Men’s Sexual Health Consult Collection
Testosterone Replacement Therapy in the VA Setting

May 2008

CME

Introduction
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Diagnosis and Evaluation of Male Hypogonadism
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Treatment Options
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Potential Adverse Effects
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Target Audience: This activity has been designed to meet the educational needs of physicians, nurse practitioners, and physician assistants who work in the Department of Veterans Affairs.

Statement of Need/Program Overview: Male hypogonadism has been found to be more common than was previously recognized and more likely to be prevalent among VA patients than among the general population. As testosterone replacement therapy (TRT) is commonly used to treat this condition, VA practitioners should have a comprehensive understanding of the diagnosis and treatment of older men with adult-onset hypogonadism, and the benefits and risks associated with TRT.

Educational Objectives: After completing this activity, the participant should be better able to:

- Recall at least three conditions common among VA patients that are closely associated with adult-onset hypogonadism
- Identify five adverse symptoms associated with adult-onset hypogonadism that testosterone replacement therapy (TRT) has been shown to ameliorate
- Describe four clear indications for TRT in adult males
- Discuss current recommendations regarding pretreatment screening and posttreatment monitoring of TRT

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ne of the more perplexing issues arising frequently in primary care settings is the problem of possible testosterone deficiency in older patients. Crude prevalence is estimated to be as high as 38.7% among men aged 45 and older, and the condition has been found to be even more widespread among men with diabetes, metabolic syndrome (generally defined as insulin resistance, obesity, dyslipidemia, and borderline or overt hypertension), and renal failure—conditions that tend to be more prevalent among VA patients than among the general population.

Determining whether a patient is a candidate for testosterone replacement therapy (TRT) is a complex matter, with several issues that must be considered. The first is whether the patient actually has a clinical syndrome that could be improved by TRT. This is not as simple as determining whether some degree of erectile dysfunction is present, because there is only limited overlap between testosterone deficiency and erectile dysfunction. Indeed, many patients with erectile dysfunction who receive testosterone replacement alone show little, if any, improvement in their sexual performance.

The second issue to address is how to confirm the presence of testosterone deficiency, if in fact the presence of certain clinical features suggests that such a syndrome may be present. Because testosterone is tightly bound to a carrier protein in the blood, the diagnosis cannot rely upon a simple measurement of total testosterone levels. Measurements of the unbound, free, or bioavailable hormone are required to get around the confounding effect that may result from variations in the amount of binding protein.

The next question is whether replacing hormone will truly improve the clinical symptoms that began the whole process. Can exogenous replacement hormone produce the same benefits that are presumed to accrue from the natural hormone that is now found to be sub-optimal in quality?

If the decision is made to proceed with therapy, which form of replacement should be used? Should the replacement be oral, injectable, or in the form of a patch or gel? Are there meaningful differences in the results that accrue from these different modalities of testosterone administration?

And, finally, do we providers violate the hoary principle of *primum non nocere*—which exhorts us to do no harm to our patients—with TRT? What about possible benefits and/or adverse effects on multiple target organs such as the prostate, the muscles, and the cardiovascular system? Unfortunately, we do not have all of the answers regarding the potential long-term effects, both good and bad, of TRT.

The readers of this supplement are truly fortunate to have three of the nation’s (and the world’s) most prominent experts in the field of andrology (male hormones) tackle the questions I have outlined above. Dr. Alvin Matsumoto from the University of Washington, Dr. Glenn Cunningham from Baylor University, and Dr. Adrian Dobs from Johns Hopkins University are as expert a group of writers as one could possibly find to address the issues of TRT. I hope that each of you enjoys their articles and that you come away with a deeper understanding of the important challenges facing us when we contemplate TRT.

### References
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tale hypogonadism is a clinical syndrome caused by inadequate testosterone (T) production (androgen deficiency) that is accompanied by a decline in sperm production by the testes.1 Whereas diminished spermatogenesis with normal T production causes male infertility without manifestations of androgen deficiency, hypogonadism resulting in androgen deficiency impairs many body functions in addition to spermatogenesis.

Since both the prevalence and incidence of androgen deficiency increase as men age, male hypogonadism is a common disorder. Its diagnosis, however, may be challenging because in addition to unequivocally low serum T levels, it should be based on clinical manifestations of androgen deficiency, which may be subtle, nonspecific, and modified by the severity and duration of androgen deficiency, previous T treatment, the patient’s age, comorbidities, and variations in androgen sensitivity.

This article discusses the basic principles and nuances of diagnosing and evaluating male hypogonadism, the clinical manifestations of androgen deficiency, and the laboratory measurements most often used to assess a man’s androgen status. It describes how to distinguish primary from secondary hypogonadism and, through a case scenario, addresses some of the major considerations in patient assessment.

A Case to Consider
A moderately obese 58-year-old black man seeks treatment for erectile dysfunction (ED). He has type 2 diabetes mellitus, complicated by painful peripheral neuropathy and stage 2 chronic kidney disease with proteinuria, hypertension, dyslipidemia, and asthma. For the past three years, he says, his erections have been poorly sustained and penile rigidity has been insufficient to complete sexual intercourse, despite normal sexual desire on both his part and that of his wife of 21 years. He also reports having experienced excessive fatigue, accompanied by reduced physical activity and a 15-lb weight gain over the past year.

Current medications include: metformin, NPH insulin, acetaminophen with codeine, hydrochlorothiazide, atenolol, lisinopril, simvastatin, niacin, and inhaled salmeterol and fluticasone. A recent asthma exacerbation was treated with a pulse and tapering doses of prednisone over two weeks.

The patient smokes one pack of cigarettes daily but no longer drinks alcohol. There is no history of coronary artery disease, prostate or bladder surgery, or genitourinary trauma.

On physical examination, he is found to have a blood pressure of 124/84 mm Hg, regular pulse of 64/min, respiratory rate of 14/min, body mass index of 35, and pain level of 4/10 (his usual level of perceived chronic
neuropathic pain). His mood is mildly depressed. He has normal skin thickness; mild frontal balding; and normal axillary, chest, and pubic hair. Approximately 3-cm nontender, palpable breast tissue is detected bilaterally. Lung and cardiovascular examinations are unremarkable. Despite moderate central adiposity, his abdomen is without striae. His penis appears normal. Testicular volumes are normal: 25 mL on the right and 30 mL on the left (by orchidometer). His prostate is mildly enlarged without palpable nodules or induration. Hair loss is evident on his lower extremities, and dorsalis pedis and posterior tibial pulses are absent to palpation. He has reduced vibratory sensation in both feet, but intact sensation to a 10-g monofilament. Thigh muscle bulk is reduced, though thigh strength is normal.

Laboratory evaluation within the past month reveals: a normal complete blood count; glycosylated hemoglobin, 8.3% (normal, 6% or less); chemistry panel, significant only for a fasting glucose of 198 mg/dL (normal, 70 to 100 mg/dL) and an estimated glomerular filtration rate of 62 mL/min/1.73 m² (normal for men his age, 93 mL/min/1.73 m²); total cholesterol, 200 mg/dL (normal, less than 200 mg/dL); triglycerides, 366 mg/dL (normal, less than 150 mg/dL); high-density lipoprotein cholesterol, 30 mg/dL (normal, above 40 mg/dL in men and above 50 mg/dL in women); low-density lipoprotein cholesterol, 97 mg/dL (normal, less than 100 mg/dL); albumin, 3.2 g/dL (normal, 3.4 to 5.4 g/dL); urine protein excretion, 1.022 mg/24 h (normal, 150 mg/24 h); thyroid-stimulating hormone, 0.89 IU/L (normal, 0.4 to 4 IU/L); prostate-specific antigen, 1.6 ng/mL (normal, below 4 ng/mL); and total T, 248 ng/dL (normal, 280 to 800 ng/dL).

Is it appropriate to evaluate this patient for hypogonadism? Does the patient presented have male hypogonadism?

**Prevalence and Incidence of Male Hypogonadism**

In community-dwelling white men, the prevalence of biochemical hypogonadism (defined as T level lower than the 2.5th percentile, or less than 325 ng/dL), was found to be 12%, 19%, 28%, and 49% in men in their 50s, 60s, 70s, and 80s, respectively. By contrast, symptomatic androgen deficiency (defined as serum total T of less than 200 ng/dL or free T of less than 8.9 ng/mL and the presence of at least three signs or symptoms consistent with androgen deficiency) was found to have a crude prevalence of 6% in a predominantly white cohort of men aged 40 through 70 years. After an average of nine years of follow-up, when the same men were aged 48 through 79 years, the prevalence rose to 12.3%, with age-specific prevalences being 7.1%, 11.5%, and 22.8% for men in their 50s, 60s, and 70s, respectively. The crude incidence rate of symptomatic androgen deficiency was 12.3% per 1,000 person-years and increased with age: 5.9%, 11.2%, and 23.3% per 1,000 person-years in men who were in their 40s, 50s, and 60s, respectively, at baseline.

In a community-based population of white, black, and Hispanic men aged 30 through 79 years, symptomatic androgen deficiency (defined as serum total T of less than 300 ng/dL, or free T of less than 5 ng/dL and either one suggestive symptom, or at least two non-specific symptoms of androgen deficiency, based on the Endocrine Society clinical practice guidelines) was found to have a prevalence of 5.6%, and there were no differences in prevalence rates among the three ethnic groups.

In this population, prevalence in men younger than 70 was 3.1% to 7% but increased to 18.4% in men aged 70 and older.

**Diagnosis of Male Hypogonadism**

Male hypogonadism should be diagnosed only in men who have clinical signs and symptoms that are consistent with androgen deficiency, and biochemical androgen deficiency confirmed by unequivocally low serum T levels (Figure). The clinical presentation of male hypogonadism depends on the stage of development during which androgen deficiency occurs.

