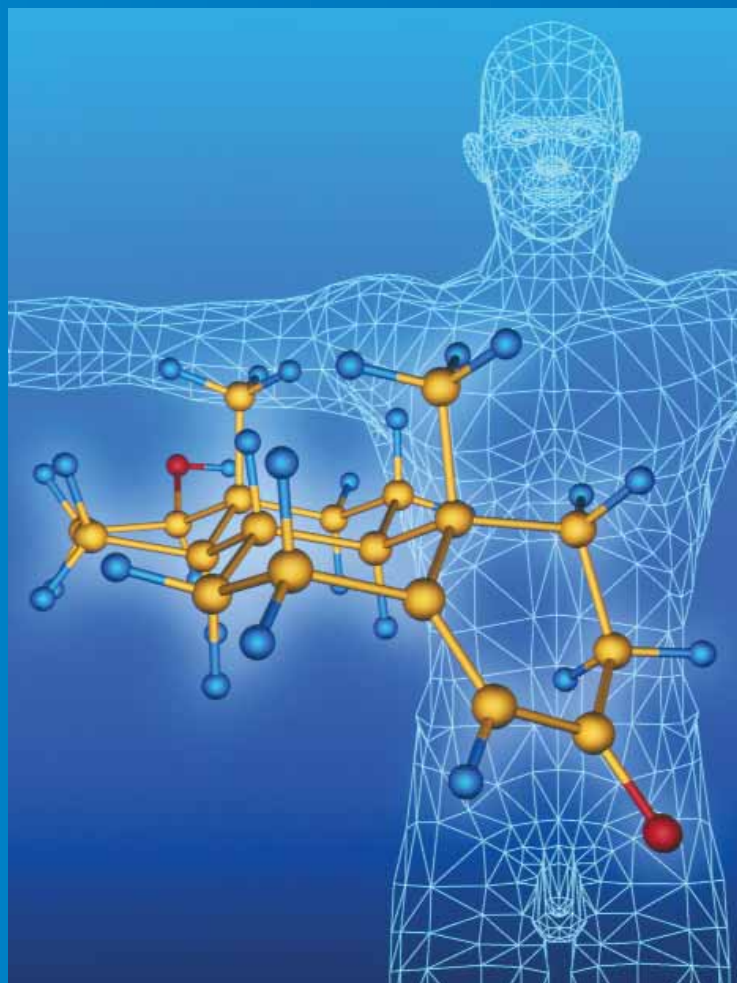


TESTOSTERONE DEFICIENCY IN MEN



Best practices
for diagnosis
and treatment

**P3. Identifying testosterone
deficiency in aging men**

RONALD S. SWERDLOFF, MD

**P6. The problem with
Henry: Diabetes and
hypogonadism**

RICHARD F. SPARK, MD

**P8. Hypogonadism in aging
men: Considerations
for treatment**

CHRISTINA WANG, MD

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TESTOSTERONE DEFICIENCY IN MEN: Best practices for diagnosis and treatment

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Learning objectives: After completing these articles, the reader should be able to:

- Identify adult male patients for whom testosterone replacement is appropriate.
- Select the most appropriate treatment options for individual patients and understand the parameters for monitoring therapy.
- Recognize the existence and implications of testosterone deficiency in patients with type 2 diabetes.

Intended audience: This educational activity has been developed for endocrinologists.

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INTRODUCTION

This is an exciting time to be in a clinical practice that deals with hormonal therapies. The body of established facts is being fed by new research into the kinds of treatment options we can offer. In the field of men's health, we know that testosterone deficiency causes decreased libido and depressed mood, and that it can contribute to fatigue, decreased bone mineral density, and decreased muscle mass. With testosterone replacement therapy (TRT) we have been able to counter the negative effects of hypogonadism for countless men with clinically deficient levels of testosterone.

Beyond the use of TRT for men who have low levels of this crucial hormone, however, there is a steady and growing consumer and clinical interest in the ability of testosterone to delay, avert, or restore the vitality and youthfulness that is associated with its role in the male metabolism.

The desire for hormonal therapies for aging men is complicated by concerns over the adverse effects that arose following the use of hormone therapies for postmenopausal women. In a report issued by the National Institute of Medicine in 2004, the need for more randomized, controlled clinical trials to further evaluate the safety and efficacy of testosterone therapy, particularly in older men (over 65) and those who do not have hypogonadism, was made evident.

Of course, when treating an aging population, one inevitably enters an arena of increased complexities and risks. This complexity applies when discussing testosterone therapy, with its potential to have positive effects as well as negative ones, especially its as yet unproven effects on the prostate and influence on long-term health outcomes.

