morning than in the evening, a total testosterone assay is preferably performed between 8:00 AM and 10:00 AM. This circadian rhythm is generally lost in elderly men, so advanced age may make the sampling time less important.

Measuring free testosterone levels may be more useful than total testosterone levels in the presence of elevated or decreased SHBG levels, which will alter the fraction of measured testosterone that is biologically available. Obesity, type 2 diabetes, and hypothyroidism are associated with low SHBG levels, whereas older age is associated with increasing SHBG levels. Measuring free testosterone levels or total bioavailable testosterone can provide more accurate measurements in these situations, although it is more labor-intensive, as it requires equilibrium dialysis or a formula-based calculation using the SHBG level. Measurement of free testosterone also is useful for confirming abnormal total testosterone levels.

A low testosterone level (< 200 ng/dL as defined by the AACE[1] or < 300 ng/dL as defined by the FDA) indicates hypogonadism, with lower levels obviating

the need for further testosterone analyses or quantification of SHBG.

Confirm abnormal levels

Abnormal testosterone levels should be confirmed by a repeat test, preferably in the morning to take advantage of the diurnal secretion pattern. If testosterone is confirmed to be abnormally low, luteinizing hormone and prolactin levels should be obtained to distinguish primary forms of hypogonadism (testicular dysfunction or failure) from secondary forms (pituitary disease or hypothalamic dysfunction with resultant decreased gonadotropin-releasing hormone secretion). An elevated level of luteinizing hormone signals testicular dysfunction. An elevated prolactin level suggests the possibility of a pituitary tumor. Prolactin measurement is also useful because prolactin elevation may suppress gonadotropins, causing secondary hypogonadism.

Indications for MRI

Magnetic resonance imaging (MRI) to detect a pituitary macroadenoma is appropriate in men with low testosterone when the luteinizing hormone level is also low or the prolactin level is elevated, especially in men younger than 50 years who have no comorbidities consistent with secondary hypogonadism. Older men with secondary hypogonadism should undergo MRI under the following circumstances:

- If the serum testosterone is very low (< 150 ng/dL) and if either (1) luteinizing hormone is normal or low or (2) prolactin is increased[31]
- If symptoms such as visual changes or headache are present.

Vigilance for sleep apnea

Because obstructive sleep apnea has been associated with low levels of testosterone as well as with testosterone replacement therapy, patients should be evaluated for obstructive sleep apnea both prior to and following initiation of testosterone therapy. It is unknown whether obstructive sleep apnea precedes testosterone deficiency or is a manifestation of it.

TREATMENT

A low testosterone level alone is not a sufficient indication for testosterone replacement therapy. However, when testosterone deficiency is accompanied by specific clinical symptoms of hypogonadism, testosterone replacement therapy is a medically valid treatment option regardless of the cause of the condition.[1,2] In men who are concerned about fertility, however, testosterone therapy should be used with caution, given that it impairs spermatogenesis. Gonadotropin-releasing hormone agonist therapy may be used instead of testosterone in some men if secondary hypogonadism is present, but this form of treatment is expensive and is usually reserved for hypogonadal men who also have fertility problems.

TABLE 2
Differential diagnosis of symptoms and signs that may suggest hypogonadism

Symptoms	Other possible diagnoses
Headache, visual problems, galactorrhea, prior irradiation to sella	Pituitary tumor
Polyuria, polydypsia	Diabetes insipidus
Cold intolerance, weight change	Pituitary tumor, hypothyroidism
Memory loss	Alzheimer disease, vascular dementia
Malaise, fatigue, anorexia, weight loss	Hypopituitarism
Dramatic symptoms and hypoglycemia	Partial deficiency of adrenocorticotropic hormone
Sudden onset of symptoms	Acute infection, inflammatory disease
Signs	
Papilledema, optic disc pallor	Pituitary tumor

The exact levels of testosterone that require testosterone replacement at various ages and under varying circumstances are not clear and may be laboratory-dependent. However, levels that fall below the generally accepted normal levels for a practitioner's usual laboratory and that are accompanied by clear symptoms indicate a trial of testosterone replacement therapy.

Goals of therapy

The goals of testosterone replacement therapy are to restore physiologic concentrations of testosterone and to alleviate symptoms of hypogonadism.[1]

The biochemical goal is to mimic normal concentrations of testosterone (350 to 1,050 ng/dL) and avoid excessively high levels. A digital rectal examination (DRE) and a prostate-specific antigen (PSA) test to rule out prostate cancer are required before initiating treatment (see below section, "Special concern: Prostate cancer").