**Fetal and Prepubertal Onset**

During fetal development, androgen deficiency or defects in androgen action (such as androgen receptor mutations) result in varying degrees of ambiguous genitalia, depending on the severity of androgen deficiency or androgen resistance. For example, men with an androgen receptor mutation resulting in complete inactivation of the receptor present as phenotypic females (known as testicular feminization), due to a lack of androgen action during fetal development of the external genitalia.

Prepubertal androgen deficiency results in delayed puberty and eunuchoidism, which is characterized by infantile genitalia (small penis and testes), long arms and legs (due to failure of long bone epiphyses to close), poor muscular development, increased body fat, reduced peak bone mass, high-pitched voice, and sparse male-pattern (axillary, chest, facial, extremity, pubic, and perianal) body hair. Because clinical manifestations of prepubertal androgen deficiency are usually obvious and associated with psychosocial distress in boys and their families, the diagnosis is rarely missed. Some boys with prepubertal androgen deficiency, however, do not seek medical care and are not diagnosed until they are adults.

**Adult Onset**

The signs and symptoms of androgen deficiency acquired after pubertal development are nonspecific and subtler, in
part because serum T levels may not be reduced severely. When substantial androgen deficiency occurs over a prolonged period—for example, in men receiving gonadotropin-releasing hormone (GnRH) agonist or antiandrogen therapy for prostate cancer—clinical signs and symptoms are more obvious and characterize the full spectrum of the adult male hypogonadism syndrome (Table 1). In most men with hypogonadism, however, the nonspecific signs and symptoms of androgen deficiency are less obvious clinically. Furthermore, clinical manifestations may be modified by the severity and duration of androgen deficiency, previous T treatment, patient age, presence of comorbidities, and variations in androgen sensitivity—resulting in more highly variable clinical manifestations, especially in older men, and greater difficulty in making a clinical diagnosis of androgen deficiency.

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**Figure.** An approach to the diagnostic evaluation of adult men suspected of having androgen deficiency that is advocated by the Endocrine Society. Reprinted (with an adapted legend) with permission from: Bhasin S, Cunningham GR, Hayes FJ. Testosterone therapy in adult men with androgen deficiency syndromes: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2006;91(6):1995-2010. Copyright 2006, The Endocrine Society.

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*a The lower limit of the normal range for total T in healthy young men is generally considered to be 300 ng/dL (10.4 nmol/L), though this varies among laboratories. 
*b In three major commercial laboratories, the lower limit of the normal range for free T in healthy young men is 5 ng/dL (0.17 nmol/L), using equilibrium dialysis or calculated from total T and SHBG, though this range, too, varies among reference laboratories, depending on assays and populations used to establish normal ranges (ranging from 4-9 ng/dL in major commercial reference laboratories). 
*c MRI should be used to identify the etiology of hypotalamic/pituitary dysfunction, on an individual basis, in men with secondary hypogonadism.

d T = testosterone. Bio T = bioavailable testosterone. SHBG = sex hormone–binding globulin. LH = luteinizing hormone. FSH = follicle-stimulating hormone. SFA = seminal fluid analysis. 1° = primary testicular failure. 2° = secondary hypogonadism. MRI = magnetic resonance imaging.
Clinical findings that are suggestive of adult male hypogonadism may be classified as sexual manifestations (ED, infertility, and shrinking or very small [especially less than 5 mL] testes); brain/behavioral manifestations (reduced libido, hot flushes, and sweating); and physical manifestations (breast discomfort, gynecomastia; loss of axillary, pubic, and facial hair; and, with more severe, long-standing androgen deficiency, low bone mineral density [BMD], low trauma fracture, and reduced muscle bulk and strength). In addition, there may be less specific manifestations of androgen deficiency that occur in men with hypogonadism, including diminished energy and vitality, poor motivation, depressed mood, irritability, sleep disturbance, sleepiness, reduced concentration and memory, decreased activity and physical performance, mild anemia, and increased body fat.

**Confirming Androgen Deficiency**

In men with clinical manifestations of androgen deficiency, hypogonadism is confirmed by presence of low serum total T levels. Serum total T levels exhibit considerable assay and biological variability, and are affected by changes in sex hormone–binding globulin (SHBG) concentrations, illness, medications, and nutritional deficiency. As with the clinical diagnosis of male hypogonadism, biochemical confirmation of androgen deficiency presents its own set of challenges.

**Initial Measurement of Total T Levels**

For the most part, circulating T is bound to serum proteins. Approximately 44% is tightly bound to SHBG, and 54% is weakly bound to albumin but dissociable into some target tissues. Only about 2% of T is free and circulates unbound to proteins. Unlike SHBG-bound T, free T and albumin-bound T are available to tissues for biological action; hence, the combination of free and albumin-bound T is referred to as bioavailable T. Total T refers to the combination of free, albumin-bound, and SHBG–bound T. Because a significant fraction of T is bound to SHBG, measurements of total T are affected directly by alterations in SHBG concentrations.

Total T is the measurement that is most readily available in local laboratories and most commonly used to assess the adequacy of androgen status in men and enroll subjects in clinical trials of T treatment of hypogonadal men. Total T measurements are performed by immunoassay and, more recently, by liquid chromatography tandem mass spectrometry. Automated immunoassays for total T are performed in most local clinical laboratories and usually are accurate enough to distinguish eugonadal from hypogonadal men. There is, however, considerable variability in total T measurements for a number of reasons.

**Variability in Total T Levels**

Assay-to-assay variability in reported total T values may be extreme. For example, total T values measured on the same College of American Pathologists external quality control sample by different automated assays ranged from 160 to 508 ng/dL, spanning the hypogonadal to eugonadal range. In addition to assay variability, T levels exhibit biological variability due to episodic secretion from the testes and a circadian variation in serum total T levels, with peak concentrations in the morning, which is blunted in healthy older men compared with young men. For this reason, it is recommended that T measurements be performed in the morning, especially in young men.

Even within individual men, there is considerable day-to-day variability in T levels, such that a single total T measurement does not adequately reflect the average T level in a man. In a study of intraindividual variation in reproductive hormone levels, 15 of 121 men who underwent repeated blood sampling over six months had serum total T levels of less than 250 ng/dL (that is, in the hypogonadal range) measured on an initial baseline sample. Of these 15 men, only six had average T levels less than 250 ng/dL and three had average T levels greater than 300 ng/dL on repeated blood sampling over the subsequent six months. Diagnostic accuracy was improved by averaging T values from the first two blood samples.
(performed one to three days apart): Five of 10 men with average total T less than 250 ng/dL on the initial two samples had average T levels greater than 250 ng/dL but none had average levels greater than 300 ng/dL on repeated blood sampling over the following six months. Similarly, in a clinical trial of T treatment, 30% of men found to be mildly hypogonadal (with a serum total T of less than 300 ng/dL), based on a single blood sample at a screening visit, were found to have normal total T levels on repeat blood sampling at a subsequent baseline visit. These findings support the importance of confirming low serum T levels on at least two occasions before diagnosing biochemical androgen deficiency, especially when T values are only slightly below the normal range.

The threshold T level, below which signs and symptoms of androgen deficiency occur and T replacement is beneficial, is not known and varies among individuals with age and comorbid conditions, and among affected target organs. So, there is no absolute value of total T below which clinical androgen deficiency or hypogonadism can be confirmed in all patients.

In general, clinicians should use the lower limit of the normal range for total T (for example, less than 300 ng/dL) established for a specific assay in the laboratory to confirm biochemical androgen deficiency in men with consistent clinical manifestations. Normal ranges, however, vary considerably as a result of disparities among the populations that are used to establish them and assay differences. In some automated clinical assays, the lower end of the normal range for total T is 170 to 200 ng/dL, which is significantly lower than the 300 ng/dL limit established over the past 30 years using traditional radioimmunoassay methods, with or without chromatography. Clinicians should question the methodology used by the laboratory or the population upon which statistical ranges are established any time the lower limit of the normal range for total T assays is below 280 to 300 ng/dL.

### Free and Bioavailable T Levels

Alterations in SHBG concentrations occur commonly, especially in men with multiple comorbidities and those taking certain medications (Table 2). Moderate obesity, nephrotic syndrome, androgens, and anabolic steroids commonly lower SHBG levels and therefore decrease total T levels. Aging, hepatitis, hepatic cirrhosis, and anticonvulsants commonly raise SHBG levels, increasing total T levels. In men who have conditions or take medications known to alter SHBG concentrations, free or bioavailable T assays, which are not affected by changes in SHBG concentrations, should be ordered to confirm biochemical androgen deficiency.

Calculated free T (computed from total T and SHBG concentrations, using published algorithms) and free T measured by equilibrium dialysis are accurate methods to assess free T levels and are unaffected by alterations in SHBG. Equilibrium dialysis is considered the gold standard method for measuring free T, but there is excellent concordance between such measurements and calculated free T levels. Calculated bioavailable T (also computed from total T and SHBG measurements) and bioavailable T measured by ammonium sulfate precipitation are accurate methods for determining the level of T that is available to tissues for biological action. Unfortunately, most clinical laboratories do not measure free or bioavailable T using these accurate methods, so care must be taken to send samples to a reputable commercial reference laboratory.

Automated, direct, free T measurements that rely on analog methods are available in many local clinical laboratories, but they should not be used because they are affected by alterations in SHBG levels and are not concordant with the equilibrium dialysis method. Also, since analog-based free T methods have recently been shown not to measure free T in the absence of proteins, they offer no advantage over total T measurements.

