Testosterone deficiency: myth, facts, and controversy

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Testosterone deficiency (TD) afflicts approximately 30% of men ages 40-79 years, with an increase in prevalence strongly associated with aging and common medical conditions including obesity, diabetes, and hypertension. There appears to be a strong relationship between TD and metabolic syndrome, though the relationship is not certain to be causal. Several studies have suggested that repletion of testosterone in deficient men with these comorbidities may indeed reverse or delay their progression. While testosterone repletion has been largely thought of in a sexual realm, we discuss its potential role in general men's health concerns: metabolic, body composition, and its association with decreased all-cause mortality.

Recent guidelines and studies have suggested variable prevalence statistics and expanded uses of testosterone repletion in certain populations with both biochemical and clinical signs of testosterone deficiency. Yet, this is not done without risk. A recent randomized placebo-controlled trial of testosterone repletion in elderly frail men with limited mobility has suggested potential negative cardiovascular risks in this older, sicker group of men. Two more recent retrospective studies of variable clinical design and interpretation suggest testosterone poses an increased cardiovascular risk in older men than 65 years and younger men with heart disease. This review examines these and other studies, with practical recommendations for the diagnosis of testosterone deficiency and repletion in middle aged and older men, including an analysis of treatment modalities and areas of concern and uncertainty.

Key Words: testosterone deficiency, diagnosis

Introduction

Hypogonadism, due to all causes, henceforth referred to as testosterone deficiency (TD), afflicts approximately 30% of men ages 40-79, and the increase in its prevalence is associated with aging.[1] Clinical symptoms of TD include fatigue, decreased libido, erectile dysfunction and negative mood states.[2-5] TD is also associated with changes in body composition, including decreased lean body mass, increased fat mass, and decreased bone mineral density.[2-5] Studies have shown a significantly increased risk of TD in association with common medical conditions, such as obesity, diabetes, and hypertension.[2-5] In addition, there appears to be a strong relationship between TD and the metabolic syndrome (Met S).[6-10] Whereas treatment of TD in the past has been initiated primarily for relief of sexual symptoms, there is now increasing interest among clinicians and the public in addressing the potential adverse metabolic and general health issues associated with TD. However, there are limited sources to guide decision-making in commonly seen cases where testosterone replacement therapy (TRT) may be considered.

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Defining testosterone deficiency

Clinical practice guidelines on testosterone deficiency in men recognize that the condition is both a biochemical and clinical state—suspected on the basis of symptoms but confirmed by laboratory findings. The Endocrine Society, whose most recent clinical practice guidelines were published in 2010,[11] defines TD as a clinical syndrome resulting from the failure of the testes to produce physiologic levels of testosterone and a normal number of spermatozoa; this is caused by disruption at one or more levels of the hypothalamic-pituitary-gonadal (HPG) axis.[11,12] Recommendations reflecting the views of the International Society of Andrology (ISA), International Society for the Study

of Ageing Male (ISSAM), European Association of Urology (EAU), European Academy of Andrology (EAA), and American Society of Andrology (ASA) also define TD as a clinical and biochemical syndrome associated with advancing age and characterized by symptoms and a deficiency in serum testosterone levels.[13] Although there is general agreement among guidelines on the common symptoms of TD, Table 1, consensus is lacking regarding biochemical parameters to confirm the diagnosis.

The Endocrine Society suggests that symptoms of TD correspond to the lower limit of normal for young men, or < 300 ng/dL, and that this may be an appropriate defining point for TD.[11,12] The American Association of Clinical Endocrinologists (AACE) proposes a TT level of 200 ng/dL as lower limit of normal.[14] The ISA/ISSAM/EAU/EAA/ASA recommendations propose 230 ng/dL as the point below which patients will usually benefit from testosterone repletion,[13] and consider those men with levels above 230 ng/dL but less than 350 ng/dL as deserving a trial of TRT if they include symptoms. Consensus is also lacking on parameters for free testosterone, which guidelines say should be measured when total testosterone is nondiagnostic.

TABLE 1. **Symptoms and signs suggestive of testosterone deficiency in men[11,13,14]**

More specific signs and symptoms
Reduced libido
Erectile dysfunction
Osteoporosis or low bone mineral density
Decreased spontaneous erection
Reduced intensity of orgasm and genital sensation
Oligospermia or azoospermia
Very small or shrinking testes
Hot flushes, sweats
Breast discomfort, gynecomastia
Loss of pubic and axillary hair, reduced shaving
Less specific signs and symptoms
Decreased energy or vitality; increased fatigue
Depressed mood
Reduced muscle mass and strength
Poor concentration and memory
Sleep disturbance; increased sleepiness
Mild anemia
Increased body fat, body mass index
Diminished physical or work performance

Prevalence of testosterone deficiency

While key studies have arrived at different numerical conclusions, they present an overall picture of TD increasing with age and in association with comorbidities including diabetes and metabolic syndrome.

The Hypogonadism in Males (HIM) study[15] is an example of a biochemical prevalence study. This was a cross-sectional study of 2162 men aged 45 years and older who had visited a primary care office for any reason, not necessarily for TD-associated complaints, in 2003 and 2004. Thirty-nine percent of the men were defined as being hypogonadal based on total testosterone of < 300 ng/dL; for every 10 year increase in age, the risk of hypogonadism increased by 17%, Figure 1. By extrapolating to national census data, the HIM authors estimated that 13.8 million men (39%) aged 45 and above who visit a primary care physician in the United States might have biochemical testosterone deficiency, which may or may not be associated with clinical symptoms.[15]

Prevalence was much lower in the Massachusetts Male Aging Study (MMAS), which assessed both TD symptoms and biochemistry in a population-based random sample of 40 to-70 year-old men.[16] In this study, testosterone deficiency was defined by the presence of at least three signs or symptoms of TD plus a TT level of < 200 ng/dL; or signs/symptoms plus TT of 200 ng/dL-400 ng/dL plus free testosterone < 8.91 ng/dL. The prevalence of TD was estimated to be between 6% and 12%.[17] An analysis of Boston Area Community Health (BACH) data (2000 to 2005) used a somewhat stricter definition of symptomatic TD and estimated its prevalence at 5.6% among men aged 30 to 79 years and furthermore noted that 87% were symptomatic and untreated.[18]

The European Male Aging Study (EMAS) took a uniquely stringent approach to defining TD in a random sample of 3369 men aged 40 to 79 years.[19] The list of qualifying TD symptoms was whittled down based on the strength of each symptom's association with low levels of total testosterone (< 317 ng/dL) and free testosterone (< 6.34 ng/dL). The three symptoms that made the final cut were sexual: poor morning erection, low sexual desire, and erectile dysfunction (ED). Defined by these symptoms and biochemical evidence, the prevalence of hypogonadism was estimated at 2.1% overall,[19] increasing from as little as 0.1% in men aged 40 to 49 to 5% in men aged 70 to 79. Prevalence also rose in line with increasing body mass index and increasing number of comorbidities. Wu (EMAS) as in the HIM study noted higher