Therefore, it is my hope that this review of TRT, which includes an overview of diagnostic procedures, a case study that explores diabetes as a comorbidity, and a review of treatment options, will provide insight and data enough to allow informed and confident clinical decisions. ■

Ronald S. Swerdloff, MD

Identifying testosterone deficiency in aging men

RONALD S. SWERDLOFF, MD

The treatment of hormonal deficiencies for female patients, particularly during the transition through menopause, has become common practice. Consequently, there is an increasing recognition by clinicians that hormonal deficiency also affects older male patients, producing a host of symptoms that may require evaluation and treatment and may render symptomatic patients potential candidates for hormone replacement therapy.

This deficiency of androgen secretion, termed hypogonadism, affects an estimated 2 million to 4 million men in the United States.^{1,2} Based on data from the Massachusetts Male Aging Study, the incidence of androgen deficiency was 12.3 per 1000 person years, a rate that increases significantly with age and can be extrapolated to an estimated 481,000 new cases per year in men aged 40 to 69.³

What are the contributing factors?

When hypogonadism occurs in newborns or young males, a genetic syndrome (such as Klinefelter's or Kallmann's) or developmental irregularity may be the cause. The condition may also be acquired through a predisposing condition such as testicular injury, mumps, orchiectomy, pituitary tumors, or irradiation to the pelvis or head.⁴ However, in adult men, the condition may increase during what appears to be the normal course of aging. Men experience a gradual decline in testosterone (T) levels, beginning as early as age 30 years, continuing through adulthood, and reaching a concentration during the seventh or eighth decade of life that is often below the normal range for a young adult man (FIGURE). The extent of this decrease, and whether it results in reduced physiologic function, is believed to vary among men. The prevalence of clinically significant hypogonadism linked with increasing age may be associated with complicating factors such as chronic illness, obesity, and medication use.²

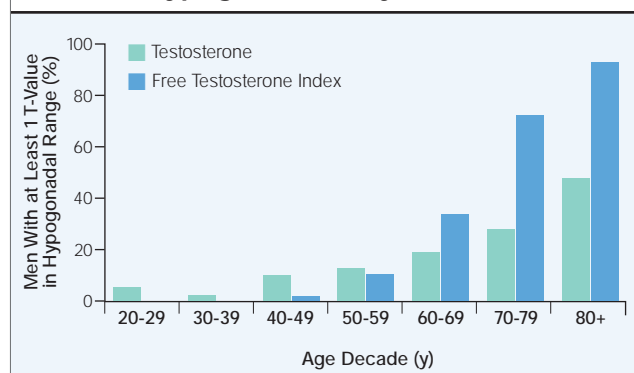
Arriving at the diagnosis

The clinical manifestations of hypogonadism in aging men differ significantly from the condition that occurs in a neonate or that which becomes evident during puberty. In younger men, the deficiency may be more severe and the clinical manifestations more striking. Older men (those over the age of 60) may experience a progressive but less apparent decline of T levels over a period of time.

In this older age-group, the condition is more difficult to recognize and may be masked by comorbid illness or overlapping illnesses. Older men with T deficiency may complain of decreased libido, sexual dysfunction, fatigue, decreased muscle strength, increased adiposity, depressed mood, and a diminished sense of well-being (TABLE). Typically, patients will complain of those symptoms that are of most importance to them. In this age-group, the most frequent concerns may be decreased libido, sometimes combined with erectile dysfunction. While decreased libido is a common manifestation of low T levels, impaired erectile function may be the result of multiple causes and is

FIGURE

Hypogonadism by decade



Adapted with permission from Harman SM, Metter EJ, Tobin JD, et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. *J Clin Endocrinol Metab.* 2001;86:724-731.

TABLE

Clinical signs and symptoms of hypogonadism in adult men

Decreased hematocrit	Loss of motivation
Decreased libido	Osteoporosis
Depression	Reduced axillary and pubic hair
Erectile dysfunction	
Fatigue	Reduced beard growth and diminished need for shaving
Gynecomastia	
Infertility	Reduced muscle mass
Irritability	Small testes and prostate

Adapted with permission from Winters S. Current status of testosterone replacement therapy in men. *Arch Fam Med.* 1999;3:257-263.

often due to a vascular abnormality at the penile level. Fatigue, decreased muscle strength, increased body fat, and depressed mood are also often reported. Clinical findings in addition to these complaints would include a decrease in testicular size or a loss of secondary sexual characteristics, such as a lessened shaving pattern. These symptoms indicate the need for a careful evaluation with the support of laboratory confirmation.

Evaluating total testosterone levels

Establishing a diagnosis of hypogonadism requires laboratory confirmation of subnormal levels of circulating T. The clinician should begin with an assay measuring serum total testosterone (TT), a test that is widely available. However, assays to measure T employ a number of methods that use a wide range of reagents. Investigators have shown that there are considerable differences among assay systems, and, therefore, variations in the test results.^{5,6}

The generally accepted reference range for TT in adult men is wide, from 260 to 1000 ng/dL (9 to 34.7 nmol/L). Additionally, T levels have circadian fluctuations. In younger men, there is a striking difference in T levels measured in the early morning versus those taken later in the day; a mean maximum level of 720 ng/dL (25 nmol/L) is reached at approximately 8 AM, and declines to a mean minimum of 432 ng/dL (15 nmol/L) at approximately 10 PM.⁷ The degree of change between morning and evening testosterone levels is less striking in older men. Nevertheless, it is best in all cases to measure the concentration in the morning so that peak results can be compared with the usual standards.