### Table 2. Conditions and Medications Associated With Alterations in SHBG

<table>
<thead>
<tr>
<th>Conditions That Decrease SHBG and Lower Total T Level</th>
<th>Conditions That Increase SHBG and Raise Total T Level</th>
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<tbody>
<tr>
<td>Moderate obesity</td>
<td>Aging</td>
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<tr>
<td>Nephrotic syndrome</td>
<td>Hepatitis, hepatic cirrhosis</td>
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<td>Hypothyroidism</td>
<td>Hyperthyroidism</td>
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<tr>
<td>Acromegaly</td>
<td>HIV disease</td>
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<tr>
<td>Medications That Decrease SHBG and Lower Total T Level</td>
<td>Medications That Increase SHBG and Raise Total T Level</td>
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<tr>
<td>Androgens</td>
<td>Anticonvulsants</td>
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<tr>
<td>Anabolic steroids</td>
<td>Estrogens</td>
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<td>Glucocorticoids</td>
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<tr>
<td>Progestins</td>
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</table>

*Conditions in bold print are particularly common conditions that are associated with alterations in SHBG levels. SHBG = sex hormone–binding globulin. T = testosterone.*
Conditions That Transiently Lower T Levels

T measurements should not be performed during acute illness, temporary use of certain medication regimens (for example, those involving CNS-active medications, opioids, or glucocorticoids), use of recreational drugs, states of nutritional deficiency (for example, starvation as a result of anorexia or an eating disorder), or during extreme exercise, because these conditions can lower serum T concentrations transiently. A careful history and clinical evaluation is needed to exclude these conditions. T measurements should be delayed until after recovery from illness, discontinuation of interfering medications or recreational drugs, and recovery from nutritional deficiency. When interfering medication regimens are not temporary (for example, when opioid pain medications are prescribed for a chronic pain syndrome), serum T levels may be persistently low and associated with clinical manifestations of androgen deficiency. In such situations, T measurement may be appropriate.

Screening for and Case Detection of Androgen Deficiency

In some, but not all, epidemiological studies, low T levels (either endogenous or induced by GnRH agonist/anti-androgen therapy) have been associated with important clinical outcomes, including metabolic syndrome and diabetes mellitus,14,15 cardiovascular disease and related mortality,15-18 fractures,19 falls and reduced physical performance,20,21 depression,22,23 mild cognitive impairment and Alzheimer’s disease,24,25 and total mortality.16,17,26 The long-term benefits and risks of T treatment on these important clinical outcomes are not known. Furthermore, there is a lack of consensus on case definition and no effective screening strategies. Screening for androgen deficiency in the general population, therefore, is not justified.

Case detection by measurement of T levels, on the other hand, should be considered within populations of men who have clinical manifestations of androgen deficiency that might improve with T therapy and have been affected by conditions or events that are associated with a high prevalence of androgen deficiency. Such conditions and events include: hypothalamic/pituitary disease; HIV-associated weight loss; chronic organ failure (kidney, liver, lung, and heart failure); type 2 diabetes mellitus; low trauma fracture or osteoporosis; infertility; and long-term use of medications that lower T levels—for example, opioids, glucocorticoids, CNS-active medications, or ketoconazole. There is, however, limited or no evidence regarding the benefits and risks of T treatment in such populations.

Distinguishing Primary from Secondary Hypogonadism

Male hypogonadism may be due to testis dysfunction (primary hypogonadism) or secondary to hypothalamic or pituitary dysfunction (secondary hypogonadism), resulting in inadequate stimulation of the testes by pituitary gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). In addition to confirmation of unequivocally low serum T levels in men with clinical manifestation of androgen deficiency, concomitant measurement of serum LH and FSH levels should be performed to classify androgen deficient men as having either primary or secondary hypogonadism.1

In men with primary hypogonadism, the serum T level is low in association with high LH and FSH concentrations (Table 3). In men with secondary hypogonadism, a low serum T level occurs in conjunction with normal or low LH and FSH levels (Table 4). Normal gonadotropin levels are inappropriate in the setting of low T levels and reduced negative feedback of T, and suggest hypothalamic or pituitary dysfunction.

Hypogonadism may be due to defects in both hypothalamic/pituitary and testis function, resulting in a combined primary and secondary hypogonadism (as can occur with aging, chronic illness, glucocorticoid use, alcohol abuse, and hemochromatosis). In such cases, a hormonal pattern consistent with either primary or secondary hypogonadism usually predominates. Most men with hemochromatosis, for example, have a hormonal pattern of secondary hypogonadism with low T, LH, and FSH levels, despite also having an element of primary testicular dysfunction.

It is important to determine whether hypogonadism is primary or secondary because the latter may be caused by hypothalamic/pituitary tumors or by infiltrative diseases that can cause tumor mass effects (such as headache, visual field defect, visual impairment, or cerebrospinal fluid rhinorrhea), excessive secretion or deficiency of other anterior pituitary hormones or hypothalamic dysfunction (for example, diabetes insipidus), any of which would

Table 3. Causes of Primary Hypogonadism

<table>
<thead>
<tr>
<th>Pathological</th>
<th>Functional</th>
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<tbody>
<tr>
<td>Klinefelter syndrome</td>
<td>Drugs (eg, cytotoxic drugs, ketoconazole, aldactone, alcohol*)</td>
</tr>
<tr>
<td>Myotonic dystrophy and other developmental disorders</td>
<td>Systemic disorders (chronic liver and renal disease*)</td>
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<tr>
<td>Orchitis, irradiation</td>
<td>Aging</td>
</tr>
<tr>
<td>Castration, trauma, anorchia</td>
<td>*Usually combined primary and secondary hypogonadism, but a hormonal pattern consistent with primary hypogonadism (low T and high LH and FSH levels) usually predominates.</td>
</tr>
</tbody>
</table>

T = testosterone. LH = luteinizing hormone. FSH = follicle-stimulating hormone.
require medical management in addition to T therapy. Also, some functional causes of secondary hypogonadism may be transient or reversible (for example, acute illness, medications such as opioids or high-dose glucocorticoids, and nutritional deficiency). Finally, infertility in men with secondary hypogonadism is usually treatable with gonadotropin or GnRH therapy.

Further Evaluation of Hypogonadism
In men with hypogonadism who desire fertility, three seminal fluid analyses should be ordered over two to three months to assess sperm counts, motility, and morphology. In men with severe androgen deficiency or low trauma fracture, assessment of BMD should be evaluated by a dual-energy x-ray absorptiometry scan. T treatment has been demonstrated to increase BMD in hypogonadal men, but there is no evidence that T prevents fractures. T should not be used as primary treatment for osteoporosis, but conventional therapies (such as bisphosphonates) have demonstrated effect in preventing fractures in hypogonadal men with osteoporosis.

In men with secondary hypogonadism, further evaluation to identify the etiology of hypothalamic/pituitary dysfunction should be undertaken on an individual basis. This may include: serum prolactin and iron studies to exclude hyperprolactinemia and hemochromatosis, respectively, or assessment of anterior pituitary functions to exclude hyperprolactinemia. Persistence of hypogonadotropic hypogonadism should be investigated by pituitary imaging and hormonal testing (LH, FSH, and prolactin). MRI or computed tomography of the hypothalamus and sella turcica may be performed to identify a hypothalamic or pituitary tumor or infiltrative disease in men with very low levels of T (less than 150 ng/dL), LH, and FSH, or isolated LH or FSH elevation, panhypopituitarism, persistent and severe hyperprolactinemia unexplained by medications, or signs or symptoms of tumor mass effect. Men with idiopathic hypogonadotropic hypogonadism should be examined for dysmorphic features such as morbid obesity, short stature, anosmia, cleft lip or palate, polydactyly, or kidney abnormalities, which may be associated with Kallmann syndrome, Prader Willi syndrome, or one of the many complex genetic disorders characterized by this condition. Morbidly obese men with low free T levels should be evaluated for obstructive sleep apnea, which may contribute to hypogonadotropic hypogonadism.

In men with primary hypogonadism and clinical features of Klinefelter syndrome (very small, firm testes; gynecomastia; infertility; azoospermia; and disproportionately long legs), a chromosomal karyotype may be obtained to confirm the diagnosis (47,XXY karyotype) and patients can be referred for genetic counseling.

Case Discussion
There are a number of potential risk factors and etiologies for ED in the patient scenario presented previously. These include diabetes mellitus (complicated by neuropathy), nephropathy, probable peripheral vascular disease, smoking, hypertension, hyperlipidemia, medications that may contribute to ED (for example, diuretics, beta-blockers, and opioids), and possibly mild depression.

Low serum T levels are commonly associated with ED. In addition, the patient's codeine use and recent pulse glucocorticoid therapy may have contributed to the low T level, since both opioid and glucocorticoid use lower serum T levels. Also, in addition to ED, the patient has other manifestations that are consistent with androgen deficiency, including excessive fatigue and reduced activity, gynecomastia, and reduced muscle bulk, though these manifestations are relatively nonspecific.

While it is unlikely that T treatment alone will adequately treat ED in a diabetic patient with moderately low serum testosterone levels, the addition of T therapy to such conventional ED treatments as phosphodiesterase type 5 inhibitors may restore sexual function in hypogonadal men with ED. Furthermore, T treatment may benefit other body functions, for example, increasing muscle mass and strength, as well as BMD. A diagnosis of hypogonadism in men who present with ED, therefore, may affect overall health management.