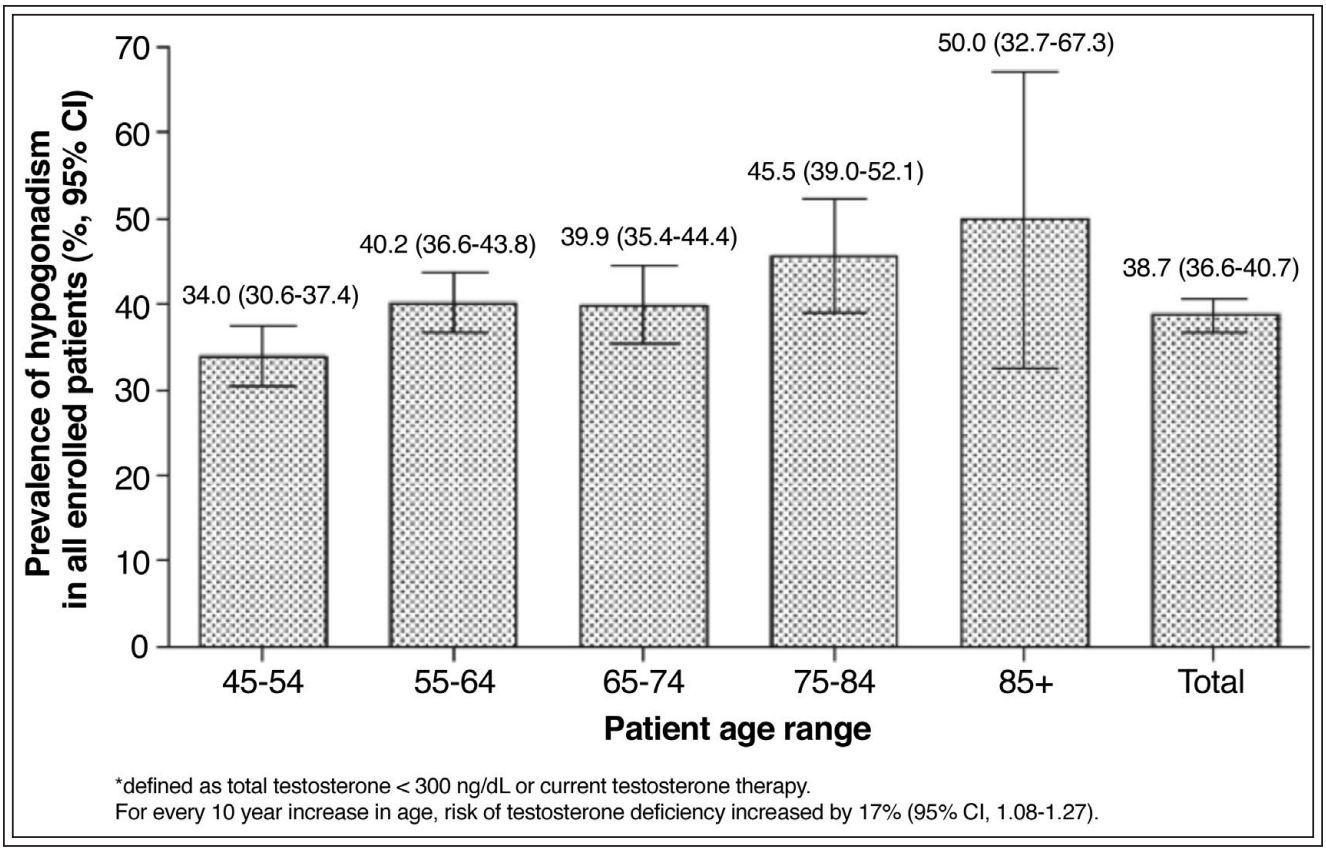

Figure 1. Age-specific prevalence of biochemically defined testosterone deficiency*[15]

TD prevalence in men with comorbidities, most significantly in those who were obese or had diabetes, hypertension, rheumatoid arthritis, hyperlipidemia, or osteoporosis. The odds of having low testosterone levels were 2.4 times higher for obese men, 2.1 times higher for men with diabetes, 1.8 times higher for men with hypertension, and 1.5 times higher for those with hyperlipidemia.[15]

As epidemiologic research continues in middle-aged and older men, the wide disparities in prevalence figures should begin to narrow. Meanwhile, more specific findings regarding TD in younger men are appearing. Obesity and diabetes are the most common comorbidities but others, such as hypertension, dyslipidemia, and chronic opiate use, steroid abuse, stress, and possibly genetic factors also drive testosterone levels.[20,21] As discussed below, long term opiate use and chronic pain are comorbidities of TD seen with increasing frequency in primary care settings.

Most importantly, the biologic potential of testosterone therapy to interfere with spermatogenesis, a particular concern in younger men being treated for TD must be noted in the primary care setting. Use of a low dose of human chorionic gonadotropin (hCG) in conjunction with testosterone replacement is a potential means of protecting spermatogenic function while improving testosterone levels.[22]

Comorbidities

The links between TD and more serious medical conditions are only beginning to be explored. At the very least it can be said that comorbid illnesses seem to explain some of the decline in testosterone that is attributed to aging. At most, one can identify specific conditions that have strong epidemiologic associations with TD, Table 2. A recent analysis of HIM data based on free testosterone levels revealed that 40% of obese men and 50% of obese men with type 2 diabetes (45 years and older) were testosterone-deficient.[23] Connections between cardiovascular disease and TD are suggested by TD's associations with diabetes and metabolic syndrome, and by such findings as an inverse relationship between testosterone level and aortic atherosclerosis, which was seen among middle-aged and older men in the Rotterdam Study.[24] Low free testosterone has also been associated with abdominal aortic aneurysm in community-dwelling men aged

TABLE 2. **Risks and comorbid illnesses associated with testosterone deficiency**[2,11,15,20,24,25,27]

Metabolic syndrome
Obesity
Hyperlipidemia
Hypertension
Elevated fasting plasma glucose and serum insulin
Elevated C-reactive protein
Diabetes mellitus (type 1 or 2)
Cardiovascular disease (including aortic atherosclerosis)
Chronic obstructive lung disease
Inflammatory arthritis
Low trauma fracture
End-stage renal disease
HIV-related weight loss
Hemochromatosis
Sellar mass, radiation to the sellar region, or other diseases of the sellar region
Chronic pain syndrome and treatment with opioids
Treatment with glucocorticoids
Radical prostatectomy

70 to 88.[25] Among men aged 50 to 91 years who were followed for 20 years in the Rancho Bernardo Study, testosterone levels were inversely related to weight, body mass index, blood pressure, fasting plasma glucose, and serum insulin. However relevant these cofactors may have been to mortality, the men with total testosterone below the 25th percentile had a 40% higher risk of death independent of obesity, lifestyle choices (eg, exercise, smoking), and even age.[26] In another recent study of elderly men (69 to 80 years), low testosterone and estradiol increased the risk of death over a 5 year period.[27]

The subject of chronic opiate use and its association with TD has not been well examined, although there is a documented increase in both therapeutic and nonmedical use of opioids in the last 10 years.[21] In that time span, primary care clinicians have become increasingly familiar with men presenting with symptoms of TD and a history of long term use of long-acting narcotics such as oxycodone and morphine. Chronic pain should accordingly be considered fairly high on the list of TD comorbidities. The mechanism of any association with TD is unclear, although suppression of hypothalamic function may be involved.

Understanding symptoms

Symptoms of TD are essential to the diagnosis even though they are individually nonspecific and may be affected by the patient's age, comorbid illnesses, duration of TD, previous testosterone therapy, and other factors. The symptoms of TD itemized in clinical practice guidelines are shown in Table 1.[11,13] According to the guidelines, any of these symptoms, even those considered "less specific," should raise suspicion of TD and prompt the clinician to measure testosterone levels.

Sexual symptoms are appropriately at the top of the list of "more specific" TD symptoms. Indeed, loss of libido is sometimes considered the hallmark of TD. Primary care clinicians might argue that fatigue is the most common presenting symptom, but the two problems, fatigue and low libido, often go hand in hand. What is true is that most patients with TD come to the attention of physicians because of the presenting problem of ED, a condition with implications even beyond the obvious quality-of-life issues and well-known to be a harbinger of cardiovascular disease.

Evidence linking ED with cardiovascular disease is not new. In 2005, a report based on data from the Prostate Cancer Prevention Trial described ED as a strong predictor of cardiovascular events in men 55 and up, and the report authors encouraged clinicians to investigate cardiovascular disease in men this age if ED is present.[28] Testosterone deficiency, meanwhile, is associated with both ED and increased cardiovascular risk.[11,17,20] Yet, in guidelines on hormonal testing in evaluation of ED, the American College of Physicians takes no position for or against testosterone measurement.[29] Many experts would disagree with this stance and instead recommend testing of testosterone as a routine and indispensable part of the ED work up.

Barriers to recognition of TD/areas of uncertainty

Judging by prescriptions for testosterone therapy, diagnoses of TD are increasing: between 1999 and 2004, prescriptions for the most popular forms of testosterone replacement increased by approximately 200%, most notably among men younger than age 65 but also in older men.[30] Nevertheless, many men with TD symptoms go unrecognized or receive a diagnosis and treatment only after multiple visits to clinicians. A study of a random sample of community-based men aged 30 to 79 years found that of those who met the criteria for TD, only 12.2% were being treated despite access to healthcare.[18] A survey of

physicians from several global regions concluded that 35% of testosterone-deficient men are not receiving treatment.[31] An Anderson/Reuters internet survey of men with TD, reported at the 2009 meeting of the Endocrine Society, indicated that 36% of the men saw two physicians before receiving a diagnosis, 19% saw three physicians, and 9% saw four. What explains these findings? Key barriers to recognition of TD include:

Lack of consensus on the definition of TD. Lack of consensus may be a valid point with respect to biochemical thresholds and ranges for defining TD, but there is agreement that TD can be appropriately identified through evaluation of both symptoms and abnormal biochemistry.