A large proportion of the T that circulates in the blood is tightly bound to sex hormone-binding globulin (SHBG), rendering it not readily available to the tissues. Other components of circulating T, which are loosely bound to albumin, can be extracted and are bioavailable to the tissues (approximately 20% to 30%). A third component, free T, makes up approximately 2% of TT.

Because the SHBG is fairly constant in younger men, the interpretation of the assay is fairly easy. Under certain circumstances, however, knowing how much testosterone is tightly bound and how much is free becomes of great importance.

Evaluating free testosterone levels

The majority of older men have TT levels that are in the low-normal range for younger men. As men age, the SHBG concentration increases; therefore, the TT concentration is relatively higher than the free T concentration. As a result, in an older patient there may be a false sense of normalcy because of the high SHBG, when the tissues actually are seeing less bioavailable or free T. For older patients, when clinical symptoms are present and the TT level is in the low-normal or abnormal range, a test of free T may give a better assessment and indicate whether the tissues might benefit by treatment with TRT.

In older men, if the blood concentration of TT is greater than 350 ng/dL, it is likely that the free T level will be normal and that other causes must be explored. If the blood concentration of TT is less than 250 ng/dL in an older man on 2 consecutive tests, it is likely that the patient has T deficiency that may require substantiation by testing the free T level. If the values fall between 250 ng/dL and 350 ng/dL, a test of TT should be repeated along with a test of free T.

This testing algorithm allows clinicians to exclude those patients whose levels are normal, to avoid excessive testing in those men whose levels are clearly abnormally low, and to focus testing primarily on the group whose situation is most unclear.

Currently, the most reliable tests for free T measurements are those performed by the method of equilibrium dialysis. Because these are difficult and costly to do, some laboratories provide free T tests by the less reliable analog method. It is best to obtain free T testing at a reference laboratory that does careful testing of free T levels by the dialysis method. The cost of such testing should come down as the use and need in the marketplace increases.

Alternatively, free or bioavailable T can be calculated using TT concentrations and SHBG levels.

Because SHBG concentrations increase with age in men, the total T concentration may be high, giving a false sense of normalcy. In such cases, calculating the free or bioavailable T becomes even more important to a correct diagnosis. The formula for making this calculation can be found on the Web site of the International Society for the Study of the Aging Male at www.issam.ch.

In the near future, most assays for T will be done by liquid chromatography-tandem mass spectroscopy, which will afford significantly greater accuracy and precision than tests available today.⁵

■ Testing for multiple levels of defects

After determining that the T level is low and free or bioavailable T levels have been confirmed, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) should be evaluated. Elevated levels indicate that the primary defect is in the testes. However, low levels signal a defect either at the pituitary or at the hypothalamic level, and further studies would be necessary to determine the cause. Additionally, prolactin should be measured whenever T, LH, and FSH levels are low. Elevated prolactin levels may indicate a pituitary tumor.

Since low T can be an important causal factor in osteoporosis, any man found to be T deficient should have a bone mineral density (BMD) test performed.⁸

■ The controversy over prostate cancer

Controversy exists as to whether older men are at increased risk for the induction of prostate cancer with testosterone replacement therapy (TRT). There is no evidence at present that TRT will produce prostate cancer or aggravate subclinical prostate cancers, but it is known that T will cause existing prostate cancer to grow.^{9,10} Therefore, before initiating TRT in T-deficient men over age 50 years, most experts urge clinicians to order a prostate-specific antigen (PSA) test and perform digital rectal examination to detect prostate abnormalities. If the PSA level is elevated, then treatment with T should be deferred until the patient is carefully evaluated for the possibility of prostate cancer.

■ Initiating testosterone therapy

In the absence of an underlying illness that would serve as a contraindication, T deficiency can be effectively treated with TRT. Such therapy should be reserved only for those patients who have identifiable symptoms that are consistent with this diagnosis and whose laboratory tests validate the chemical aspect of the disorder.

Although some physicians are treating individuals in the older age-group with a cocktail of antiaging medications that includes TRT, any benefits of this practice are as yet unconfirmed.