### Table 4. Causes of Secondary Hypogonadism

<table>
<thead>
<tr>
<th>Pathological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kallmann syndrome, idiopathic hypogonadotropic hypogonadism</td>
</tr>
<tr>
<td>Hemochromatosis*</td>
</tr>
<tr>
<td>Hyperprolactinemia (pituitary adenoma, drugs)</td>
</tr>
<tr>
<td>Hypopituitarism (tumor, infiltrative disease, destruction, surgery)</td>
</tr>
<tr>
<td>Complex genetic syndromes (eg, Prader-Willi syndrome*)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs (CNS drugs [opioids], glucocorticoids*, estrogens, progestins, anabolic steroids, GnRH agonist)</td>
</tr>
<tr>
<td>Acute illness and chronic disease (liver, renal, lung, or heart disease, or type 2 diabetes mellitus)</td>
</tr>
<tr>
<td>Nutritional deficiency (starvation), wasting syndrome (eg, in HIV disease)</td>
</tr>
<tr>
<td>Morbid obesity, obstructive sleep apnea</td>
</tr>
<tr>
<td>Aging*</td>
</tr>
</tbody>
</table>

*Usually combined primary and secondary hypogonadism, but a hormonal pattern consistent with secondary hypogonadism (low T and normal or low LH and FSH levels) usually predominates.

CNS = central nervous system. GnRH = gonadotropin-releasing hormone. T = testosterone. LH = luteinizing hormone. FSH = follicle-stimulating hormone.
and it is appropriate to evaluate such patients for androgen deficiency. In the case presented previously, serum free or bioavailable rather than total T levels should be used to evaluate whether androgen deficiency is present because moderate obesity, proteinuria with mild hypoalbuminemia, and a recent pulse of prednisone would decrease SHBG levels, lowering total T concentrations.

The patient’s repeat total T was low at 240 ng/dL (normal, 280 to 800 ng/dL). The SHBG level, however, was in the low-normal range at 25 nmol/L (normal, 10 to 80 nmol/L). Calculated free and bioavailable T were both normal at 53 pg/mL (normal, 34 to 194 pg/mL) and 128 ng/dL (normal, 84 to 402 ng/dL), respectively. Normal free and bioavailable T levels are consistent with eugonadism rather than hypogonadism, and the patient’s low total T is attributable to low-normal SHBG levels, likely due to moderate obesity, urinary protein loss, and recent glucocorticoid use.

References
A 76-year-old man with primary testicular failure secondary to war trauma sustained 40 years ago reports dissatisfaction with his testosterone replacement therapy (TRT). For many years, he has been using testosterone enanthate (TE) 200 mg IM every two weeks. He was doing relatively well with the treatment until recently, after his wife passed away. Now he is bothered by the mood swings and the lethargy that he feels shortly before his next injection is due. Although these symptoms are not new, he says he has recently been feeling low and is, therefore, more sensitive to them.

The patient recalls that, while using TE, he had a healthy libido despite some erectile dysfunction. He is, however, no longer interested in continuing the treatment for this goal.

He has no problem voiding, reports no excessive daytime sleepiness, and has no history of fractures or height loss, though he has never had a dual energy x-ray absorptiometry (DEXA) bone scan.

Past medical history includes dyslipidemia, for which he is currently taking simvastatin 20 mg daily. In addition, he takes aspirin 81 mg daily to lower his risk of clot-related events. A cardiac catheterization performed within the past few years showed some blockage.

Recent blood work reveals the following levels: hemoglobin (Hb), 16.2 g/dL (normal, 13.8 to 17.2); hematocrit (Hct), 49.2% (normal, 42% to 52%); low-density lipoprotein (LDL) cholesterol, 65 mg/dL (normal, less than 100 mg/dL); high-density lipoprotein (HDL) cholesterol, 52 mg/dL (normal, above 40 mg/dL); triglycerides, 104 mg/dL (normal, less than 150 mg/dL); prostate-specific antigen (PSA), 0.8 ng/mL (normal, below 4 ng/mL); total testosterone, 369 ng/dL (normal, 280 to 800 ng/dL); luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, undetectable (normal, 2 to 12 mIU/mL and 1 to 12 mIU/mL, respectively). He also has been told he has elevated blood glucose levels and has, therefore, reduced his carbohydrate intake and lost some weight.

On physical exam, the patient appears to be healthy and in no distress. His vital signs are within the normal range. He has a nontender, Tanner stage II gynecomastia on the left side, which he says developed recently. Genitourinary examination reveals no palpable testis in the left scrotal sack, and an atrophic right testis measuring approximately 7 mL. Digital rectal exam (DRE) reveals a nonenlarged prostate with no nodules. Body hair, virilization, and all other aspects of his physical examination are normal.

How do we evaluate and manage this patient’s treatment?

The ideal TRT would be one that mimics the normal physiologic state and is safe, efficient, and easy to use. A number of TRT modalities are in current use, many of which have been approved for use in the United States (Table 1). Each has a unique profile that may determine its acceptability for the specific patient.

This article reviews existing TRT modalities, discusses their advantages and disadvantages, and describes the pharmacokinetics of each. It provides recommendations.
for pretreatment screening and post-treatment monitoring of TRT, while clarifying matters that require consideration by the treating clinician in the previous case scenario.

### Intramuscular Injections

Intramuscular testosterone has been used for years due to its effectiveness and low cost. Whereas free testosterone has a half-life of only 10 minutes, the esterification process renders testosterone less polar and more lipid soluble, thereby prolonging its duration of action. Delivery of these esters through an oil-based depot injection allows their slow release.

TE and testosterone cypionate (TC) have similar pharmacokinetic profiles. Both produce peak, often supraphysiologic levels within two to three days of injection and decline slowly, often to subnormal levels in one to two weeks.\(^1\)\(^2\) Such roller-coaster pharmacokinetics cause swings in mood, energy level, sexual function, and libido.

Placebo-controlled data show that sexual functioning, which closely follows fluctuations in circulating testosterone levels, has a dose-related response to TE therapy.\(^3\) Although there is no placebo-controlled evidence that mood swings and energy levels vary more with injectable testosterone than with other modalities, the concept is widely held to be true. Higher dosing prolongs the interval between consecutive injections, but it also produces higher peaks and lower nadirs in circulating testosterone, thereby exacerbating symptom fluctuation.

The most commonly recommended dosing regimen for TE or TC is 100 to 200 mg IM every two weeks\(^1\) or, as the American Association of Clinical Endocrinologists recommends, when testosterone levels are just above the lower limit of normal, in the range of 250 to 300 ng/dL.\(^4\) The Endocrine Society recommends measuring levels midway between injections and adjusting dose or frequency to achieve levels in the midnormal range.\(^5\)

Testosterone propionate is rarely used in an injectable form because its pharmacokinetic profile requires administration every two to three days.

### Table 1. Testosterone Replacement Therapies Approved for Use in the U.S.\(^1\)

<table>
<thead>
<tr>
<th>Delivery System (Drug)</th>
<th>Route of Delivery</th>
<th>Standard Dosage for Androgen Deficiency</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Estimated Monthly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone esters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone enanthate</td>
<td>IM</td>
<td>100 mg every week or 200 mg every 2 weeks</td>
<td>Inexpensive; administered every 2 weeks</td>
<td>Roller-coaster pharmacokinetics; requires injection</td>
<td>$100</td>
</tr>
<tr>
<td>Testosterone cypionate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone pellets</td>
<td>SC</td>
<td>Two to six 75-mg pellets every 3 to 6 months</td>
<td>Convenient 6-month biological duration</td>
<td>Expensive; requires small incision; high rate of extrusion; available only through manufacturer</td>
<td>$150</td>
</tr>
<tr>
<td>Buccal testosterone</td>
<td>Buccal</td>
<td>30 mg BID</td>
<td>Testosterone levels within physiologic range</td>
<td>Expensive; twice-daily dosing; possible oral irritation</td>
<td>$250</td>
</tr>
<tr>
<td>Testosterone patch</td>
<td>Nonscrotal topical</td>
<td>5 mg/day</td>
<td>Mimics circadian rhythm</td>
<td>Expensive, daily administration; skin irritation</td>
<td>$250</td>
</tr>
<tr>
<td>Testosterone gel</td>
<td>Topical</td>
<td>5 g/day</td>
<td>Testosterone levels within physiologic range</td>
<td>Expensive; daily administration; possible transference to intimate contacts</td>
<td>$300</td>
</tr>
</tbody>
</table>

Adapted with permission from Edelstein D, Dobs A, Basaria S. Emerging drugs for hypogonadism. Expert Opin Emerg Drugs. 2006;11(4):685-707.\(^1\)
Intramuscular testosterone injections are deep and may produce pain, site reactions, or pruritis. As with all forms of testosterone that undergo aromatization to estradiol (all formulations mentioned in Table 1), administration may cause gynecomastia early in the treatment process, mild cases of which usually resolve within a few months. Some reports also have described short episodes of coughing following injections. Such episodes are thought to result from pulmonary microembolisms caused by the oily vehicle.

**Implantable Testosterone**

Developed in the 1940s, implantable testosterone is the oldest form of TRT. Pellets, each containing 75 mg of crystalline testosterone, are implanted subcutaneously to provide slow release over four to six months. Depending on the dose required, two to six pellets are implanted under the skin of the lower abdomen, upper thighs, deltoid, or gluteal muscles every three to six months.

Pellets tend to provide stable physiologic levels of testosterone. Although implantable testosterone, like the injectable forms, can cause levels to peak initially, the decline is gradual, over six months, so that mood swings and energy fluctuations are seldom recognized by the patient.

Because pellets require surgical implantation, their use can be painful. They also have a high rate of extrusion. Furthermore, since their duration of action is long and reversibility is difficult, testosterone pellets are unsuitable for treating elderly patients, in whom adverse effects are more common. Testosterone pellets are not often used in the United States.