Lack of confidence in diagnostic tests. The Endocrine Society acknowledges that, among other shortcomings, assays for total testosterone vary over three orders of magnitude depending on a patient's age, gender, and coexisting diseases. Most assays have adequate sensitivity in men but are "relatively inaccurate," and the manner in which most assays are performed is "decidedly unsatisfactory."[32] The most widely accepted tests are the rather expensive testing performed by mass spectrometry or equilibrium dialysis.

Non-use of screeners. Although validated questionnaires are available to assess clinical manifestations of TD,[33] they are not widely used in primary care offices. Most are too lengthy and are used mainly in research. This practice gap is one reason that men suffering from depression, for example, end up being treated with psychotropic drugs when the etiology of their depression is TD. Shorter, more practical screeners for TD are continuing to be developed.[34]

Nonspecificity of signs and symptoms. Clinicians and patients alike may attribute TD symptoms to other conditions, most commonly normal aging—a natural decline. Yet, these symptoms, no matter how vague, may be having a profound impact on the patient's quality-of-life and well-being, and should be explored as part of overall health management.

Perception that TD is difficult to manage. This perception is based on the lingering but unsupported belief that testosterone therapy increases the risk of prostate cancer and must, at minimum, be intensively monitored with prostate-specific antigen (PSA) testing. Indeed, a 2007 survey of physicians worldwide found that responders showed a "very powerful" fear of inducing prostate cancer by way of testosterone therapy; 68% of respondents (especially those based in Europe) associated therapy with greater risks than benefits.[31] While it is true that the long term outcomes of testosterone therapy are not well defined, therapy has never been proved to cause the development or progression of prostate cancer. To the contrary, some findings suggest that TD is the riskier condition with respect to cancer. Testosterone replacement even for men with a history of treated prostate cancer is no longer considered unusual.[35,36] The Endocrine Society recommends initial PSA testing and digital rectal examination for all patients when testosterone therapy is being considered. If all factors are normal, these tests should be repeated at 3 months, but thereafter they need be repeated only in accord with standard screening recommendations.[11] While these remain a source of controversy, we usually screen at baseline, 3-6 months, and thereafter, annually, if PSA is stable.

Primary care evaluation

Most patients who are experiencing TD want to know why they have the condition and where it originated. Although it is sometimes possible for the clinician to arrive at a definitive etiology of individual cases, more often the cause is multifactorial and complex.[37,38] The possible sites of origin are the testes, where testosterone is produced; and the brain, where the production process is regulated via the hypothalamic-pituitary-gonadal (HPG) axis. These two sites are the basis of a general classification scheme for TD in which hypogonadism is considered primary if it is testicular in origin and secondary if it results from hypothalamic or pituitary dysfunction, Table 3.[39,40] Each type of hypogonadism can result from an inherited trait or be acquired in life, and each type can occur in men of any age. However, most cases of hypogonadism in men aged 50-70 years are a mixed form, involving testicular failure as well as central defects of the HPG axis.[39,40] This form corresponds to what is often called adult-onset or late-onset hypogonadism, or LOH.[38]

Relatively few cases of TD are primary; those that occur are usually congenital in origin, such as Klinefelter's syndrome, the most common primary form.[39] Other primary causes include mumps orchitis, cryptorchidism, chemotherapy/radiation therapy, and testicular trauma.[40] Causes of secondary hypogonadism include hypothalamic or pituitary lesions, cranial trauma, hyperprolactinemia, and Kallmann syndrome (genetic). Aging, acute illnesses, certain medications, and chronic illnesses including alcoholism, diabetes, cardiovascular disease, and sickle cell disease are believed to play causative roles in mixed hypogonadism.[40,41]

Although all forms of hypogonadism involve TD, they differ somewhat in their characteristic gonadotropin

TABLE 3. **Primary and secondary forms of hypogonadism**[14,39,40-42]

Primary hypogonadism
Congenital anorchidism
Cryptorchidism (undescended testes)
Mumps orchitis
Genetic and developmental conditions: Klinefelter's syndrome (1 in 1000 live births. Most patients have 47, XXY genotype anomaly; however, mosaicism is also seen); androgen receptor and enzyme defects
Sertoli-cell-only syndrome
Noonan syndrome: phenotypic and genotypic males with physical signs of classic female Turner syndrome
Radiation treatment/chemotherapy
Testicular trauma/surgical procedures
Autoimmune syndromes (anti-Leydig cell disorders)
Secondary hypogonadism
Kallmann syndrome (pituitary macroadenoma)
Pituitary tumor, granulomas, abscesses
Genetic conditions: Kallmann's syndrome, Prader-Willi syndrome
Hyperprolactinemia
Cranial trauma
Radiation treatment
Various medications
Mixed hypogonadism (seen chiefly in men aged 50-70 years old)
Alcoholism
Aging
Chronic infections (eg, human immunodeficiency virus [HIV])
Corticosteroid treatment
Hemochromatosis
Systemic disease (liver failure, chronic kidney disease sickle-cell disease

profiles. Primary hypogonadism is marked by increased luteinizing hormone (LH) and follicle-stimulating hormone (FSH), the result of reduced feedback from testosterone; secondary hypogonadism is characterized by low or low-normal levels of LH and FSH; and the mixed form varies according to the predominance of primary or secondary hypogonadism. All forms also involve impaired spermatogenesis.[11,43] The clinical guidelines of the Endocrine Society recommend measurement of LH and FSH in hypogonadal men to distinguish between primary and secondary hypogonadism.[11] A more rational approach is to reserve FSH measurement for hypogonadal patients who have fertility concerns. LH is directly relevant to testosterone production and, in the absence of fertility questions, is the only gonadotropin of interest for TD classification. Measurement of serum prolactin, for insight on pituitary function, is appropriate when the serum testosterone level is < 150 ng/dL or when secondary hypogonadism is suspected.[13]

Identifying candidates for screening

There is lack of agreement on the relevance of TD to ED—that is, whether ED is sufficiently symptomatic of hypogonadism to prompt screening and testosterone measurement. The Endocrine Society guidelines[11] do not specify ED as suggestive of TD. The American College of Physicians does not recommend for or against routine hormonal blood tests or hormonal treatment for ED, citing the wide-ranging prevalence rates of ED in hypogonadal men (12.5%-35%) and the lack of conclusive evidence about the impact of testosterone therapy on ED.[29,44] On the other hand, several other international medical societies[13] recognize ED as among the hallmark symptoms of TD requiring biochemical corroboration. Most primary care physicians will know from their own experience that ED is the portal to testosterone measurement. It should by no means go unappreciated as a possible manifestation of TD.

National and international guidelines concur in recommending TD screening for men deemed at risk due to coexisting illnesses, Table 2. The conditions include infertility, type 2 diabetes, metabolic syndrome, chronic obstructive pulmonary disease, inflammatory arthritis, cardiovascular disease, and chronic use of glucocorticoids and opioids.[11,13,14,42] Clinicians should maintain a high index of suspicion of TD in patients with these comorbidities. Even those at-risk patients who report no symptoms typical of hypogonadism require a thorough clinical and biochemical workup for TD.

*Key learning point:

For men with sellar mass, HIV-associated weight loss, low trauma fracture, or use of medications that affect testosterone production, measurement of testosterone should be considered regardless of hypogonadal symptoms.

There is little support for the use of formal questionnaires as a screening method for TD, especially as an isolated method in the work up. The Aging Males' Symptoms and the Androgen Deficiency in Aging Men scales, two of the better known symptom inventories used in TD screening, demonstrate high sensitivity for identifying men with TD but very low specificity (< 40%),[45,46] making them unreliable for screening. In a recent trial with 587 community-dwelling men aged 60-80 years with known TD, the scores from these scales correlated more closely with age than with testosterone, and they did not reflect changes in symptoms after a 6 month regimen of testosterone therapy.[45] This latter finding is unfortunate because some clinicians find the instruments useful as a reference for evaluating the effects of treatments.[42] However, the screeners may be helpful in identifying patients with a high likelihood of TD, and for educating the clinician about high-yield questions to ask in the TD work up. Even so, the current array of questionnaires are too time-consuming for most primary care clinicians to routinely utilize, especially given the lineup of other screeners suggested for primary care (for depression, dementia, and cancer, to name a few) that compete for time and resources. Newer screeners for TD are in development with fewer questions, and thus shorter completion time; these are likely to become available in the next 2 years.