■ Large-scale studies are underway

Aging patients fear becoming debilitated, frail, and unable to undertake the same activities that they could when they were younger. Although TRT has been shown to benefit libido, mood, muscle mass and strength, BMD, and hematocrit in younger hypogonadal men, such benefits in older men have not yet been thoroughly assessed.¹¹

Large-scale, well-designed clinical trials are in the planning phases at the National Institutes of Health and are anticipated to reach completion within 6 years. Results should be more definitive than those of the small studies that have been done to date. Until then, it appears reasonable to treat hypogonadism (low serum T level *and* clinical symptoms) in older men with TRT, in the absence of underlying or comorbid conditions. ■

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The problem with Henry: Diabetes and hypogonadism

RICHARD F. SPARK, MD

Henry, a 48-year-old diabetic patient, came to the office for a second visit to review his status. Other than diabetes, he has no current medical problems. No microalbumin is present in the urine, the hemoglobin A1c level is improved although not ideal, and the ophthalmologist's report indicates no diabetic retinopathy. Although there was no mention of sexual problems at his initial visit, Henry now complains of a lack of libido and an inability to obtain a firm erection. He admits to having had difficulty for the past 18 months, even after trying "one of those pills my neighbor said always worked for him." When asked why he didn't bring up the problem sooner, he said he was too embarrassed to mention it.

For years the sexual dysfunction of diabetic men was considered an inevitable, irreversible complication of diabetes. Like Henry, many diabetic men are not comfortable discussing their sexual function—or lack thereof—even with a physician they have known for many years. But once the subject of sexual difficulties surfaces, the treating physician is obligated to find the cause, and, if possible, offer a treatment.

Testosterone (T) deficiency, or hypogonadism, is now recognized as a common occurrence in diabetic men, increasing in occurrence with age, but it is often overlooked in deference to more immediate concerns (FIGURE 1). The initial care of a diabetic man is properly focused on patient education to stabilize glycemic control with diet, exercise, and oral agents or insulin, if necessary. A preoccupation with early estimates of the integrity of systems that are at risk, such as the kidney, retina, and vascular tree, often dominates the early stages of doctor-patient interaction. In addition, the recognition of T deficiency in a diabetic man often requires the physician to look beyond standard tests used to diagnose the disorder. Add to this the fact that patients are often reticent to discuss sensitive issues that may provide a clue to the presence of T deficiency, and it is easy to see why the problem is not readily addressed.

Impotence, or erectile dysfunction (ED), is common in diabetic men, occurring 3 times more often than in non-

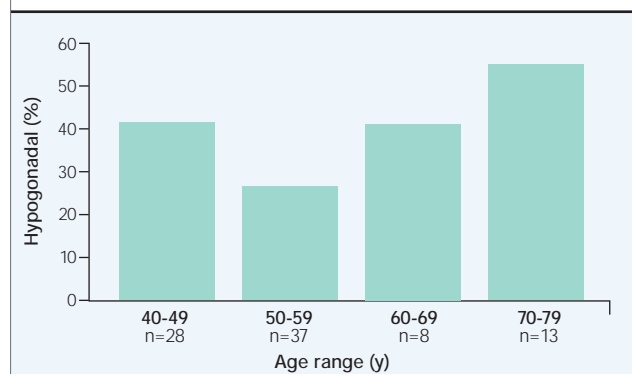
diabetic men. Approximately 20 million diabetic men, or between 25% and 50% of those with diabetes, are affected, in numbers that increase with age.¹ Diabetic complications including irreversible diabetic neuropathy and diabetic vascular disease have routinely been implicated as the major causes of ED in these patients. Only recently has T deficiency been recognized as another more therapeutically malleable cause of ED in diabetic men.

■ Making the diagnosis in a patient with diabetes

The diagnosis of T deficiency in diabetic men is more difficult than in nondiabetic men because serum T levels alone do not always suffice to distinguish eugonadal from hypogonadal diabetic men. Serum T measurements reflect not the biologically active *free T* fraction but rather the T bound to sex hormone binding globulin (T + SHBG) (FIGURE 2). Since SHBG levels increase with age and decrease with adiposity, total testosterone (TT) may appear normal even when T secretion is diminished, as in SHBG + T, or artificially low when T secretion is normal but SHBG is low, as in obesity SHBG + T. A more

FIGURE 1

Percentage of patients with type 2 diabetes and hypogonadism



Adapted with permission from Dhindsa S, Prabhakar S, Sethi M, et al. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metab.* 2004;89:5462-5468.

precise estimate of the active free T can be acquired by measuring free T by dialysis, or by circumventing perturbations in SHBG levels by direct measurement of both SHBG and T levels and calculating the free T index (FTI).

In Henry's case, serum T was low-normal at 306 ng/dL (10.625 nmol/L), but the SHBG level was elevated at 64 nmol/L, so that the FTI (T nmol/dL/SHBG nmol/dL) of 0.166 nmol/L (expected normal >0.30 nmol/L) was compatible with the diagnosis of T deficiency. When levels of Henry's pituitary hormones were tested, luteinizing hormone (LH) was elevated at 25 mIU/mL (normal, 2-10 mIU/mL), and follicle-stimulating hormone (FSH) was also high at 17 mIU/mL (normal, 2-12 mIU/mL). These findings confirmed that Henry had primary hypogonadism.