**Transbuccal System**

One of the newest TRT modalities is transbuccal testosterone. Administered through a small, convex, tablet-like system that adheres to the gum tissue above the incisors, transbuccal testosterone is absorbed slowly, as it is hydrated by the buccal mucosa. Since buccal testosterone is transported directly into the superior vena cava from the buccal venous system, it avoids the first-pass effect of hepatic metabolism.

Tablets contain 30 mg testosterone each and are applied twice daily. Levels peak within 30 minutes, attain steady state within 24 hours, and drop to below normal two to four hours after the tablet is removed. Transbuccal administration maintains testosterone at levels within the physiologic range, comparably to testosterone gel, or nearly so.

Associated adverse effects are mild to moderate and include gum or mouth irritation or tenderness and bitter taste. Other potential concerns include inadvertent swallowing of the tablet resulting in decreased blood levels of testosterone and transfer of salivary testosterone to the partner.

**Transdermal Testosterone**

Transdermal TRT is delivered in the form of a non-scrotal patch or gel. It requires daily administration and has the benefit of mimicking testosterone’s normal circadian rhythm, peaking in the morning and declining slowly to its nadir at night (Figure 1). Another advantage to this modality is that, unlike injectable and oral testosterone formulations, which tend to lower HDL levels significantly, transdermal therapy does not disturb serum lipids. One caveat to consider when prescribing transdermal TRT is that testosterone absorption varies widely among individuals.

**The TRT Patch**

The first testosterone patch was developed for placement on scrotal skin to maximize the hormone’s absorption. Scrotal patches should be applied to shaved skin; this inconvenience, plus the poor adherence of the patch to the scrotal skin area, are limitations which led to its demise. The nonscrotal transdermal patch was developed to overcome some of these problems.

Due to the limited ability of nonscrotal skin to absorb testosterone, nonscrotal patches contain permeation enhancers. Although both 2.5- and 5-mg patches are available, the usual dose is 5 mg daily, using one or two patches. At this dosage, the patient actually absorbs approximately 4.5 of the 5 mg applied daily. The patch is applied at nighttime to the abdomen, upper arms, back, or upper thighs.

The most common problem encountered with this system is the high incidence of skin irritation at the application site, which is caused by permeation enhancers and occurs in at least one third of users. Applying a glucocorticoid cream, such as 1% triamcinolone acetonide, under the patch generally reduces the contact dermatitis without interfering with testosterone absorption.

All transdermal preparations increase dihydrotestosterone (DHT) concentrations, due to the presence of type 1 5α-reductase within the skin. Removal of the patch returns DHT levels to the hypogonadal range within 24 hours.

**TRT Gel**

TRT gel was designed to further improve transdermal delivery systems. Although it is the most expensive of the TRT modalities, transdermal gel is currently the most commonly used, followed by injections, patches, and, finally, oral tablets.

The gel, containing 1% testosterone, is available in 2.5-, 5-, or 10-g tubes or packets, and as a 75-g pump delivering doses of 1.25 g per compression. Generally, the gel is applied to dry skin on the shoulder, abdomen, or upper arm after bathing. It dries within 10 minutes.
Patients are advised to cover the application site with clothing for at least two hours after application to prevent transferring the gel to others by contact and to avoid bathing or swimming for two to six hours after application, depending on the brand.

Approximately 10% of the gel is absorbed into the stratum corneum of the skin, which serves as a reservoir for the testosterone, allowing its slow release over several hours. Testosterone levels peak in 16 to 22 hours, reaching steady state in one to two days, and tending to remain stable thereafter. Levels return to baseline within four days of discontinuation.

Compared to the patch, the gel rarely causes skin irritation. It also allows for greater flexibility of dosing than do other modalities, as it is available in variable doses and as a pump. Levels of DHT, however, seem to be significantly higher than those attained with patch use. This is likely due to the fact that the gel covers a greater skin surface area than the patch, causing more testosterone to convert to DHT. PSA levels are elevated with gel use but remain within the normal range.

**Oral Testosterone**

Alkylation of testosterone allows its escape from significant hepatic metabolism but also imparts risk for cholestasis, lipid disturbances, and hepatic adenoma, as well as other hepatic complications. Oral forms of testosterone, such as 17-α-methyltestosterone and fluoxymesterone, have been associated with a few reports of hepatotoxicity and are therefore not recommended.

Mesterolone, an oral DHT derivative, is rarely used because of its weak androgenicity. Testosterone undecanoate (TU) is an oral testosterone ester delivered by an oily vehicle that escapes hepatic metabolism through absorption into the lymphatics. It has been used in Europe for decades but was never approved for use in the United States. Its advantages include convenience of administration and a relatively safe profile, but its short half-life causes testosterone levels to fluctuate, necessitating multiple daily dosing.
**Novel Testosterone Therapy**

A long-acting intramuscular injection of the testosterone ester TU is currently undergoing phase III trial for approval in the United States. It has been approved for use in Europe. TU is the first injectable testosterone to be taken every three months. It maintains stable physiologic levels for 12 weeks and appears to be well accepted. Compared to TE, TU produces a more stable rise, modest maximal concentration, and gradual decline of testosterone, thereby minimizing the mood and libido fluctuations seen with TE (Figure 2). As reviewed by Harle and colleagues, its safety and tolerability profile is also favorable: Incidence and severity of common adverse effects are not greater than those associated with TE, and no serious adverse events have been noted.

Although intramuscular TU is not yet approved in the United States, the recommended dose will probably be 1,000 mg every 10 to 14 weeks, with an additional loading dose of 750 mg to be administered at four weeks. Because TU has a long half-life and its safety in older men is yet to be reported, it may have a greater role in treating younger patients. For older men, the switch to TU may be considered if transdermal agents have been used for three to six months, thus ensuring tolerability.

**Choice and Evaluation of Treatment**

TRT modalities are numerous, and all have advantages and disadvantages in terms of safety, convenience, efficacy, ability to mimic physiologic levels, and adverse effects. Choice of treatment must take into account the patient’s age, existing medical conditions, previous and current response to treatment, and preference, as well as cost.

Since elderly patients experience more of the adverse effects associated with TRT, such as polycythemia, it would be preferable to treat them with modalities that have a shorter duration of action, so that such effects would be easily reversible upon discontinuation of treatment.

Safety issues of prostate enlargement, elevation of PSA levels, polycythemia, and sleep apnea are evaluated before and during therapy (Table 2). Before initiation of treatment, levels of PSA, Hb, Hct, and testosterone should be obtained; a DRE should be performed; voiding symptoms should be assessed; and a DEXA scan should be ordered to assess baseline bone status.

One month after the initiation of treatment, PSA, Hct, testosterone levels, and treatment response should be assessed so that the dose may be modified if necessary. Ideally, a midnormal level of testosterone is the target of therapy, but testosterone levels should be correlated to

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**Figure 2.** Serum testosterone levels (mean ± SEM) during a 30-month study period in a trial comparing testosterone undecanoate (TU) IM administered at 12-week intervals and testosterone enanthate (TE) IM administered at three-week intervals. After 30 weeks of therapy, all patients switched to TU injected at 12-week intervals. Reprinted with permission from Schubert M, Minnemann T, Hübler D, et al. Intramuscular testosterone undecanoate: Pharmacokinetic aspects of a novel testosterone formulation during long-term treatment of men with hypogonadism. J Clin Endocrinol Metab. 2004;89(11):5429-5434.
the patient's signs and symptoms because dose-response levels vary among individuals. The previous parameters should be assessed at 6 months and annually thereafter to evaluate the treatment. If the patient has osteopenia or osteoporosis at baseline, measurement of lumbar spine and/or femoral neck BMD every other year of testosterone replacement is indicated. It is important to ask about voiding symptoms, especially in men with a history of benign prostatic hyper trophy. TRT is contraindicated in patients with severe BPH as it may increase prostate size to that of normal men, thereby exacerbating voiding symptoms. Such adverse effects of TRT as fluctuations in mood and libido, gynecomastia, acne, and treatment modality--specific symptoms should be assessed at each visit. As for choosing the TRT modality, patient preference is a major factor in determining the success of therapy. That, along with patient motivation, lifestyle, and adherence to the prescribed regimen determine how effective treatment is in restoring physiologic testosterone levels and achieving clinical improvement.

Case Discussion
In the case described previously, the patient presented with two symptoms commonly associated with TRT: (1) fluctuation in mood and libido, a frequent occurrence with injectable forms of TRT due to the fact that testosterone levels decline to baseline by the end of the second week when readministration is due; and (2) gynecomastia, which is common to patients using aromatizable forms of TRT, particularly older men in whom levels of sex hormone--binding globulin are elevated. Men with a genetic susceptibility to alopecia are particularly vulnerable to TRT-related gynecomastia. The patient's sexual functioning and normal total testosterone level seem to suggest that his testosterone is adequately replaced. His undetectable gonadotropin levels, however, indicate that his testosterone has been over-replaced, a problem that is common with IM forms of TRT. To better assess the situation, it is advisable to measure serum testosterone levels midway between IM injections.

Although the rest of his blood work shows normal values, his Hct level is in the upper range of normal. Given his age and unclear history of cardiovascular disease, his Hct should be monitored routinely for polycythemia. Liver safety is a concern mainly for patients using oral TRT, but it would be prudent to order liver function tests. Although he has no history of fractures or height loss, it is important to obtain a DEXA scan to evaluate the efficiency of his treatment. His nonenlarged prostate and normal virilization are signs that his therapy is safe and his response is good.