Contraindications

The presence of prostate cancer or male breast cancer is an absolute contraindication to testosterone replacement. Studies of PSA changes following testos-

terone replacement have yielded varying results, ranging from no increase to a rise of 0.96 ng/mL in PSA value.[32] The presence of voiding symptoms attributable to benign prostatic hyperplasia (BPH) has also been considered an absolute contraindication, but clinical studies have been equivocal. Some believe that close monitoring of the testosterone level can help to prevent an increase in prostate size beyond that of a similarly aged eugonadal man.

Conditions considered to be relative contraindications to testosterone replacement, which include sleep apnea and social or mood disorders, are more likely to be exacerbated by testosterone preparations that cause a supraphysiologic testosterone level.

Three-month trial warranted

In appropriate candidates, a 3-month trial of testosterone replacement may be useful to determine the response. Such a trial does not appear to have serious adverse effects,[33] although more studies are needed to confirm whether a therapeutic trial of this length should be more formally recommended.

If treatment does not resolve symptoms within 3 months and if testing demonstrates a resolution of biochemical testosterone deficiency, treatment should be stopped and the patient should be evaluated for a different cause of his symptoms.

Three actions are important when considering testosterone replacement:

- Identify the key symptom or finding that is related to low testosterone and use it to monitor the efficacy of replacement therapy
- Evaluate for potential risk factors for adverse events with replacement therapy
- Ascertain that the testosterone level is low enough to allow replacement and still remain in the physiologic range.

Testosterone formulations

The ideal form of testosterone replacement therapy should be convenient and minimize adverse effects.

Intramuscular injections of the testosterone esters testosterone enanthate and cypionate can be administered in the office or by the patient's family. With these formulations, the testosterone concentration peaks within a few days of administration and may be supraphysiologic, after which concentrations slowly decline over the following 2 to 3 weeks. Injections are given at 2- to 3-week intervals. The wide swings of plasma testosterone levels cause some men to develop undesirable physiologic and emotional effects (eg, breast tenderness, hyperactivity) during peak-level periods and to develop fatigue, depression, or anger during periods of lower levels. Some patients report peaks and valleys of mood and energy. Starting with lower doses, especially in older men, and titrating upward as tolerated will lessen mood fluctuations and abrupt changes in sexual interest.

Transdermal formulations provide the closest approximation of normal circadian plasma concentrations of testosterone. These are applied nightly and provide peak levels that follow a physiologic decline over the day. Scrotal patches are not popular because of the need to shave the skin before application, and because adherence to the scrotal skin is poor. Transdermal patches applied in the evening can provide physiologic testosterone levels, but transient skin irritation may occur. A low-dose steroid cream applied prior to patch placement can diminish skin irritation without hindering testosterone absorption. Doses can be difficult to adjust, and patches are more expensive than injection therapy.

Rapid-absorbing gels can be applied directly to nonscrotal skin once daily. The gel dries quickly and produces less irritation than patches, but there is a risk that unabsorbed gel may be transferred to the patient's sexual partner. About 10% of men experience absorption problems. The dose can be easily titrated, with packets or tubes of gel designed to deliver testosterone at dosages of 5 or 10 g/day. Gels are the most expensive form of testosterone replacement. As with injections, starting with lower doses in older men may help diminish adverse effects.

Buccal mucosal system administration of testosterone twice daily can restore testosterone concentrations to the physiologic range within 4 hours. The small mucosal adhesive tablet is placed in a comfortable area of the gum just above one of the upper front teeth. The tablet needs to be pressed firmly for 30 seconds to promote adhesion so that it will remain in the mouth for a full 12 hours. The used tablet is discarded at the end of the 12-hour period. Steady state is achieved within 24 hours of dosing in most patients. The incidence of adverse events is low, although buccal/gingival irritation, taste perversion, and bitter taste have been reported.

Oral preparations for testosterone replacement that are available in the United States are alkylated to avoid first-pass liver metabolism. These preparations are rarely prescribed because they can cause serious liver toxicity.

Other potential benefits of testosterone therapy

Studies of testosterone replacement therapy in hypogonadal men have demonstrated several potential benefits beyond improvement in the symptoms of

hypogonadism. Although these potential effects, outlined below, continue to be explored, it is unclear whether they are long-term benefits.