Although primary hypogonadism has been reported to occur in diabetic men, secondary hypogonadism is more common.² In one recent study of 103 consecutive men referred for management of their diabetes, 34 (33%) had low serum free T by equilibrium dialysis or FTi, as well as lower LH and FSH levels than 69 age-matched eugonadal diabetic counterparts.³ Thus, when the proper assays are performed, as many as one-third of diabetic men will be discovered to have T deficiency, most often manifesting as secondary hypogonadism.

Selecting the best measure

The key to discovering T deficiency in diabetic men is to perform the proper assay. Some assays are more reliable than others, particularly in regard to estimating the biologically active free T level. The free T level established by equilibrium dialysis, though tedious and time-consuming, is considered the gold standard, while the accuracy of the analog free T assay has frequently been called into question.⁴⁻⁶

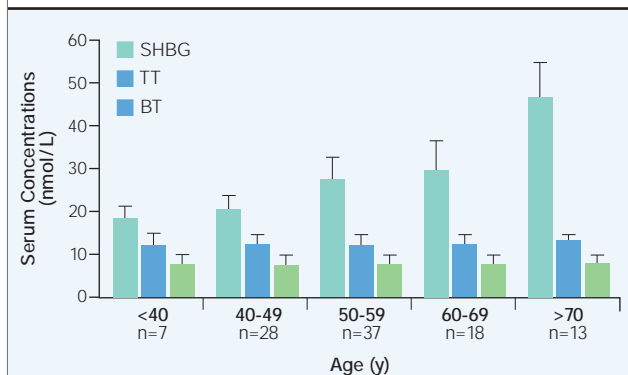
Increasing testosterone levels

In poorly controlled, insulin-dependent diabetic men, subnormal serum T values may increase spontaneously and promptly with proper treatment of the diabetes.⁷ But for the majority of men with hypogonadism and diabetes, T levels remain low and diminished sexual function persists even with intensive glycemic control. Only when T levels are normalized with T supplements are nighttime erections, measured by nocturnal penile tumescence, as well as the capacity to engage in sexual intercourse, fully restored.⁸

Like any other hormone-deficient state, T deficiency responds well to hormone replacement therapy that is targeted to restore serum T levels to the normal adult

FIGURE 2

Serum concentrations of TT, SHBG, and BT according to age



Key: BT, bioavailable testosterone; SHBG, sex hormone-binding globulin; TT, total testosterone
Adapted with permission from Dhindsa S, Prabhakar S, Sethi M, et al. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metab.* 2004;89:5462-5468.

male range (260-1000 ng/dL). In Henry's case, T gel therapy was initiated. Serum T levels increased, LH levels declined, and Henry gradually started to improve in a predictable pattern. He reported a gradual restoration of his interest in sex, and confidence in his ability to function sexually, with each successive month of therapy.

Recent data suggest that T deficiency (hypogonadism) is not only common in diabetes mellitus but is also an integral component of the even more prevalent metabolic syndrome (ie, obesity, insulin resistance, lipid abnormalities, and high blood pressure). Further, it has been suggested that timely institution of T therapy may not only alleviate sexual and other symptoms of T deficiency but also have a salutary effect on insulin resistance, lipid profile, and hypertension. These observations, culled from a MEDLINE review, are sufficiently provocative and intriguing to warrant additional prospective studies.⁹ ■

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Hypogonadism in aging men: Considerations for treatment

CHRISTINA WANG, MD

A deficiency of testosterone (T) can rob a man of vitality and libido, impair muscle and bone strength, diminish his sense of well-being, and negatively affect his quality of life. A progressive and individually variable decline in T, beginning about age 40, normally accompanies aging. Although studies are underway, at present there are insufficient evidence-based data to assure the clinician that testosterone replacement therapy (TRT) will benefit some or all of the symptoms of T deficiency in older men.¹ In the interim, many experts in the field recommend that older men who are symptomatic, have been properly diagnosed with hypogonadism and have no contraindications to treatment, are reasonable candidates for TRT.^{2,3}

Before initiating treatment, clinicians should obtain baseline tests beginning with a serum T level, taken in the morning, to establish that it is below the normal range for an adult man; test the prostate-specific antigen (PSA) level, which should be lower than the normal range adjusted for age; and perform a digital rectal examination to make certain there are no irregularities suggestive of prostate cancer. They should ask whether a patient has any symptoms of lower urinary tract obstruction since increased prostate size is a possible consequence of TRT. Also, they should test hemoglobin (Hb), and hematocrit (Hct) levels to make sure they are within the normal range, which differs with the sexes (for men, the normal ranges are: Hb, 13-17 g/dL; Hct, 40%-52%). Testosterone increases Hb and Hct; therefore, patients whose levels are outside the normal ranges should not undergo TRT.