This algorithm, Figure 2, may initially appear to be a bit simplified. Yet it is useful for the primary care clinician with perhaps the addition of two caveats. First, if total testosterone is low on the first draw and in a patient with at least a single symptom of TD (T < 300 ng/dL) then a second morning (7 am to 11 am) draw must be done with a LH added to distinguish primary from secondary TD. If the initial T is < 150 ng/dL, then one should add a prolactin level to this second test. Second, if the prolactin returns at > 35 ng/mL, one should order an MRI of the pituitary to determine

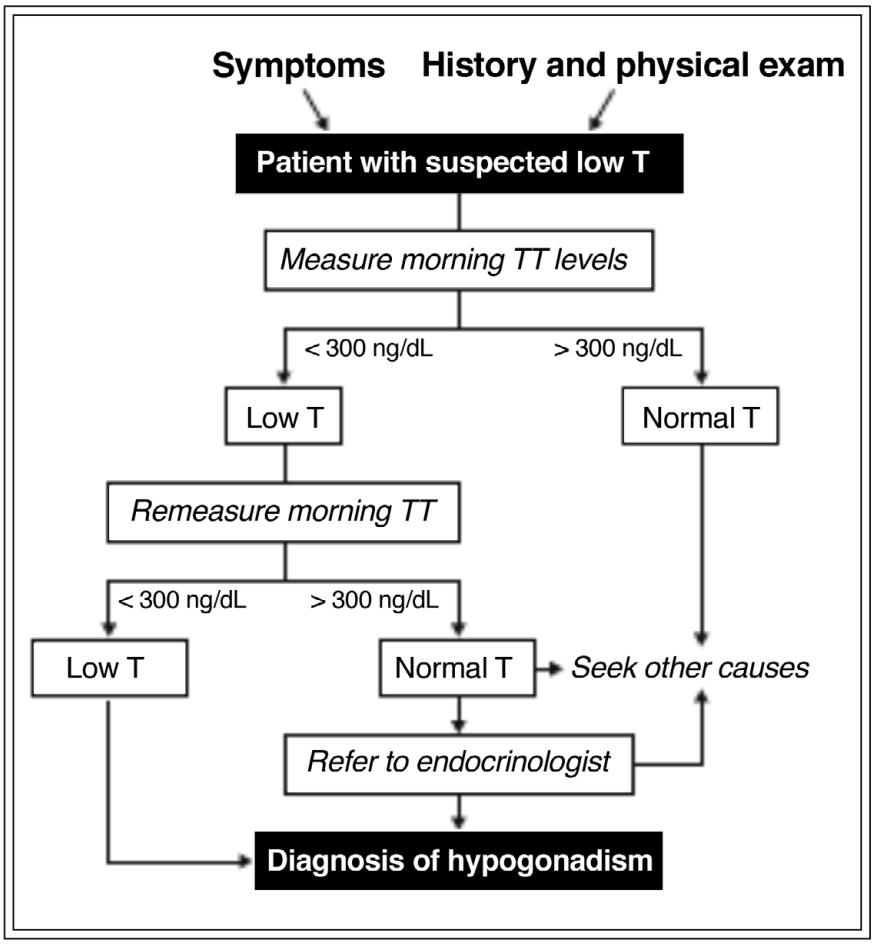

Figure 2. Evaluation of testosterone deficiency.[11,12,32,40,42,47]

the presence of a microadenoma. If such an adenoma is found, then referral is made to an endocrinologist for the appropriate therapy with a dopamine agonist.

Therefore, in the case TD, in this algorithm the use of serum LH is of value since the level of this hormone indicates where the failure is located: in the testes if the serum LH is high (primary TD), or at the level of the hypothalamus or pituitary if the serum LH is low or normal (secondary TD). Secondary TD necessitates the measurement of a serum prolactin because if T < 150 ng/dL, as it may result from hyperprolactinemia, a condition often associated with curable diseases like pituitary tumor. MRI is required as above as proposed by the Endocrine Society if T is below this threshold [< 5.2 nmol/L; 150 ng/dL]. This was based on as single study of 159 men with ED who had T levels < 8 nmol/L and non-elevated LH. Eleven potentially serious hypothalamic or pituitary lesions were identified (6.7%).[48] Secondary TD may also require screening for hemochromatosis with measurement of transferrin saturation and serum ferritin.

Key learning points:

There are no generally accepted lower limits of normal TT.

There is, however, general agreement that:

- TT > 12 nmol/L (3.5 ng/mL or 350 ng/dL) does not usually require substitution
- Based on the data of young hypogonadal men, men with TT < 8 nmol/L (2.3 ng/mL or 230 ng/dL) usually benefit from T treatment

Between these levels:

- Measuring FT by equilibrium dialysis or calculating it from TT and SHBG levels may be helpful in case of TT between 8 nmol/L and 12 nmol/L. A lower limit of 225 pmol/L (65 pg/mL) is accepted by many.
- A T trial for 3-6 months may be envisaged in those patients who are symptomatic, while alternative causes of the symptoms have been excluded. Beyond that time, T therapy would be continued only in case of substantial benefit

Measuring testosterone: what do the values mean?

Different thresholds exist for treatment according to specific guidelines and thus vary in regard to the lower level for therapy, Table 4. Total testosterone (TT) has been the traditional measure for use in corroboration of hypogonadism. Testosterone levels in healthy men follow a circadian rhythm, with levels peaking in the morning. Accordingly, guidelines recommend measurement of TT in a blood sample taken during morning hours, preferably after the patient has fasted. A positive finding should be repeated, especially if borderline.[11,42]

It is generally agreed that a TT level of > 350 ng/dL does not require treatment and suggests non-testosterone sources of symptoms. Otherwise, the recommendation is to consider treating men with "unequivocally low" testosterone along with symptoms. Clinicians should be aware that TT measurements do not necessarily correspond with the patient's clinical presentation. Some research supports symptom-specific levels of TT below which the prevalence of the symptom starts to increase.[49] Other research finds no symptom-specific thresholds but further evidence that the severity of symptoms increases with decreasing testosterone level, especially the severity of psychological symptoms.[50]

TT represents the total of free testosterone plus hormone bound to sex hormone-binding globulin (SHBG) and albumin. TT levels are subject to alterations in SHBG that occur in association with obesity, old age, diabetes, medications, and other confounders.[11] Measurement of free testosterone can be of diagnostic value in cases where TT does not correspond with the clinical picture. However, this practice is limited by the availability of assays and, again, a lack of consensus on threshold values. Many clinicians who regularly see men with TD suggest a threshold of 8 ng/dL to define hypogonadism by calculated free testosterone. For measurement via the analog free testosterone assay, values < 1.5 ng/dL have been proposed as a lower limit of normal.[51]

Treatment

The goal of TRT is to safely restore testosterone to normal physiologic levels, thereby ameliorating symptoms associated with TD and improving patient health and well-being. At the biochemical level, the goal is to raise total testosterone to a range considered normal for healthy young men, 300 ng/dL-1050 ng/dL.[11,38,39,40] The Endocrine Society specifies a mid-range goal of 400 ng/dL-700 ng/dL for repletion. Note that these are physiologic (eugonadal) testosterone levels, not supraphysiologic levels; there is no basis for recommending TRT dose escalations in pursuit of greater efficacy, and the practice may increase the risk of treatment side effects.[52] TRT should also achieve physiologic levels of key testosterone

TABLE 4. **Biochemical definitions of hypogonadism**[11,13,14,44]

Society guidelines	Total testosterone		
	ng/mL	ng/dL	nmol/L
EAA, ISA, ISSAM	< 3.40	< 340	< 12 (mild)
EAU, ASA, ISSM	< 2.31	< 231	< 8 (severe)
ES	< 3.00	< 300	< 10.4
AACE	< 2.00	< 200	7

EAA = European Academy of Andrology; ISA = International Society of Andrology; ISSAM = International Society for the Study of the Aging Male; EAU = European Association of Urology; ASA = American Society of Andrology; ISSM = International Society for Sexual Medicine; ES = Endocrine Society; AACE = American Association of Clinical Endocrinologists

metabolites, including estradiol, a sex hormone with major influence on male bone density.[53]

Improvements in TRT formulations and refinements in delivery systems allow more individualization of TRT. In particular, the availability of higher-potency, lower-volume transdermal formulations address the important problem of skin-to-skin transfer of hormone. Yet patients must be cautioned about this risk prior to beginning a topical testosterone formulation.

However, long term controlled data documenting the benefits and risks of TRT are missing, and uncertainties still surround the nature of key associations, such as TRT and cardiovascular disease. Clinicians and patients might ultimately decide not to use TRT, but for those who choose treatment, available knowledge and improved treatment options should enable them to proceed with greater confidence that the effort will be safe and beneficial.