Next steps in treatment would include informing the patient that benefits of TRT are not limited to sexual effects and, depending on the results of his DEXA scan, advising him that it would be prudent to continue with TRT since his levels are in the low range of normal with treatment. If DEXA scanning reveals osteoporosis, other etiologies besides androgen deficiency need to be explored. Hypovitaminosis D, for example, is a factor that commonly contributes to osteoporosis in the elderly. Since the patient is no longer tolerating the mood swings associated with injectable TRT, recommending a switch to transdermal therapy would be warranted. Transdermal therapy is more appropriate for hyperlipidemic patients since, in the recommended dose range, it does not affect serum lipid levels. In addition, its shorter duration of action makes it safer to use in a man of his age. Finally, the patient would likely find it more convenient to use a TRT that he could apply at home than to visit a physician's office every two weeks for an injection.
After therapeutic options are discussed with the patient, if he is willing to try another form of TRT, he should be provided with detailed instruction on how to use the new modality. His response to and tolerability of the new treatment should be reassessed in one month.

References

Testosterone replacement therapy (TRT) is the most important aspect of treatment in patients with such conditions as Klinefelter syndrome, and it is key to the treatment of primary hypogonadism and many types of secondary hypogonadism. Clinicians prescribing this therapy, however, must take certain precautions to ensure that the route of administration, the dosage, and the therapy itself are appropriate for each particular patient. In addition, they must ensure that, throughout the course of treatment, patients’ physiologic parameters are monitored in accordance with recommended guidelines.

In this article, we present and discuss three cases involving men who were treated with TRT and subsequently experienced adverse effects. In the first case, a young man treated with TRT developed vesicular acne and exhibited a decline in high-density lipoprotein (HDL) cholesterol levels. In the second and third cases, men in their 60s developed erythrocytosis and prostate cancer, respectively. Case discussions clarify how such outcomes might have been avoided.

Case 1: A Young Man With Klinefelter Syndrome

A 22-year-old white man was referred for management of Klinefelter syndrome. The diagnosis was suspected two months earlier when a urologist evaluated him for pelvic pain. The patient was given a diagnosis of infectious epididymitis/prostatitis and was treated with antibiotics. The urologist, who recommended further evaluation, noted that the patient had small testes.

Pubertal development had started at age 14. The patient's growth rate accelerated around age 16, and he reached his maximal height at age 20. He grew a beard at age 18, though he had started shaving at age 15.

The patient reported no breast enlargement and no breast tenderness. He was able to masturbate, but failed to consummate sexual intercourse on one occasion.

In elementary school, the patient was diagnosed with a learning disability that necessitated enrollment in special education classes. He was a nonsmoker and a social drinker. He worked as a forklift operator.

Physical Examination

- Vital signs (VS): temperature (T), 98.9°F; heart rate (HR), 72 bpm, regular; respiratory rate (RR), 16/min; blood pressure (BP), 110/80
- General appearance: well-developed young man; height, 70 in; weight, 182 lb; body mass index (BMI), 26.1; pubic symphysis to sole, 38 in; arm span, 71.25 in
- Skin and hair: beard over chin, moderately heavy body hair, unremarkable skin
- Chest: no gynecomastia
- Genitourinary (GU): well-developed scrotum and penis; testes, less than 1 cm bilaterally and firm; prostate, somewhat smaller than normal for age 22
- Nervous system (NS): normal neurologic examination; responses, slow but appropriate

Laboratory Findings

- Complete blood count (CBC), chemistry panel, and thyroid function tests, normal; no lipid profile was obtained
- Serum hormones: total testosterone...
one, 270 and 209 ng/dL on separate days (reference range, 241 to 827 ng/dL); luteinizing hormone (LH), 35.4 mIU/mL (reference range, 1.5 to 9.3 mIU/mL); follicle-stimulating hormone (FSH), 48.6 mIU/mL (reference range, 1.6 to 8 mIU/mL) • Semen analysis: azoospermia in a 4-mL ejaculate • Chromosomal analysis of peripheral blood: karyotype 47 XXY

Clinical Course
The patient was started on testosterone cypionate injections, 150 mg IM every two weeks, administered at his primary care physician’s office. A few months following initiation of treatment, the patient reported an increase in facial hair. He became more assertive and more active socially. To gain muscle mass, he began an exercise program.

Therapy was guided by the patient’s self-reported improvement in symptoms and by serial measurements of total testosterone. His hematocrit level was monitored and remained within the normal range. After one year of treatment, his weight had increased to 205 lb, and his BMI to 29.4.

Subsequently, the patient started self-administering testosterone cypionate injections, 75 mg once a week. The primary care physician had stopped administering these injections to the patient. The patient’s mother became concerned that her son was overtreating himself. Clinical and biochemical findings supported the mother’s concern. There were no changes in the patient’s behavior or weight, but he had developed severe vesicular acne over his back, his HDL cholesterol level had fallen to 30 mg/dL (normal, above 40 mg/dL), his triglycerides were elevated at 179 mg/dL (normal, less than 150 mg/dL), and his low-density lipoprotein (LDL) cholesterol level was 115 mg/dL (normal, less than 100 mg/dL). His total cholesterol was 181 mg/dL and total testosterone levels, seven days after the injection, were 796 and 601 ng/dL, on separate occasions four weeks apart.

Discussion
TRT is the mainstay of treatment in Klinefelter syndrome. It is used to correct testosterone deficiency, induce and maintain virilization, and improve psychosocial status. There is, however, a potential for testosterone overuse and abuse in young men eager to improve their appearance and physical performance.

The previous case raises the possibility of testosterone abuse in an athletic young man with Klinefelter syndrome and illustrates two potential sequelae of abuse: namely, acne and adverse effects on lipid profiles. Furthermore, since the historic assumption of infertility in men with nonmosaic Klinefelter syndrome has recently come into question, the potential effects of treatment on fertility should be discussed with all patients who have this condition.

Usual Treatment. Klinefelter syndrome is the most common cause of primary hypogonadism in males. It is estimated that one in 500 boys are born with an additional X chromosome (47 XXY), the karyotype that causes Klinefelter syndrome.1 TRT is the mainstay of treatment; 200 mg IM of a testosterone ester (either testosterone enanthate or testosterone cypionate) administered every 10 to 14 days is a common regimen. Such regimens, however, are associated with supraphysiologic levels of testosterone for a few days after the injection, followed by a decline to subphysiologic levels before the next injection.2 A dose of 50 to 100 mg IM every seven days, or 100 to 200 mg IM every 14 days, can reduce the extreme levels. A midnormal level midway between injections is a reasonable goal.

Serum testosterone levels measured on day seven of a seven-day injection cycle reflect the lowest testosterone levels after an injection. If the patient is on a seven-day injection cycle and the seven-day level is above 500 ng/dL, the findings suggest overdose, particularly if the patient presents with acne or another potential dose-related adverse effect.

Potential Abuse. Testosterone esters and other androgens are used widely by professional and amateur athletes, as well as by nonathletes wishing to enhance their appearance. The annual prevalence of anabolic steroid abuse among young adults during the year 2006 was estimated to be 1.8%, 1.1%, and 1%, respectively, for adults aged 18, 19 to 20, and 21 to 22.3 When initiating testosterone therapy, particularly in young patients, it is important to choose a delivery system that is unlikely to facilitate overuse or abuse. In the opinion of these authors, the potential for abuse with injectable testosterone cypionate or testosterone enanthate is greater than with transdermal delivery systems, since these injectable forms can be administered in very large doses. However, due to its efficacy and lower cost in comparison with that of other modes of delivery, injectable testosterone cypionate and enanthate remain widely used.

Acne. Sebum production is an androgen dependent process, and acne is a well recognized concomitant of puberty that also can result from treatment with supraphysiologic, or even physiologic, doses of testosterone. While physiologic replacement doses of testosterone cause minimal or no change in HDL and total cholesterol levels, the same cannot be said for supraphysiologic doses of testosterone.4

Dyslipidemia. Kouri and colleagues examined the relationship between anabolic androgenic steroids and lipid-protein levels in healthy young men receiving testosterone cypionate IM for six weeks in doses gradually escalating from 150 mg/week up to 600 mg/week.5 They found that it reduced HDL cholesterol and increased the
ratio of total cholesterol to HDL cholesterol, with this effect reaching its full magnitude even at very modestly supraphysiologic doses and persisting for several weeks after discontinuation of the drug.

Findings were different for Singh and colleagues, who also studied the effects of TRT on lipid profiles. They randomly assigned 61 eugonadal men, aged 18 to 35, to one of five groups receiving monthly injections of long-acting gonadotropin-releasing hormone agonist, to suppress endogenous testosterone secretion, and weekly injections of testosterone enanthat at doses of 25, 50, 125, 300, or 600 mg for 20 weeks. There were no changes in total cholesterol, LDL cholesterol, very-low-density lipoprotein cholesterol, or triglyceride levels at any dose of testosterone. Only the highest dose of testosterone (600 mg/week) was associated with a significant reduction in HDL cholesterol.

Fertility Issues. Traditionally, all men with nonmosaic Klinefelter syndrome have been considered sterile. Recent reports, however, suggest otherwise. Schiff and colleagues were able to retrieve sperm with microdissection testicular sperm extraction in 72% of men with nonmosaic Klinefelter syndrome, despite very limited testicular volume, extensive tubular sclerosis, and markedly elevated FSH levels. Once sperm were obtained, intracytoplasmic sperm injection resulted in pregnancy in 46% of cycles. However, Schiff and colleagues observed low rates of sperm retrieval (20%) in men who previously received exogenous androgens. They surmised that such treatment may have suppressed the hypothalamic-pituitary-testis axis, impairing FSH secretion and reducing intratesticular androgen levels, thereby impairing spermatogenesis. The authors concluded that the failure to find sperm in men who have undergone TRT and subsequent intratesticular suppression could suggest a permanent adverse effect of long-term TRT in men with Klinefelter syndrome.