Because TRT can be associated with changes in cholesterol, elevations in liver function, and abnormalities on liver scan and biopsy, a baseline serum lipid panel and liver function tests should be obtained prior to treatment. If the patient has symptoms of a sleep-related breathing disorder (sleep apnea), the condition must be treated with mechanical means before beginning T therapy, since sleep apnea can be aggravated by T treatment, especially in older men.^{2,3}

■ When testosterone replacement therapy is contraindicated

There are several absolute contraindications to TRT (TABLE 1). Men with prostate cancer or male breast cancer should not be placed on TRT due to its potential to stimulate tumor growth in neoplasms that are androgen-dependent. Men with lower urinary tract symptoms due to prostate disease should be evaluated and treated before TRT is considered. Sensitivity to ingredients in T formulations is also a contraindication.

Sleep apnea and polycythemia are relative contraindications to TRT.⁴ Although still controversial, it may be prudent to use TRT with caution in patients with severe congestive heart failure or untreated heart failure, since early in the replacement phase T may cause an accumulation of fluid that could become an aggravating factor.^{2,3}

Clinicians should consider that the action of T may be impaired or altered by the use of other drugs, including progestins, estrogens, antiandrogens (flutamide, cyproterone acetate) and others such as cimetidine, 5-alpha reductase inhibitors, aromatase inhibitors, and spironolactone.

TABLE 1

Contraindications for testosterone replacement therapy

Carcinoma of the prostate (history or current)
Carcinoma of the breast (history or current)
Symptoms of lower urinary tract obstruction
Abnormal results on digital rectal examination
Elevated prostate-specific antigen level
Polycythemia (hematocrit >52%)
Sleep apnea
Sensitivity to ingredients in testosterone formulations

TABLE 2

Testosterone preparations currently available in the United States

Formulation	Brand Name	Dosage	Advantages	Disadvantages
Buccal tablet	Striant®	30 mg every 12 hours	Provides sustained release of T; through the buccal mucosa	In rare cases, may result in gum or mouth irritation, bitter taste, gum pain or tenderness, headache
Gel (1%)	AndroGel®	5 g (50 mg T)* 7.5 g (75 mg T)* or 10 g (100 mg T)* applied daily	Readily absorbed into skin; provides steady level of testosterone; easy to apply	Site of application should be covered; direct contact with women and children should be avoided; may cause itching or irritation at site of application
	Testim®	1 or 2 tubes, 5 g (50 mg or 100 mg T) applied daily		
IM injection	Depo testosterone® Delatestryl®	50-400 mg every 1-4 weeks	Dosing interval of several weeks; relatively low cost	Fluctuation in levels of T from supraphysiologic right after injection to subnormal at end of dosing interval; pain and redness at injection site; requires office visit for administration
Oral	Android® Testred® Virilon®	10-50 mg/day in divided doses	Easy to administer; relatively low cost	Potentially toxic to liver and may adversely affect lipid profile, decreasing HDL and increasing LDL
Patch	Androderm®	2.5 mg, 2x/day; 5 mg, 1x/day	Achieves normal T levels; mimics circadian T levels; easy to administer; does not interfere with normal activity	Local skin irritation in many patients, affecting patient adherence to treatment; occasional allergic contact dermatitis
Scrotal patch	Testoderm®	4-6 mg applied daily	Achieves normal T levels; mimics circadian T levels; easy to administer	Scrotal itching, discomfort, or irritation

Key: HDL, high-density lipoprotein; LDL, low-density lipoprotein; IM, intramuscular; T, testosterone

* Unit dose packets and metered dose pump

Options for TRT

A range of options is available in the United States for treating hypogonadism in older men (TABLE 2). The variety of formulations includes injectable T esters, transdermal patches, transdermal gel, and mucoadhesive buccal tablets. Oral 17-alkylated androgen T tablets should not be used in older men as they may cause liver toxicity or unfavorable changes in cholesterol levels.⁵

Factors that influence the selection include pharmacokinetics, adverse effects caused by specific preparations, frequency of administration, flexibility of dosing, adherence, and cost.^{5,6} Most often, the decision is based on patient preference and medical history. Dosages depend on the formulation and pharmacokinetics of the preparation selected. Whatever the choice, the goal is to achieve and maintain a serum T level as close to the

midnormal range as possible (adult male reference range, 260-1000 ng/dL) to restore virilization, allow optimal sexual function, and maintain testosterone actions on metabolic functions (fat, muscle, and bone).

Intramuscular injectables

Before the advent of newer formulations, intramuscular (IM) injections of T esters in oil suspension were the gold standard for the treatment of hypogonadism. The 2 preparations currently available in the United States, testosterone enanthate and testosterone cypionate, have similar pharmacokinetics.⁷ Large fluctuations of serum T levels between injections can occur, sometimes causing undesirable changes in sexual function and mood.⁸

Injections are most effective when given every 2 weeks, with a dosage per injection of 150-200 mg for an

older man. Peak levels occur at approximately 72 hours after the injection, declining over the next 1 to 2 weeks.⁹ Shorter time intervals at lower dosages (ie, 75-100 mg) will maintain relatively more normal levels, but such a regimen is less convenient.¹⁰ Longer than 2-week intervals and higher dosages are possible, but are associated with greater fluctuations in T levels.¹¹