Lifestyle interventions

TRT is only the pharmacologic component of TD therapy. Positive health behaviors, such as exercise, diet, and avoidance of smoking, are considered a means of preventing TD, and they correlate significantly with higher testosterone levels over time in population-based research.[54] In a small but compelling study of men with TD along with newly diagnosed type 2 diabetes and metabolic syndrome, intervention with supervised diet and exercise improved not just testosterone levels but glucose parameters, lipid levels, and waist circumference. For men randomly assigned to receive both lifestyle therapy and TRT (in the form of a gel, 50 mg/day), these improvements were significantly greater versus lifestyle changes alone. All of the subjects receiving lifestyle + TRT achieved current targets for glycemic control—without the use of antihyperglycemic medications before or during the 52-week trial.[55] More studies of this combination would be helpful to further define its impact, but at present there are no arguments to be made against the use of both lifestyle change and TRT when intervening in hypogonadism.

Benefits and risks of TRT

The purpose of TRT is to alleviate hypogonadal symptoms, but the broader goal is to give the patient a better quality-of-life, reduce major morbidity and disability, and "add life to years."[43] Yet, of course there is no evidence that this is true. Therapy is also not recommended generally for men with low testosterone but without symptoms of hypogonadism. However, accumulating evidence and clinical experience suggest that for men with unequivocal TD, biochemical and symptoms, therapy can achieve clear symptomatic improvements with a low risk of side effects. Evidence about the greater goals of TRT, particularly the impact of therapy on cardiovascular disease and prostate cancer, remains limited but encouraging.

Benefits

TRT is associated with improvements in many domains of sexual function, including sexual desire, sexual activity, and sleep-related erections.[11,56-58] ED itself may not respond as well to TRT if vascular disease is also present, a more common finding in older men.[59] However, in hypogonadal men aged 18-80 years, the addition of TRT to sildenafil has significantly improved erectile function that was unresponsive to sildenafil alone.[60] Testosterone replacement also improves bone mineral density, chiefly in the spine and femoral neck, especially at years 2-3.[61,62] Some experts point out that effects on bone are moderate;[11] others say the effects are marked enough to serve as a measure of TRT efficacy.[63] Unfortunately, studies have not been large enough to examine the key question of whether TRT can reduce fracture risk along with bone density improvements.[43,56,63]

Testosterone therapy is associated with reduced body fat mass, improved muscle mass and strength, and a possible positive effect on lipid levels and glucose control.[11,43,58,64,65] Therefore, one does not often note a change in body mass index, as fat mass is replaced by lean muscle mass. Functionally important changes in strength have been reported particularly for older, frail hypogonadal men[64] and those with mobility limitations.[66] Mood, cognition, energy, and quality-of-life have also been credited to TRT.[49,58,64] Its effect on mood extends to improving depression.[49]

Risks and contraindications

Testosterone therapy that restores the hormone to physiologic levels is generally well tolerated. Even the most common adverse effects associated with therapy are usually mild and infrequent if testosterone is kept in the normal range. However, the clinician should be alert to increased hemoglobin and hematocrit, a small decrease in high-density lipoprotein (HDL) cholesterol, fluid retention, gynecomastia, acne, and exacerbation of sleep apnea.[11,47,67,68] Most effects are more common (though still infrequent) in older men. Infertility, on the other hand, is common in younger men and usually reversible. Some adverse effects are associated with the mode of TRT delivery. Erythrocytosis, for example, occurs in as many as 44% of men receiving injected TRT but only 3%-18% of those using testosterone gels or patches.[68] Hepatotoxicity is associated only with certain oral testosterone formulations, which are not approved for use in the United States and Canada.[68]

TRT and prostate cancer

Growth of prostate cancer is one of the more serious potential adverse effects of TRT. Continuing research on TRT and prostate cancer has been helping to allay general concerns about a causal association, especially if cancer is confined to the prostate gland.[69] Nevertheless, treatment guidelines list untreated prostate cancer (and breast cancer) as a definite contraindication to therapy; and high risk of prostate cancer (unevaluated prostate nodule or induration, or PSA > 4 ng/mL) as a relative contraindication. Hematocrit > 50% and uncontrolled congestive heart failure are additional relative contraindications.[11,13]

Although TRT has been available and in use for decades, uncertainties about its links to prostate cancer have never been fully resolved because trials of sufficient size and duration are unavailable. However, analyses of existing clinical data suggest that TRT has no specific effect on PSA levels in hypogonadal men and does not increase their risk of prostate cancer.[69,70] This finding may perhaps be explained by the "saturation model," which holds that androgen receptors in prostate tissue are sensitive to testosterone increases only when levels are low and the testosterone receptors are unfilled; once filled, the tissue is no longer sensitive to testosterone levels.[71] Whether this model applies in hypogonadal men receiving TRT is unclear, but data from small studies suggest that it does, and that even men with untreated prostate cancer may thus be safely treated with TRT.[72]

TRT and cardiovascular risk

The first of the two recent studies reporting risks with testosterone prescriptions, published in the Journal of the American Medical Association by Vigen et al, was a retrospective analysis of a dataset of 8709 men in the VA health system who had undergone coronary angiography.[73] Among men with testosterone concentrations less than 300 ng/dL, the authors reported an increased rate of heart attacks, strokes, and deaths in men who received a testosterone prescription compared with men who did not. No significant differences in event rates were noted for any year of follow up; however, the overall event curves demonstrated a significant increase in events for testosterone-treated men of 29%. Strangely, the percentage of men who suffered an event was actually lower by one half for the testosterone group compared with the no-testosterone group (10.1% versus 21.2%) compiled by the raw data.[73] The authors came to an opposite conclusion resulting from complex statistical modeling based on more than 50 variables. This modeling failed to include substantially lower baseline testosterone levels in the T group, despite evidence that lower T values are associated with increased cardiovascular (CV) risk and mortality. In addition, the authors improperly excluded 1132 men who suffered stroke or heart attack prior to receiving a testosterone prescription. Without that exclusion, the rate of events in the no-testosterone group would have been increased by 71%, reversing the results. It is impossible to conclude from this study that testosterone prescriptions increase rates of cardiovascular events.

The second study published in PLoS One by Finkle et al was a retrospective analysis of insurance claims data in 55,593 men in which the only information available were diagnosis codes, procedure codes, and prescription data.[74] The primary reported result was an increased rate of non-fatal myocardial infarction (MI) within 90 days after filling a testosterone prescription compared with the prior 12 months. The authors also compared these rates with pre- and post-prescription rates for PDE5i, reporting no increase in MI following PDE5i prescription. Subgroups by age revealed

increased risk of MI with men over 65 years old without a prior history of heart disease, and for men less than 65 years old with a prior history of heart disease. The authors concluded that the risk of MI is substantially increased in older men and in younger men with pre-existing known heart disease.[74]

This study has received even greater media attention, and appears to have led to the Food and Drug Administration (FDA) decision to review CV risks with testosterone. Neither the study by Vigen et al[73] nor the more recent publication by Finkle et al[74] provide any credible evidence that testosterone use is associated with increased CV risk. Both studies were retrospective, highly statistical, and reported only a minor effect size. These study characteristics make it unlikely that these results are reproducible or accurate.[75] Even if the results were exactly as described, both studies could more plausibly be interpreted as showing the CV benefits of T therapy and the risks of untreated low T, as demonstrated repeatedly by a wealth of studies over the past 30 years.[76]

Although the authors of both studies cite a study by Basaria et al as support for increased CV risk with testosterone, that placebo-controlled study was not designed to assess CV risk; it was to address mobility in older men.[77] As a placebo controlled study of 1% testosterone, it did utilize supraphysiologic (mean 100 mg) dosages in several elderly men of mean age 74 years. The study was terminated early due to the fact that 23 of the 106 men in the testosterone group had experienced adverse CV-related events including myocardial infarction, arrhythmias, and hypertension compared with 5 men of 103 men in the placebo group. At the time the study was stopped the testosterone group had significantly greater improvements in leg-press and chest-press strength, and in stair climbing. Though the study's report of increased adverse events in the T group compared with placebo was based on a wide variety of events of questionable significance, such as pedal edema, palpitations, and premature ventricular contractions,[78] it did raise a disturbing trend that needs to be answered with future randomized controlled trials.