In contrast, a recent report by Liu and colleagues suggested full recovery of spermatogenesis within a predictable period after treatment withdrawal (67% within six months, 90% within 12 months, 96% within 16 months, and 100% within 24 months). The report is based on an integrated analysis of about 90% of all published data on individuals using androgen-containing hormonal regimens for male contraception. It is thus premature to argue against the routine use of TRT to treat Klinefelter syndrome at the time of diagnosis. Nonetheless, clinicians should discuss fertility concerns when reviewing options for increasing serum testosterone levels in younger hypogonadal men.

Case 2: A 65-Year-Old Man With Secondary Hypogonadism

A 65-year-old Asian Indian man presented with symptoms of fatigue, decreased libido, and erectile dysfunction (ED). Seven years earlier, at the age of 58, he had presented to another physician, seeking treatment for these same symptoms, which had been gradual in onset over a six-month period. At that time, his testosterone level was low and his LH level was normal, which indicated that the low testosterone was the result of hypothalamic or pituitary dysfunction. The patient was diagnosed with secondary hypogonadism and treated with testosterone cypionate 200 mg IM every two weeks.

At the time of the present consultation, the patient reported no trouble sleeping, his wife said he does not snore or have episodes of apnea, and he had noted no change in his exercise tolerance. He drank two alcoholic beverages per week and had never smoked.

He worked as an electrical engineer. He lived in India until age 40. He was married and had one adopted child. His father died of a heart attack at age 70, and his mother was alive and well at age 88. He had one female sibling, who was healthy.

Physical Examination

- VS: T, 98.2°F; HR, 80 bpm, regular; RR, 18/min; BP, 125/80 • O₂ saturation: 97% • General appearance: well developed man; height, 68 in; weight, 163 lb; BMI, 25.1
- Chest: no gynecomastia • Skin and hair: body hair, light; skin is brown with no lesions • GU: testicular volume, 20 mL bilaterally; prostate, normal

Laboratory Findings

- Chemistry panel and CBC, normal with hemoglobin at 12.8 g/dL (reference range, 13 to 17 g/dL) and hematocrit at 38% (reference range, 37% to 49%)
- Serum hormones: total testosterone, 255 ng/dL (reference range, 270 to 1,070 ng/dL); LH, 4.3 mIU/mL (reference range, 2.1 to 12 mIU/mL); FSH, 5.1 mIU/mL (reference range, 1 to 12 mIU/mL)
- Cranial magnetic resonance imaging: no abnormalities of the pituitary or hypothalamus

Clinical Course

The patient was diagnosed with idiopathic acquired secondary hypogonadism. He was treated with a nonscrotal TRT patch for two weeks, after which treatment was discontinued because of skin irritation. He subsequently was treated with testosterone enanthate 200 mg IM every two weeks for the next five years, usually seeing his physician at one- to two-year intervals. Recently, he felt well, but he was found to have a hematocrit of 57%. He was instructed to stop testosterone injections.

The patient had no evidence of hypoxia and no symptoms suggestive of sleep apnea. His hematocrit level had dropped to 45% within six weeks of stopping testosterone injections. His TRT is now administered as a transdermal gel, which rarely causes skin irritation.
Discussion
Erythrocytosis is the most common adverse effect associated with TRT. In fact, a baseline hematocrit level above 48% is a relative contraindication to testosterone treatment. In most studies in which men with low testosterone levels are treated with TRT, the mean hematocrit rises 2.5% to 5% over baseline values. Hematocrit and hemoglobin levels outside the normal range are unusual in young men treated with TRT, but are relatively common in middle-aged and older men who receive this therapy. 

During puberty, the hemoglobin level in normal boys increases 3% to 4% in conjunction with serum testosterone. This is why normal hematocrit and hemoglobin levels are higher for men than for women. Testosterone can increase renal production of erythropoietin and can stimulate red blood cell precursors directly.

The magnitude of change in hemoglobin levels brought about by TRT seems to be related to the dose and route of administration. TRT delivery systems and dosing regimens that provide near physiologic serum testosterone levels are associated with a lower incidence of erythrocytosis. Parenteral injections of testosterone enanthate or cypionate, which transiently cause supraphysiologic levels of testosterone, produce higher hematocrit values compared with transdermal systems.

The Endocrine Society recommends that hypogonadal men not be treated with TRT if their initial hematocrit is greater than 48%. They advise clinicians to determine the patient’s hematocrit level at baseline, three months, 12 months, and then annually. If the hematocrit is greater than 54%, treatment should be stopped to allow the hematocrit to decrease into the acceptable range. The patient should be questioned and in some cases evaluated for hypoxia and sleep apnea before TRT is restarted at a lower dose or with a delivery system that is less likely to cause erythrocytosis. If no other cause of erythrocytosis is found, therapy can be resumed at a reduced dose.

Erythrocytosis is a concern because an elevated hematocrit level directly increases blood viscosity. Increased blood viscosity, in turn, reduces the rate of blood flow, which could be critical in men with cerebrovascular disease.

Case 3: A 63-Year-Old Man With ED
On September 12, 2006, a 63-year-old African American man presented to an endocrine clinic for treatment of ED that had progressed over the previous two years and had improved, partially, by sildenafil. (Laboratory values obtained during this earlier period of treatment are included below.) His libido was strong, but he reported a loss of morning erections. He was diagnosed with idiopathic acquired secondary hypogonadism in 2005, but it was not treated.

The patient had multiple medical problems, including obesity and type 2 diabetes mellitus, which are known causes of hypogonadism. He also had dyslipidemia, hypertension, and coronary artery disease. Eight years previously, a cerebrovascular accident precipitated legal blindness, depression, and degenerative arthritis.

Medications included: losartan, hydrochlorothiazide, metoprolol, metformin, glyburide, rosiglitazone, atorvastatin, aspirin, bupropion, fluoxetine, amitriptyline, and sildenafil.

Physical Examination
- VS: T, 98°F; HR, 80 bpm, regular; RR, 18/min; BP, 138/70
- General appearance: pleasant man with generalized obesity; height, 68 in; weight, 249 lb; BMI, 37.9
- Skin and hair: body hair, moderately heavy; skin unremarkable
- Eyes: some arteriolar narrowing, but no hemorrhages or exudates
- Chest: no gynecomastia
- GU: testes, 4.5 cm × 2.3 cm bilaterally with diminished consistency; prostate, moderately enlarged with no nodules or induration
- Cardiovascular system: regular sinus rhythm with S4 gallop and a grade 2/6 systolic ejection murmur heard at the apex; palpable pedal pulses; no carotid or femoral bruits detected on auscultation
- Lungs: clear to percussion and auscultation
- Abdomen: obese with no palpable organomegaly
- Back: normal curvature
- Extremities: obese with 1+ pretibial edema
- NS: sensation to vibration and to monofilament, intact in the extremities; biceps and patellar deep tendon reflexes, 1+; ankle reflexes, absent

Laboratory Findings
- February 8, 2005: Serum hormones: total testosterone, 131 ng/dL (reference range, 175 to 781 ng/dL); LH, 6 mIU/mL (reference range, 1.8 to 8.16 mIU/mL); FSH, 6.82 mIU/mL (reference range, 1.27 to 19.26 mIU/mL); prolactin, 7.62 ng/mL (reference range, 2.6 to 13.1 ng/mL)
- April 21, 2005: Serum hormones: total testosterone, 174 ng/dL (reference range, 241 to 827 ng/mL); bioavailable testosterone, 20 ng/dL (reference range, 40 to 250 ng/mL)
- July 10, 2006: CBC: hematocrit, 37.7% (reference range, 42% to 52%); hemoglobin, 12.9 g/dL (reference range, 14 to 18 g/dL); Glycosylated hemoglobin (HbA1): 7.6% (reference range, 4.2% to 5.8%)
- Prostate-specific antigen (PSA): 0.710 (reference range, less than 4 ng/mL)
- September 7, 2006: Total testosterone: 261 ng/dL (reference range, 175 to 781 ng/dL)
- October 12, 2006: Total testosterone: 240 ng/dL (reference range, 175 to 781 ng/dL)

Clinical Course
The patient was started on testosterone gel 7.5 g/day on November 7, 2006. By November 20, 2006, his serum testosterone had increased to 430 ng/dL, and he reported...
no adverse effects. His erectile function was minimally improved with TRT alone and significantly improved with TRT and adjunctive sildenafil. A digital rectal examination (DRE) on February 15, 2007 revealed the prostate to be moderately enlarged without nodules or induration.

On March 8, 2007, laboratory findings were as follows: hematocrit, 39.8% (reference range, 42% to 52%); hemoglobin, 13.4 g/dL (reference range, 14 to 18 g/dL); Hba1c, 8.5% (reference range, 4.2% to 5.8%); PSA, 0.92 ng/mL (reference range, less than 4 ng/mL).

Unbeknownst to the clinician who prescribed the testosterone gel, the patient had undergone previous prostatic biopsy. A sextant biopsy was performed in April 2006 because an area of the prostate had been indurated on DRE. One of 17 cores contained high-grade prostatic intraepithelial neoplasia (HGPIN). For this reason, the patient was scheduled for a repeat biopsy one year later. The patient’s PSA level at the time of the initial biopsy was 0.92 ng/mL.

On April 7, 2007, the patient was seen in urology for follow-up. Prostate volume by ultrasound was 30.2 mL. He had a sextant biopsy of the prostate with 12 cores, and 5% of one core contained adenocarcinoma, Gleason grade 3+3=6. On April 16, 2007, his PSA level was 0.87 ng/mL.

After the April 2007 biopsy revealed a low-grade prostate cancer in 5% of one core, the testosterone treatment was stopped and the patient received radiation therapy.