Bone density, lean body mass. Prevention of bone loss and improvement in body mass composition have been observed with testosterone replacement therapy. In men older than 65 years with low levels of bioavailable testosterone, 12 months of transdermal testosterone increased bone mineral density in the femoral neck compared with placebo ($P = .015$) and increased lean body mass ($P = .001$ vs baseline).[34] Additional studies have demonstrated improvements in lean body mass and percentage of body fat in hypogonadal men with 20 weeks of injectable or topical testosterone therapy compared with placebo.[35–37] In a meta-analysis of 29 randomized controlled trials of testosterone replacement in middle-aged and elderly men, Isidori et al found testosterone therapy to be associated with significant improvements in total body fat, fat-free body mass, and lumbar spine bone mineral density.[38]

Insulin sensitivity. Simon et al reported a significant improvement in indexes of insulin sensitivity ($P < .01$) after 3 months of therapy with a dihydrotestosterone gel compared with placebo in a group of healthy men with low levels of plasma total testosterone.[39] Whether such therapy can affect the management of type 2 diabetes or reverse components of metabolic syndrome remains unknown at this time.

Functional capacity. Malkin et al conducted a randomized, double-blind, placebo-controlled trial to assess the effect of testosterone therapy (5 mg/day for 12 months) in men with chronic heart failure; therapy was given to maintain serum testosterone levels within the physiologic range.[40] They found testosterone replacement to be associated with an increase in walking distance that correlated with a rise in bioavailable testosterone.

Sexual function. Erectile function scores have improved with testosterone therapy in men treated for sexual dysfunction,[18–20] including when used as an adjunct to PDE-5 inhibitor therapy.[22,23] In a meta-analysis of 17 randomized, placebo-controlled trials in men who were mildly or moderately hypogonadal (but not eugonadal), Isidori et al found that, compared with placebo, testosterone therapy was associated with more nocturnal erections, sexual thoughts, and successful intercourse attempts and with higher scores of erectile function and overall sexual satisfaction.[41] The effect of therapy was progressively weaker with increasing baseline testosterone levels.[41] In men with erectile dysfunction who were nonresponders to sildenafil, addition of a 1% testosterone gel produced significantly greater improvement in erectile function and a trend toward better orgasmic function and overall sexual satisfaction compared with placebo.[23]

Risks and adverse events

The risk-benefit ratio of long-term testosterone replacement therapy is unclear. Despite more than 50 years of clinical use, the long-term safety of testosterone replacement has yet to be demonstrated in controlled clinical trials.[1,2] Potential concerns include the following:[42]

BPH. Although prostate volume increases significantly during testosterone therapy, usually to the level of men without hypogonadism, exacerbation of voiding symptoms attributable to BPH has not been demonstrated.

Cardiovascular effects. The overall body of evidence indicates no association between testosterone and development of cardiovascular disease.[42] Past concerns about adverse lipid effects of testosterone replacement no longer seem warranted; in fact, testosterone therapy may confer beneficial lipid effects, but the jury is still out.

Erythrocytosis. The incidence of erythrocytosis reported in clinical trials of testosterone replacement has been 3% to 18% with transdermal forms and up to 44% with injectable short-acting forms; variations in rates depend on the dose and route of administration.[42] Although hemoglobin and hematocrit levels rarely rise above normal with testosterone therapy, they should be monitored when therapy is initiated. No thromboembolic events have been reported in relation to testosterone therapy.

Gynecomastia. Breast tenderness and swelling resulting from changes in SHBG levels occurs in a small number of men who receive testosterone replacement, but is usually reversible.

Sleep apnea. Exacerbation or development of sleep apnea, especially in those with risk factors for it, occurs infrequently with testosterone therapy.

Hepatotoxicity is associated with oral forms of testosterone, although apparently not with other formulations.