An unbiased examination of the literature reveals a much different result. A wealth of evidence indicates that low levels of testosterone are associated with CV risks and known risk factors for CV disease, such as obesity, diabetes, and the metabolic syndrome.[79] Nine of eleven longitudinal studies have demonstrated increased mortality rates in men with lower levels of testosterone and improved survival in those with higher testosterone.[51] The other two showed no effect. In placebo-controlled trials men who received testosterone demonstrated increased angina-free exercise capacity,[80] and improved functional capability in men with congestive heart failure.[81] Two retrospective studies demonstrated reduced mortality, by half, in men with T < 300 ng/dL who received testosterone prescriptions compared with men who did not.[82,83] To date, there is not a single study that provides any definitive evidence that T therapy increases CV risk, and a wealth of information suggesting testosterone may be beneficial for CV health. We therefore await a randomized placebo control effort of > 900 men placed on testosterone and placebo examining CV safety for 1 year to conclusively examine CV trends.

TRT formulations

Testosterone was isolated, purified, and introduced to clinical medicine in the mid-20th century. Today's options for TRT include oral or buccal agents, injections, transdermal systems (patches, gels, and solutions), and subcutaneous pellets, Table 5. Some formulations incorporate adaptations designed to improve the bioavailability and pharmacokinetics of the hormone, with the goal of slowing its metabolism by the liver after oral or parenteral administration.[38] Others were developed for convenience and dosing flexibility. Formulations are differentiated not only by route of delivery but by side effects, ability to normalize testosterone, expense, convenience, and tolerability. TRT may be a lifetime therapy for hypogonadal men, so initial and subsequent decisions about the best formulation for therapy should be made carefully and collaboratively between clinician and patient.[84]

Factors in choosing TRT

Transdermal patches, gels, and solutions

The skin is a favorable route for delivery of stable concentrations of testosterone. Transdermal patches were the first technology to apply this principle using skin in both genital and nongenital areas.[85] While effective at mimicking physiologic testosterone levels, skin patches cause adverse skin reactions at the patch site in about 30% of patients.[86] Testosterone gel formulations were introduced in 2000 and have largely supplanted patches as the most widely prescribed form of TRT. Although testosterone gel formulations are convenient (applied by hand to the shoulders, upper arms, or abdomen) and associated with a lower risk of skin irritation (approximately 6%), they leave unabsorbed testosterone on the skin surface, which can then transfer to the skin of intimate partners or children.[87] A goal

TABLE 5. **Testosterone therapy: formulations, advantages, and disadvantages**[38,51,56]

Formulation	Standard regimen	Disadvantages	Advantages
Transdermal agents			
Hydroalcoholic gel 1%-2% (US) gel 1% (Canada)	50-100 mg/day = 5-10 g of gel	Risk of transfer to intimate contacts; occasional skin irritation.	Convenience; flexible dosing; less skin irritation than with patch; less risk of transfer with higher-potency gels; ie, 1.62%, 2%; mimic physiologic T levels.
Skin patch	5 mg/day, applied at bedtime	Local irritation; urticarial.	Convenience; mimics physiologic T levels and diurnal rhythm.
Underarm T solution 2%	60-120 mg/day (30 mg/pump)	Risk of transfer to intimate contacts.	Mimics physiologic T levels.
Intramuscular agents			
T enanthate T cypionate	300 mg/3 weeks 200 mg/2 weeks	Injection site pain. Wide peaks and troughs in T level associated with mood swings.	Long-acting relatively inexpensive if self-administered; flexible dosing.
T undecanoate in oil (US)	750 mg/10 weeks	Injection site pain. Potential pulmonary emboli.	Infrequent administration.
Buccal agents (US)	30 mg bid	Unpleasant taste; oral irritation; twice-daily dosing.	Mimic physiologic T levels.
Subcutaneous T pellets (US)	6-12 75 mg pellets/3-6 months	Invasive placement; risk of extrusion and local infection; mood swings. Expensive.	Infrequent administration (2x-3x year).
Oral agents			
T undecanoate capsules	40-80 mg 2-3 times/day with meals	T levels and clinical responses vary. Must be taken with meals. Not approved in United States. Available in Canada	Convenience; easily titrated.

T = testosterone

has been to reduce the risk of transfer by increasing the concentration of testosterone beyond the traditional 1%, so that a smaller volume of gel can be applied. Better permeation of the product after initial application would also lessen the transfer risk. In the last 3 years, new formulations with higher concentrations of testosterone in roughly half the volume of gel have been approved by the FDA and are making their way into clinical practice.[88] An underarm solution containing 2% testosterone has also been approved.[38] With any topical TRT, transfer can be further limited by covering the treated skin area or washing off residual testosterone from the skin.

Testosterone injections

Testosterone preparations delivered via intramuscular injection are absorbed directly into the blood stream. Testosterone cypionate and testosterone enanthate have half-lives that allow intervals of 2 weeks between injections (usually into the buttocks).[38] However, there is considerable fluctuation in testosterone levels in the interim, and these may negatively impact the patient's emotional stability, sexual activity, and sense of well-being.[38] Moreover, patients may be unwilling or unable to perform self-injection or tolerate injection site pain. A long-acting injectable form of testosterone undecoanate in castor oil, Aveed, recently approved by the FDA, not available in Canada, extends the time interval between injections to 10 weeks. A study showed that this formulation, given to 117 hypogonadal men at baseline and at 4 weeks, safely produced consistently therapeutic testosterone levels during the next 10 weeks.[89]

Pellets and buccal modalities

Subcutaneous pellets use is rising significantly and transbuccal agents are a less widely used formulation. They have unique advantages in convenience, but major disadvantages as well. Buccal tablets are associated with gum problems and bad taste in 10%-20% of treated men.[56] Pellets need not be reimplanted for 4-6 months, and they are generally well tolerated,[90] but the implantation procedure is invasive; infection or pellet extrusion occurs in 5%-10% of treated men. Implantation must also be done by an individual so trained in the procedure.[38] However, the use of this treatment is growing broadly in the United States and has been a staple of TRT in Europe for over 12 years.

Oral preparations

Testosterone undecanoate is an oral testosterone ester delivered by an oily vehicle that escapes hepatic metabolism through absorption into the lymphatics.[40] It has been used in Europe and Canada for many years 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.[40,56] The testosterone pharmacokinetic profile is irregular.

Before initiation of TRT

TRT should not begin without specific steps to assure safety going forward. The clinician should perform a baseline digital rectal exam and measure PSA in patients of all ages to rule out prostate cancer. The PSA level should be < 4 ng/mL (if age < 50 then total PSA < 2.5) and should be measured again after 6 months of TRT regardless of the treatment formulation. Although hemoglobin and hematocrit levels rarely rise above normal with most formulations of TRT, they should be checked at the start of therapy and every 6 months thereafter. Liver function and lipid levels should also be evaluated.[39]

Monitoring patients on testosterone therapy

Patients on TRT should be evaluated 3-6 months after the start of treatment and then annually to determine if symptoms have improved and to check if the patient is experiencing any adverse effects, Table 6.[11] Since testosterone frequently stimulates erythropoiesis, a rise in hematocrit values is not unusual and should be monitored.[11] Hematocrit values above 54% typically require cessation of TRT until the values decrease to a safe level.[11] The Endocrine Society suggests PSA surveillance in men 40 years and older who have a baseline PSA greater than 0.6 ng/mL.[11] This means getting a baseline PSA, another at 3-6 months, and then afterward at an interval determined by the patient's age, race, and risk factors.[11] A urology consult should be sought if PSA rises by > 1.4 ng/mL within any 12 month period, if digital rectal examination reveals a prostate abnormality, or if the IPSS score is greater than 19.[11]

Conclusions

Testosterone deficiency is a complex, multi-factorial disease state that is bi-directionally related to conditions such as obesity and diabetes that are common in

TABLE 6. **Endocrine Society guidelines for testosterone replacement therapy monitoring[11]**

	Baseline	Every visit	3 months	Annually	1-2 years
Symptom response		√	√	√	
Adverse events		√	√	√	
Formulation-specific AEs		√			
Testosterone levels	√		√		
Hematocrit*	√		√	√	
BMD lumbar/femoral neck‡	√				√
Digital rectal examination†	√		√		
Prostate-specific antigen†	√		√		

*if hematocrit is > 54%, stop therapy, evaluate patient for hypoxia and sleep apnea, consider reinitiation at reduced dose if levels have declined to a safe level.
‡for patients with osteoporosis or low trauma fracture, consistent with standard of care.
†after 3 months perform in accord with screening guidelines for patient age/race/risk factors.

primary care physician patient populations. Because the constellation of signs and symptoms of TD include a number of vague and/or non-specific factors (i.e. lack of energy and low mood) a diagnosis of TD must be made cautiously and only after ruling out other potential physiological or psychological causes. Prior to (or concurrent with) a trial of testosterone therapy, clinicians should explore with their patients therapeutic lifestyle changes, such as weight loss and exercise, which are known to restore depressed testosterone levels as well as improve a wide range of other health parameters. Decisions about whether or not to pursue TRT must rest firmly on a foundation of good patient education about the potential risks and benefits of hormonal therapy.