The patient had not volunteered that he had undergone previous prostatic biopsies, and apparently, he was not asked. His medical record was large, and this information was overlooked. The highest PSA in his medical record was 1.39 ng/mL in 2002.

Discussion
Middle-aged and older men who are treated with TRT must be monitored for symptoms of lower urinary tract obstruction. They should have a baseline DRE of the prostate and a PSA measurement, and these parameters should be rechecked at three months, 12 months, and then annually. Monitoring should begin at age 40 or 45 for African American men and men with a family history of prostate cancer.

ED is very common in men with type 2 diabetes. Usually, it is caused by vascular or neurologic disease that involves the penis. Testosterone deficiency contributes to the ED in some patients. This patient’s ED may have been improved by increasing the sildenafil dosage from 50 to 100 mg. Whether TRT improves erectile function in men who have an inadequate response to a phosphodiesterase type 5 (PDE5) inhibitor is unproven, though many clinicians believe that it does in some patients.

Testosterone deficiency is common in men with type 2 diabetes and in those with metabolic syndrome. Whether TRT can improve insulin sensitivity and reduce some effects of metabolic syndrome is also unclear at this time. When considering TRT therapy for middle-aged and older men, it is essential to assess the patient’s prostate history and lower urinary tract symptoms, perform DRE of the prostate, and measure PSA. Both benign prostatic hyperplasia and prostate cancer are very common in middle-aged and older men, and the prostate is an androgen responsive organ. Lower urinary tract symptoms of prostate problems include frequency of urination, nocturia, hesitancy, urgency, and weak urinary stream. Since TRT has been shown to increase prostate volume to that of eugonadal men of similar age it could increase lower urinary tract symptoms, though this has seldom been observed in clinical trials.

In the Prostate Cancer Prevention Trial, prostate biopsy detected cancer in 6.6% of subjects with PSA levels below 0.5 ng/mL, 10.1% of those with PSA levels from 0.6 to 1 ng/mL, 17% of those with PSA levels from 1.1 to 2 ng/mL, 23.9% of those with PSA levels from 2.1 to 3 ng/mL, and 26.9% of those with PSA levels from 3.1 to 4 ng/mL. Information from this group has been used to develop a prostate cancer risk calculator. According to the data available in July 2006, the patient in the previous case had an 11% risk of prostate cancer and a 2% risk of high-grade prostate cancer.

It is not known whether TRT increases the risk of an occult prostate cancer becoming a clinical cancer. There does not seem to be an increase in the incidence of clinical prostate cancer in the controlled trials of TRT in older men, but these trials have not been powered to address this question. Usually, TRT causes some increase in the mean PSA level, but it should not exceed acceptable limits. We have estimated that it would require a five-year study involving 6,000 men to detect a 30% increased risk of clinical prostate cancer in men treated with TRT compared with men given placebo.

No trial of this size is currently planned. Prospective population-based studies have not found that higher endogenous testosterone levels are associated with increased risk of prostate cancer.

It is thought that HGPIN lesions frequently are associated with prostate cancer. A recent study from the Johns Hopkins University School of Medicine reported on 791 patients who had HGPIN on initial biopsy and follow-up biopsy within one year. The investigators concluded that, for patients diagnosed with HGPIN on extended initial core sampling, repeat biopsy within the first year is unnecessary in the absence of other clinical indicators of cancer. Schlesinger and colleagues also concluded that prostate cancer detection rates have fallen for patients initially diagnosed with HGPIN. They attributed this
to extended biopsy techniques at initial biopsy, a lower detection rate for the remaining small cancers that may accompany HGPIN, and the fact that HGPIN cases may lack concomitant cancer.

Few investigators have reported on testosterone treatment of men with HGPIN. Although this lesion is viewed as preneoplastic, it is not treated by prostatectomy, radiation treatment, or androgen ablation. Most authorities think that making men eugonadal is unlikely to influence the development of prostate cancer. Rhoden and Morgentaler, who routinely perform prostate biopsy in hypogonadal men, found HGPIN on biopsy in 20 men prior to treatment with TRT. Repeat biopsy was performed when a change was noted on DRE or when PSA levels increased 1 ng/mL or more. The mean change in PSA in the 20 men with HGPIN was similar to that of the 55 men without HGPIN. A DRE abnormality was detected in one man, and he was found to have prostate cancer on repeat biopsy. Four additional men in the HGPIN-negative group and two in the HGPIN-positive group underwent repeat biopsy for elevated PSA levels and none had cancer. The patient in the previous case did not meet these criteria for repeat biopsy, though prostate cancer was detected on repeat biopsy.

The Endocrine Society recommends that men with hypogonadism who are middle-aged and older and are treated with TRT be evaluated with a DRE and PSA at baseline, three months, and then in accordance with evidence-based guidelines for prostate cancer screening, depending on the age and race of the patient. Urologic consultation is recommended if there is: (1) a verified serum or plasma PSA concentration greater than 4 ng/mL; (2) an increase in serum or plasma PSA concentration greater than 1.4 ng/mL within any 12-month period of testosterone treatment; (3) a PSA velocity of more than 0.4 ng/mL per year using the PSA level after six months of testosterone administration as the reference (PSA velocity should be used only if there are longitudinal PSA data for more than two years); or (4) detection of a prostatic abnormality on DRE.

References


1. Which of the following statements is/are true?
   a. Normal ranges for total testosterone (T) vary considerably as a result of disparities among the populations that are used to establish them and assay differences.
   b. Within individual men, there is considerable day-to-day variability in T levels, such that a single total T measurement does not adequately reflect the average T level in a man.
   c. Serum total T levels are affected by changes in SHBG concentrations, illness, medications, and nutritional deficiency.
   d. All of the above

2. The diagnosis of male hypogonadism should be based on unequivocally low serum T levels and clinical manifestations of androgen deficiency.
   a. True
   b. False

3. Administration of ___ causes T levels to peak within two to three days of administration and to decline slowly, often to subnormal levels, in one to two weeks, causing swings in mood, energy level, sexual function, and libido.
   a. Testosterone esters (TE)
   b. Testosterone pellets
   c. Buccal testosterone
d. Testosterone gel

4. T’s normal circadian rhythm is mimicked by ___; it also does not disturb serum lipids.
   a. Transbuccal testosterone
   b. Testosterone esters
   c. Transdermal testosterone
d. Testosterone pellets

5. Currently, the most commonly used form of testosterone replacement therapies (TRT) is ___, even though it is the most expensive option.
   a. T patch
c. T gel
   b. T pellet
d. TE (IM injection)

6. Before initiation of treatment, which of the following should be ordered?
   a. Levels of prostate-specific antigen (PSA), hemoglobin, hematocrit, and T
   b. Digital rectal exam (DRE) and PSA level
   c. Dual energy x-ray absorptiometry scan
d. All of the above

7. Erythrocytosis is the most common adverse effect associated with TRT.
   a. True
   b. False

8. Middle-aged and older men who are treated with TRT should have DRE and PSA levels checked at ___.
   a. 3 months
c. Annually
   b. 12 months
d. All of the above

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Select the single best answer for each of the following questions and mark your answer on the answer form.
To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

To what extent do you agree with the following statements? (Please circle the appropriate number on the scale.)

1 = Strongly Disagree 2 = Disagree 3 = Somewhat Disagree 4 = Somewhat Agree 5 = Agree 6 = Strongly Agree

Because of normal variability in an individual's serum testosterone (T) levels, low T levels should be confirmed on at least two occasions, using specimens drawn in the morning before diagnosing biochemical androgen deficiency.

Strongly Disagree 1 2 3 4 5 6 Strongly Agree

It is important to determine whether male hypogonadism is primary or secondary.

Strongly Disagree 1 2 3 4 5 6 Strongly Agree

Having a pre-treatment baseline hematocrit level above 48% is a relative contraindication to testosterone replacement therapy (TRT).

Strongly Disagree 1 2 3 4 5 6 Strongly Agree

If a patient's hematocrit level rises above 54%, TRT should be suspended until the hematocrit decreases to the acceptable range.

Strongly Disagree 1 2 3 4 5 6 Strongly Agree

In geriatric patients, TRT modalities with shorter durations of action should generally be chosen because these patients experience more adverse events than do younger patients.

Strongly Disagree 1 2 3 4 5 6 Strongly Agree

Please answer the following questions by circling the appropriate rating:

1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

**Extent to Which Program Activities Met the Identified Objectives**

After completing this activity, I am now better able to:

Recall at least three conditions common among VA patients that are closely associated with adult-onset hypogonadism

1 2 3 4 5

Identify five adverse symptoms associated with adult-onset hypogonadism that testosterone replacement therapy (TRT) has been shown to ameliorate

1 2 3 4 5

Describe four clear indications for TRT in adult males

1 2 3 4 5

Review current recommendations regarding pretreatment screening and post-treatment monitoring of TRT

1 2 3 4 5

**Overall Effectiveness of the Activity**

The content presented:

Was timely and will influence how I practice

1 2 3 4 5

Enhanced my current knowledge base

1 2 3 4 5

Addressed my most pressing questions

1 2 3 4 5

Provided new ideas or information I expect to use

1 2 3 4 5

Addressed competencies identified by my specialty

1 2 3 4 5

Avoided commercial bias or influence

1 2 3 4 5

**Impact of the Activity**

Name one thing you intend to change in your practice as a result of completing this activity:

__________________________

Please list any topics you would like to see addressed in future educational activities:

__________________________

Additional comments about this activity:

__________________________

**Follow-up**

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

☐ Yes, I would be interested in participating in a follow-up survey.

☐ No, I’m not interested in participating in a follow-up survey.

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**Posttest Answer Key**

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