Special concern: Prostate cancer

The major safety concern with testosterone replacement therapy raised in the 2003 Institute of Medicine report was the risk of prostate cancer.[6] Based on the available evidence at that time, the report concluded that "the influence of testosterone on prostate carcinogenesis and other prostate outcomes remains poorly defined, but could greatly influence the risk-benefit ratio for supplementation in both young and

TABLE 3
Summary recommendations for prostate monitoring before and during testosterone replacement therapy

Before initiating therapy

Normal digital rectal examination (DRE)

Prostate-specific antigen (PSA) level < 4.0 ng/mL

Evaluate individual risk of prostate cancer[47]

During therapy

Measure PSA:
—At 3 to 6 months
—Semiannually as long as treatment continues

Perform DRE:
—Annually or semiannually as long as treatment continues

Refer for urologic evaluation and possible prostate biopsy in any of the following cases:
—Prostate is abnormal on DRE
—PSA > 4.0 ng/mL
—PSA rises by more than 1 ng/mL after 3 to 4 months on testosterone therapy
—PSA rises at rate > 0.75 ng/mL/yr[42]
—PSA rises at rate > 0.4 ng/mL/yr over an observation period of less than 3 years (using PSA after 6 months on testosterone as reference point)[47]

elderly populations." The report cited preclinical and clinical evidence that androgens may promote or inhibit prostate cancer growth.

Indeed, the fear of unmasking occult prostate cancer prevents many physicians from using testosterone replacement therapy. However, there appears to be no evidence that testosterone replacement increases the risk of prostate cancer even in those men at highest risk for it.

Three recent clinical studies suggest that higher endogenous testosterone concentrations are associated with less aggressive forms of prostate cancer:

- An examination of total testosterone levels in 82 men with localized prostate cancer demonstrated that pretreatment levels were lower among the men with non–organ-confined cancer than among those with organ-confined cancer.[43]
- An evaluation of total testosterone in 326 men about to undergo radical prostatectomy for clinically localized cancer found that lower preoperative testosterone levels were associated with advanced pathologic stage.[44]
- A retrospective study of 279 patients with clinically localized prostate cancer determined that poorly differentiated prostate cancer was associated with significantly lower testosterone levels.[45]

An additional study showed that 1 year of testosterone therapy produced no greater increase in PSA values in hypogonadal men with prostatic intraepithelial neoplasia, a precancerous prostate lesion, than in those without this lesion.[46]

We recommend that clinicians perform a baseline DRE and obtain a baseline PSA measurement before starting testosterone replacement, regardless of patient age. The PSA level should be checked 6 months after initiation of testosterone therapy, regardless of the route of administration. The PSA level should then be monitored semiannually as long as the patient remains on testosterone replacement, and a DRE should be performed annually or semiannually. **Table 3** presents recommendations for PSA monitoring during testosterone replacement therapy.[42,47]

Use of PSA monitoring for prostate cancer screening remains controversial in primary care (see separate article in this supplement on screening for urologic malignancies). At minimum, the risks and benefits of such screening should be discussed with the patient, especially if he is 50 years of age or older.

APPROPRIATE FOLLOW-UP AND MONITORING

Monitoring guidelines for patients receiving testosterone replacement therapy have been published by leading professional societies, including the AACE and the American Society for Reproductive Medicine.[1,2] These guidelines recommend periodic follow-up of patients receiving testosterone replacement, with routine examination of the prostate and regular determinations of PSA levels, similar to those outlined above.

Before starting testosterone replacement therapy, a baseline DRE should be performed and baseline values for the following should be obtained:

- Total serum testosterone
- PSA
- Hematocrit/hemoglobin
- Liver function enzymes
- Lipid profile (total cholesterol, low-density lipoprotein cholesterol, HDL cholesterol, and triglycerides).

Once therapy is started, dose adjustment is guided by serum testosterone monitoring and clinical response. Morning serum testosterone should be tested 1 or 2 months after therapy is started by monitoring the nadir testosterone level—ie, prior to the next injection, 3 to 12 hours after application of a transdermal patch, or at any time after the patient has been receiving topical gel treatment for several days. Normal testosterone levels range from 350 to 1,050

ng/dL; to optimize treatment response, we aim for the middle to upper portion of this range. Final dose adjustment, however, may also depend on the patient's response since some men respond well to levels in the low normal range. Supraphysiologic levels should be avoided for more than transient periods.

Laboratory values should be monitored periodically to ensure patient safety. Intermittent follow-up hematocrit measurements are appropriate, as is intermittent evaluation for sleep apnea. Patients should also be monitored for acne, breast tissue increase or tenderness, and skin irritation (if receiving topical preparations).

WHEN TO REFER

Referral to a specialist is indicated for patients whose hypogonadism is refractory to testosterone replacement. In patients receiving testosterone therapy, a rate of change in PSA level greater than 0.75 ng/mL per year, regardless of the baseline PSA level, should prompt further investigation with a prostate biopsy, as should detection of a nodule on DRE **(Table 3)**.

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