TRT can improve the health and quality-of-life in testosterone-deficient men by stimulating libido and sexual function, improving muscle mass and strength, raising bone density, and raising mood levels. Some emerging evidence suggests that TRT may also improve glycemic control, insulin sensitivity, and metabolic syndrome in men with diabetes or metabolic syndrome. Many believe that TD itself is related to a significant increase in CVD risk; others support a notion that TRT may be associated with an increased CVD risk. Only forthcoming randomized-controlled trials will answer this question. Most clinicians with experience in prescribing TRT will continue to do so without any significant concern of increased CVD risk.

Recent refinements of TRT formulations and delivery systems, particularly the availability of higher-potency, lower-volume transdermal formulations, may allow greater individualization of dosing and may reduce the risk of adverse events such as skin-to-skin transfer of hormone. Although long term, high-quality data documenting the benefits and risks of TRT are missing, available knowledge and improved treatment options can allow providers and their patients to address TD with greater confidence that their efforts will be safe and beneficial.

Disclosures

Dr. Martin Miner has been a consultant for Abbvie and Endo. He has also done research for Forest. Dr. Jack Barkin has been a clinical investigator, speaker and medical advisory board member and consultant for Abbott, Lilly, Bayer, Paladin, Actavis, AstraZeneca, Astellas, Pfizer and Triton. Dr Matt T. Rosenberg has been a speaker and consultant for Astellas, Easai, Ferring, Forest, Horizon, Ortho-McNeil, Lilly, Pfizer and Bayer. □

References

1. Allan CA, McLachan RI. Age related changes in testosterone and the role of replacement therapy in older men. *Clin Endocrinol* 2004;60(6):653-670.
2. Dandona P, Rosenberg MT. A practical guide to male hypogonadism in the primary care setting. *Int J Clin Pract* 2010; 64(6):682-696.
3. Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. *Endocr Rev* 2005;26(6):833-876.
4. Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. *J Clin Endocrinol Metab* 2006;91(11):4335-4343.
5. Wang C, Swerdloff RS, Iranmanesh A et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. *J Clin Endocrinol Metab* 2000;85(8):2839-2853.
6. Kupelian V, Page St, Araujo AB et al. Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the Met S in non-obese men. *J Clin Endocrinol Metab* 2006;91(3):843-850.
7. Laaksonen DE, Niskanen L, Punnonen K et al. Testosterone and sex hormone–binding globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care* 2004;27(5): 1036-1041.
8. Muller M, Grobbee DE, den Tonkelaar I, Lamberts SWJ, van der Schouw YT. Endogenous sex hormones and metabolic syndrome in aging men. *J Clin Endocrinol Metab* 2005;90(5):2618-2623.
9. Laaksonen DE, Niskanen L, Punnonen K et al. Sex hormones, inflammation and the metabolic syndrome: a population-based study. *Eur J Endocrinol* 2003;149(6):601-608.
10. Heufelder AE, Saad F, Bunck MC, Gooren L. Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. *J Androl* 2009;30(6):726-733.
11. Bhasin S, Cunningham GR, Hayes SJ et al. Task Force, Endocrine Society. Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95(6):2536-2559.
12. Bhasin S, Cunningham GR, Hayes FJ et al. Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2006;91(6): 1995-2010.
13. Wang C, Nieschlag E, Swerdloff R et al. ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment, and monitoring of late-onset hypogonadism in males. *Aging Male* 2009;12(1):5-12.
14. Petak SM, Nankin HR, Spark RF et al. American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients—2002 update. *Endocr Pract* 2002;8(6):440-456.
15. Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM Study. *Int J Clin Pract* 2006;60(7):762-769.
16. Araujo AB, O'Donnell AB, Brambilla DJ et al. Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts Male Aging Study. *J Clin Endo Metab* 2004;89(12):5920-5926.
17. Araujo AB, Esche GR, Kupelian V et al. Prevalence of symptomatic androgen deficiency in men. *J Clin Endocrinol Metab* 2007;92(11): 4241-4247.
18. Hall SA, Araujo AB, Esche GR et al. Treatment of symptomatic androgen deficiency. *Arch Intern Med* 2008;168(10):1070-1076.
19. Wu FC, Tajar A, Beynon JM et al, EMAS Group. Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med* 2010;363(2):123-135.

20. Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. *J Clin Endocrinol Metab* 2008;93(1):68-75.
21. Manchikanti L, Fellows B, Ailinani H, Pampati V. Therapeutic use, abuse, and nonmedical use of opioids: a ten-year perspective. *Pain Physician* 2010;13(5):401-435.
22. Coviello AD, Matsumoto AM, Bremner WJ et al. Low-dose human chorionic gonadotropin maintains intratesticular testosterone in normal men with testosterone-induced gonadotropin suppression. *J Clin Endocrinol Metab* 2005;90(5):2595-2602.
23. Dhindsa S, Miller MG, McWhirter ML et al. Testosterone concentrations in diabetic and nondiabetic obese men. *Diabetes Care* 2010;33(6):1186-1192.
24. Hak AE, Witteman JC, de Jong FH, Geerlings MI, Hofman A, Pols HA. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study. *J Clin Endocrinol Metab* 2002;87(8):3632-3639.
25. Yeap BB, Hyde Z, Norman PE, Chubb SAP, Golledge J. Associations of total testosterone, sex hormone-binding globulin, calculated free testosterone, and luteinizing hormone with prevalence of abdominal aortic aneurysm in older men. *J Clin Endocrinol Metab* 2010;95(3):1123-1130.
26. Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. *J Clin Endocrinol Metab* 2008;93(1):68-75.
27. Tivesten A, Vandenput L, Labrie F et al. Low serum testosterone and estradiol predict mortality in elderly men. *J Clin Endocrinol Metab* 2009;94(7):2482-2488.
28. Thompson IM, Tangen CM, Goodman PJ, Probstfield JL, Moinpour CM, Coltman CA. Erectile dysfunction and subsequent cardiovascular disease. *JAMA* 2005;294(23):2996-3002.
29. Qaseem A, Snow V, Denberg TD et al. Hormonal testing and pharmacologic treatment of erectile dysfunction: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2009;151(9):639-649.
30. Edelstein D, Dobs A, Basaria S. Emerging drugs for hypogonadism. *Expert Opin Emerg Drugs* 2006;11(4):685-707.
31. Gooren LJ, Behre HM, Saad F, Frank A, Schwerdt S. Diagnosing and treating testosterone deficiency in different parts of the world. Results from global market research. *Aging Male* 2007;10(4): 173-181.
32. Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. Position Statement: Utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. *J Clin Endocrinol Metab* 2007;92(2):405-413.
33. Rosen RC, Araujo AB, Connor MK et al. Assessing symptoms of hypogonadism by self-administered questionnaire: qualitative findings in patients and controls. *Aging Male* 2009;12(2-3):77-85.
34. Rosen RC, Araujo AB, Connor MK et al. The NERI hypogonadism screener: psychometric validation in male patients and controls. *Clin Endocrinol* 2011;74(2):248-256.
35. Morgentaler A. Testosterone and prostate cancer: what are the risks for middle-aged men? *Urol Clin N Am* 2011;38(2):119-124.
36. Morgentaler A, Lipshultz LI, Bennett R, Sweeney M, Avila D Jr, Khera M. Testosterone therapy in men with untreated prostate cancer. *J Urol* 2011;185(4):1256-1260.
37. Miner MM. Low testosterone medscape CME expert column series. issue 1: testosterone deficiency in men: common and under-recognized. 2011. Available at: http://www.staging.medscape.org/viewarticle/746602. Accessed August 3, 2011.
38. Corona G, Rastrelli G, Forti G, Maggi M. Update in testosterone therapy for men (CME). *J Sex Med* 2011;8(3):639-654.
39. Miner MM, Sadovsky R. Evolving issues in male hypogonadism: evaluation, management, and related comorbidities. *Cleveland Clin J Med* 2007;74(Suppl 3):S38-S46.
40. Dandona P, Rosenberg MT. A practical guide to male hypogonadism in the primary care setting. *Int J Clin Pract* 2010; 64(6):682-696.
41. Swerdloff RS, Wang C. The testis and male sexual function. In: Goldman L, Ausiello D, eds. Goldman: Cecil Medicine. 23rd ed. Philadelphia, PA: Saunders Elsevier 2008:253.
42. Arver S, Lehtihet M. Current guidelines for the diagnosis of testosterone deficiency. *Front Horm Res* 2009;37:5-20.
43. Bassil N, Morley JE. Late-life onset hypogonadism: a review. *Clin Geriatr Med* 2010;26(2):197-222.
44. Buvat J, Maggi M, Gooren L et al. Endocrine aspects of male sexual dysfunctions. *J Sex Med* 2010;7(4 Pt 2):1627-1656.
45. Emmelot-Vonk MH, Verhaar HJ et al. Low testosterone concentrations and the symptoms of testosterone deficiency according to the Androgen Deficiency in Ageing Males (ADAM) and Ageing Males' Symptoms rating scale (AMS) questionnaires. *Clin Endocrinol (Oxf)* 2011;74(4):488-494.
46. Morley JE, Perry HM 3rd, Kevorkian RT, Patrick P. Comparison of screening questionnaires for the diagnosis of hypogonadism. *Maturitas* 2006;53(4):424-429.
47. Am Society Androl Position Statement: Testosterone Deficiency. *J Androl* 2006;27(2):133-134.
48. Citron JT, Ettinger B, Rubinoff H et al. Prevalence of hypothalamic-pituitary imaging abnormalities in impotent men with secondary hypogonadism. *J Urol* 1996;155(2):529-533.
49. Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. *J Clin Endocrinol Metab* 2006;91(11):4335-4343.
50. Lackner JE, Rücklinger E, Schatzl G, Lunglmayr G, Kratzik CW. Are there symptom-specific testosterone thresholds in aging men? *BJU Int* 2011;108(8):1310-1315.
51. Traish AM, Miner MM, Morgentaler A, Zitzmann M. Testosterone deficiency. *Am J Med* 2011;124(7):578-587.
52. Aaronson AJ, Morrissey RP, Nguyen CT, Willix R, Schwarz ER. Update on the safety of testosterone therapy in cardiac disease. *Expert Opin Drug Saf* 2011;10(5):697-704.
53. Lunenfeld B, Nieschlag E. Testosterone therapy in the aging male. *Aging Male*. 2007;10(3):139-153.
54. Yeap BB, Almeida OP, Hyde Z et al. Healthier lifestyle predicts higher circulating testosterone in older men: the Health In Men Study. *Clin Endocrinol* 2009;70(3):455-463.
55. Heufelder AE, Saad F, Bunck MC, Gooren L. Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. *J Androl* 2009;30(6):726-733.
56. Bhasin S, Basaria S. Diagnosis and treatment of hypogonadism in men. *Best Pract Res Clin Endocrinol Metab* 2011;25(2):251-270.
57. Isidori AM, Giannetta E, Gianfrilli D, et al. Effects of testosterone on sexual function in men: results of a meta-analysis. *Clin Endocrinol (Oxf)* 2005;63(4):381-394.
58. Permpongkosol S, Tantirangsee N, Ratana-olarn K. Treatment of 161 men with symptomatic late onset hypogonadism with long-acting parenteral testosterone undecanoate: effects on body composition, lipids, and psychosexual complaints. *J Sex Med* 2010;7(11):3765-3774.
59. Morgentaler A. A 66-year-old man with sexual dysfunction. *JAMA* 2004;291(24):2994-3003.
60. Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *J Urol* 2004;172(2): 658-663.
61. Kenny AM, Prestwood KM, Gruman CA, Marcello KM, Raisz LG. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. *J Gerontol A Biol Sci Med Sci* 2001;56(5):M266-M272.
62. Isidori AM, Giannetta E, Greco EA et al. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. *Clin Endocrinol (Oxf)* 2005; 63(3):280-293.

63. Neischlag E, Behre HM, Bourchard P et al. Testosterone replacement therapy: current trends and future directions. *Hum Reprod Update* 2004;10(5):409-419.
64. Srinivas-Shankar U, Roberts SA, Connolly MJ et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 2010;95(2):639-650.
65. Isidori AM, Giannetta E, Greco EA et al. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. *Clin Endocrinol (Oxf)* 2005; 63(3):280-293.
66. Travison TG, Basaria S, Storer TW et al. Clinical meaningfulness of the changes in muscle performance and physical function associated with testosterone administration in older men with mobility limitation. *J Gerontol A Biol Sci Med Sci.* 2011;66(10): 1090-1099.
67. Fernández-Balsells MM, Murad MH, Barwise A et al. Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011;96:905-912.
68. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. *N Engl J Med* 2004; 350(5):482-492.
69. Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous Hormones and Prostate Cancer Collaborative Group. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *J Natl Cancer Inst* 2008;100(3):170-183.
70. Shabsigh R, Crawford ED, Nehra A, Slawin KM. Testosterone therapy in hypogonadal men and potential prostate cancer risk: a systematic review. *Int J Impot Res* 2009;21(1):9-23.
71. Morgentaler A, Traish AM. Shifting the paradigm of testosterone and prostate cancer: the Saturation Model and the limits of androgen-dependent growth. *Eur Urol* 2009;55(2):310-320.
72. Morgentaler A, Lipshultz LI, Bennett R, Sweeney M, Avila D Jr, Khera M. Testosterone therapy in men with untreated prostate cancer. *J Urol* 2011;185(4):1256-1260.
73. Vigen R, O'Donnell CI, Baron AE et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 2013;310(17): 1829-1836.
74. Finkle WD, Greenland S, Ridgeway GK et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One* 2014;9(1):e85805.
75. Ioannidis JP. Contradicted and initially stronger effects in highly cited clinical research. *JAMA* 2005;294(2):218-228.
76. Morgentaler A, Kacker R. Testosterone and cardiovascular risk—deciphering the statistics. *Nat Rev Urol* 2014;11(3):131-132.
77. Basaria S, Coviello AD, Travison TD et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010; 363(2):109-122.
78. Traish AM, Guay AT, Morgentaler A. Death by testosterone? We think not! *J Sex Med* 2014;11(3):624-629.
79. Oskui PM, French WJ, Herring MJ, Mayeda GS, Burstein S, Kloner RA. Testosterone and the cardiovascular system: a comprehensive review of the clinical literature. *J Am Heart Assoc* 2013;2(6):e000272.
80. English KM, Steeds RP, Jones TH, Diver MJ, Channer KS. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double blind, placebo-controlled study. *Circulation* 2000;102(16): 1906-1911.
81. Stout M,Tew GA, Doll H et al. Testosterone therapy during exercise rehabilitation in male patients with chronic heart failure who have low testosterone status: a double-blind randomized controlled feasibility study. *Am Heart J* 2012;164(6):893-901.
82. Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab* 2012;97(6):2050-2058.
83. Muraleedharan V, Marsh H, Kapoor D, Channers KS, Jones TH. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. *Eur J Endocrinol* 2013;169(6):725-733.
84. Edelstein D, Basaria S. Testosterone undecanoate in the treatment of male hypogonadism. *Expert Opin Pharmacother* 2010;11(12):2095-2106.
85. Steidle CP. New advances in the treatment of hypogonadism in the aging male. *Rev Urol* 2003;5(Suppl 1):S34-S40.
86. Calof M, Singh AB, Lee ML et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *J Gerontol A Biol Sci Med Sci* 2005;60(11):1451-1457.
87. Lakshman KM, Basaria S. Safety and efficacy of testosterone gel in the treatment of male hypogonadism. *Clin Interv Aging* 2009:4:397-412.
88. Kaufman JM, Miller MG, Garwin JL, Fitzpatrick S, McWhirter C, Brennan JJ. Efficacy and safety study of 1.62% testosterone gel for the treatment of hypogonadal men. *J Sex Med* 2011;8(7): 2079-2089.
89. Morgentaler A, Dobs AS, Kaufman JM et al. Long acting testosterone undecanoate therapy in men with hypogonadism: results of a pharmacokinetic clinical study. *J Urol* 2008;180(6): 2307-2313.
90. Kaminetsky JC, Moclair B, Hemani M, Sand M. A phase IV prospective evaluation of the safety and efficacy of extended release testosterone pellets for the treatment of male hypogonadism. *J Sex Med* 2011;8(4):1186-1196.