The cost of IM injectables is relatively inexpensive compared with other options, at about \$30 to \$50 per month. Their administration may necessitate office visits, which may be inconvenient for patients; however, many patients are able to learn to administer the injections themselves. Some patients experience local pain, bleeding, or bruising at the injection site, and some have allergic reactions to sesame oil, the injection vehicle for T enanthate, or cottonseed oil, the vehicle for T cypionate.⁵

Recently, longer-acting IM injectables, already approved for use in Europe, have been developed and are being tested in phase 3 clinical trials in the United States.¹² These longer-acting injections, which contain 1000 mg of testosterone undecanoate, require administration only once every 12 weeks, a convenience that may provide a distinct advantage for younger patients. However, for older patients such long-acting therapy may pose a greater risk; once T has been injected, it cannot be retracted if, for example, PSA levels start to rise.³

Transdermal patches

Transdermal T patches offer a more convenient means of T replacement than injectables, but, at about \$100 per month, are a more costly alternative. The patch delivers doses of 2.5 mg or 5 mg of synthetic T. There are 2 varieties; 1 is applied to the scrotum, and the other may be applied to the upper arms, back, or abdomen. Several studies have shown that this system of TRT is effective.^{8,13,14} However, about 30% of patients will develop a mild-to-moderate rash in the area where the nonscrotal patch was applied. In clinical trials, about 12% of men experienced blister formation.¹⁵ Between 5% and 15% of patients discontinue use of the patch because of skin irritation.

Transdermal gel

Another method of application for TRT is a transdermal hydroalcoholic gel containing 1% testosterone. The gel, in dosages of 5 g, 7.5 g, or 10 g (containing 50 mg, 75 mg, or 100 mg of T, respectively), is applied once daily over large areas of the body, usually to the upper arms or shoulders, and, depending on the product, to the abdomen. As the gel dries, T is absorbed into the skin where it is slowly released, providing a fairly steady T level in the blood. Long-term use of T gel has been

shown to be safe and effective in men with low T levels.¹⁶

Testosterone gel affords a greater degree of convenience than either the transdermal patch or IM injections. It is equally as effective as the patch, with fewer side effects.^{16,17} However, it is more costly, at around \$140 to \$150 per month. Following application, patients must wash their hands to remove any residue. Patients who expect to come into close touch with women or children must be careful to either wear protective clothing over the area where the gel was applied or shower before skin contact, so that T is not transferred to others.

Buccal tablets

A mucoadhesive sustained-release T buccal tablet received FDA approval in June 2003. The tablet is placed on the upper gums, where it gradually softens and conforms to the shape of the gum. Applied twice daily every 12 hours, it supplies 30 mg of synthetic T at a steady rate throughout the day.¹⁸

A randomized study compared the buccal tablet to the transdermal patch in 67 patients (33, buccal tablet; 34, patch) for 7 days.¹⁹ Of the patients treated with the buccal system, 97% had average steady-state T concentrations within the physiologic range.

Patients using the buccal tablet can eat, drink, brush their teeth, chew gum, and perform all other normal functions with the mouth. Common side effects include irritation, redness, pain, tenderness, swelling, toughening, or blistering of gums. Some patients experience stinging of the lips, toothache, and/or an unpleasant or bitter taste in the mouth. The average cost of this system is about \$150 per month, similar to the transdermal preparations.

Monitoring and duration of therapy

Older men undergoing TRT should be screened carefully and followed periodically through the course of therapy.^{2,3} The first visit after initiating TRT should allow for dosage and formulation adjustments as needed. During TRT, it is essential to monitor patients for the appearance of prostate disease, erythrocytosis, and other adverse events of androgen treatment.^{2,3} Although there is no evidence that TRT produces prostate cancer, case studies have shown that T causes existing occult prostate cancer to grow.^{20,21} Therefore, the patient's PSA level should be measured after 1 month of therapy, since a rise from baseline would indicate the growth of preexisting occult prostate cancer.

If the patient's PSA level is within normal range, it should be rechecked at 3 months, the end of the first year, and every 6 or 12 months afterward depending on the level.^{2,3,22} If the PSA reaches an age-appropriate cutoff

(usually a value of >4 ng/mL will raise concern for the physician), the patient should stop treatment and have his PSA repeated. If the PSA level is still high, he should be referred to a urologist to determine the reason for the increase.^{2,3,22} The PSA velocity should also be closely watched. There is currently no nationally recommended guideline, but 1 recommendation suggested the velocity should be less than 0.45 ng/mL per year after it stabilizes within 6 months of the start of TRT.²² If the PSA level rises quickly, for example by more than 1 ng/mL in any 12 months, the patient should be carefully watched and referred to a urologist for biopsy and follow-up if the clinician suspects prostate cancer. However, a sudden rise of PSA to a very high level may not indicate prostate cancer but may be evidence of chronic prostatitis. Should this be the case, TRT should be discontinued, the patient should be put on a course of antibiotics, and careful follow-up testing of PSA levels should be performed.

Routine monitoring during TRT should be done at 3 months, 6 months, and then annually. Physical examination should include an assessment for symptom improvement and questions to determine if the patient is having difficulties with sleep apnea or voiding. Because an increase in the size of the prostate can push on the bladder, urinary frequency can be monitored at baseline, 3 months, and 1 year using The International Prostate Symptom scale. Blood tests at each routine visit should include measures of Hb, Hct, and PSA. In the absence of contraindications, treatment may be continued indefinitely as long as the patient improves. Other blood chemistries may be checked according to the practice guidelines for preventive care or treatment for other co-existing diseases.

■ Risks associated with TRT

In older men, the risks of TRT are not yet known. The stimulation of tissues that are androgen-sensitive raises concerns, such as the possible growth of occult adenocarcinoma of the prostate. Other risks associated with TRT in aging men include aggravation of benign prostatic hyperplasia, polycythemia, sleep apnea, gynecomastia and breast carcinoma, fluid retention, hypertension, lipid alterations, and atherosclerosis.²³

■ Goals and future directions

The wide range of normal T levels makes it impossible at present to merely establish a laboratory-based goal for measuring the success of TRT. This is especially true when treating an older male patient. Increasing the serum T level so that it is within the lower half or third

of the normal range is desirable. The more pertinent goal in treating hypogonadism in older men is evidence of an improvement of symptoms. If the patient complains of fatigue or poor sex drive, reversal of those symptoms would indicate successful treatment with TRT. Improved muscle mass and bone density may also be observed.⁵

The clinical benefits and long-term safety of TRT are yet to be fully evaluated in this population. Long-term studies with large cohorts of older men diagnosed with clinical hypogonadism in which these factors are evaluated will yield valuable information. ■

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CME POSTTEST

For each of the following questions, please circle the best response.

1. During which decades of life do adult men experience a gradual decline in testosterone (T) that reaches a concentration which is often below the normal range for a young adult man?
 - a. Fifth and sixth
 - b. Sixth and seventh
 - c. Seventh and eighth
2. Which complaints of older men are associated with T deficiency?
 - a. Decreased libido, decreased muscle strength, and a diminished sense of well-being
 - b. Sexual dysfunction, increased adiposity, and depressed mood
 - c. All of the above
3. The generally accepted reference range for total T (TT) in adult men has a wide span, from approximately 260 to 1000 ng/dL.
 - a. True
 - b. False
4. Because T has a circadian fluctuation, mean maximum and minimum serum levels
 - a. Are reached at approximately 8 AM (average level, 720 ng/dL [25 nmol/L]) and 10 PM (average level, 432 ng/dL [15 nmol/L])
 - b. Are reached at approximately 2 AM (average level, 518 ng/dL [18 nmol/L]) and 2 PM (average level, 345 ng/dL [12 nmol/L])
 - c. Vary from patient to patient, depending on age and body mass index.
5. If the blood concentration of TT is less than 250 ng/dL in an older man on 2 consecutive tests,
 - a. Underlying cardiovascular causes for this abnormal T level should be sought
 - b. The patient is well within the norms for his age
 - c. It is likely that the patient has T deficiency that requires substantiation by testing the free T level.
6. Normal hemoglobin (Hb) and hematocrit (Hct) levels for a man
 - a. Are the same as the normal levels for a woman, matched for age
 - b. Are as follows: Hb is 13-17 g/dL; Hct is 40% to 52%
 - c. Are unaffected by testosterone therapy.
7. Absolute contraindications for T therapy include
 - a. Only men with a history of prostate cancer or current prostate cancer
 - b. Men with prostate cancer, breast cancer, or sensitivity to ingredients in T formulations
 - c. Sleep apnea and polycythemia.
8. With which T formulation do peak levels occur after approximately 72 hours and decline over the next 1 to 2 weeks?
 - a. Buccal tablets
 - b. Intramuscular injections
 - c. Transdermal patches
9. When monitoring a patient on T therapy, if the patient's prostate-specific antigen (PSA) level is within normal range,
 - a. It should be rechecked at 3 months, at the end of the first year, and afterward every 6 months
 - b. There is no need for a repeat PSA until therapy is discontinued
 - c. It should be checked at baseline and annually thereafter.
10. In men with diabetes,
 - a. Primary hypogonadism is discovered on genetic testing in 20% of the cases
 - b. As many as one-third will be discovered to have T deficiency when the proper assays, such as equilibrium dialysis, are performed
 - c. Serum T levels will often spontaneously decrease, even in the absence of treatment for diabetes.

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To obtain 1 AMA category 1 credit for this course of study, complete the CME posttest on this page, as well as the CME credit application and program evaluation. Mail to the address below. A fee of \$20 is required. This CME is valid through October 2006; no credit will be given after this date.

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