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Review Article

Optimizing Diagnostic Accuracy and Treatment Decisions in Men With Testosterone Deficiency

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ABSTRACT

Objective: This narrative review offers a guideline-based approach for optimizing diagnostic evaluation and treatment decision making in men being evaluated for testosterone deficiency.
Methods: A narrative review.
Results: Testosterone deficiency is a clinical syndrome that results from the inability of the testes to produce normal amounts of testosterone and is characterized by a constellation of symptoms and signs associated with consistently low testosterone concentrations. The diagnosis of testosterone deficiency is made by the ascertainment of symptoms and signs; the measurement of total and, if indicated, free testosterone levels in early-morning fasting samples on ≥2 days; the measurement of luteinizing hormone and follicular-stimulating hormone levels to distinguish primary from secondary hypogonadism; and an additional evaluation to ascertain the cause of testosterone deficiency. Nonspecificity of symptoms and signs, variations in testosterone levels over time, inaccuracy in the measurement of total and free testosterone levels, variations in binding protein concentrations, and suboptimal reference ranges contribute to diagnostic inaccuracy. Testosterone treatment is indicated for men with symptomatic testosterone deficiency. Testosterone treatment should be avoided in men with prostate or breast cancer, erythrocytosis, thrombophilia, increased risk of prostate cancer or severe lower urinary tract symptoms without prior urologic evaluation, a recent major adverse cardiovascular event, uncontrolled heart failure, or severe untreated sleep apnea. Testosterone replacement therapy should be accompanied by a standardized monitoring plan.
Conclusion: A shared decision of the patient and physician to treat should be guided by the consideration of the burden of symptoms, potential benefits and risks, patient's values, and the cost and burden of long-term treatment and monitoring.

The Changing Epidemiology of Testosterone Deficiency in Men

Testosterone deficiency, a clinical syndrome that results from the inability of the testes to produce normal amounts of testosterone, is characterized by a constellation of symptoms and signs associated with consistently low circulating testosterone concentrations.[1] The prevalence and incidence of organic testosterone deficiency, due to known diseases of the testes, pituitary, or hypothalamus in the general population, are unknown. In the Boston Area Community Health Survey,[2] the prevalence of symptomatic androgen deficiency in men aged 30 to 79 years was 5.6%. In the European Male Aging Study,[3] 0.1% of men aged 40 to 49 years, 0.6% of those aged 50 to 59 years, 3.2% of those aged 60 to 69 years, and 5.1% of those aged 70 to 79 years had at least 3 sexual symptoms associated with a total testosterone level of <317 ng/dL and a free testosterone level of <63.4 pg/mL; furthermore, prevalence was higher among men with obesity and chronic diseases.[2,4]

Only a small fraction of men receiving testosterone therapy have a known condition of the testes, pituitary, and hypothalamus.[5,6] In a national cohort of men receiving care in the Veterans Administration Healthcare System, only 6.3% of men receiving testosterone

Abbreviations: CDC, Center for Disease Control and Prevention; FGF, fibroblast growth factor; FSH, follicular-stimulating hormone; GnRH, gonadotropin-releasing hormone; IHH, idiopathic hypogonadotropic hypogonadism; LH, luteinizing hormone; SD, standard deviation; SHBG, sex hormone-binding globulin.

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treatment had an identifiable disorder of the testes, pituitary, or hypothalamus[5]; the use of opioids and obesity were the strongest predictors of the receipt of a testosterone prescription.[5] Men, aged 40 to 74 years, are the most frequent recipients of testosterone prescriptions,[6,7] suggesting that a sizable proportion of testosterone therapy is prescribed for age-related declines in testosterone levels, for which testosterone therapy has not been approved. Prescription-based opioid use and prior anabolic androgenic steroid use have emerged as important contributors for men receiving a testosterone prescription.[5,8] Comorbid conditions, such as obesity, depression, and diabetes, are associated with increased likelihood of receiving a testosterone prescription.[5]

Before the advent of testosterone assays, most hypogonadal men were diagnosed based on the presence of clinical features such as the loss of secondary sex characteristics, delayed pubertal development, infertility, gynecomastia, and small testes. In men with severe organic hypogonadism, the diagnosis of testosterone deficiency was readily apparent. Today, a majority of patients being evaluated for hypogonadism in the United States are middle-aged and older men,[5,6] whose symptoms overlap with those associated with aging and whose testosterone levels are either low to normal or only slightly below the lower limit of the normal range; in men with nonspecific symptoms and testosterone levels that are only slightly below the lower limit of the normal range, the risk of misdiagnosis is high. This review offers a guideline-based approach for reducing inaccuracy in the diagnostic evaluation of testosterone deficiency and enabling more patient-centric decision making about treatment.

Diagnostic Evaluation of Men Suspected of Having Testosterone Deficiency

Evaluation for testosterone deficiency should be performed in men who seek medical attention for conditions that are associated with high risk of testosterone deficiency and in whom testosterone treatment might be beneficial, such as men presenting with low sexual desire, erectile dysfunction, infertility, gynecomastia, HIV-associated weight loss, osteoporosis, or low trauma fracture; men using opioids, glucocorticoids, and androgenic anabolic steroids; and men treated with cancer chemotherapeutic agents or pelvic radiation.[9–16] Population-level screening of men for testosterone deficiency is not recommended.[1]

In the diagnostic evaluation of men who present with symptoms suggestive of testosterone deficiency,[1,9] the first step is to ascertain symptoms and perform a general health evaluation to exclude the possibility of a systemic illness, such as cancer, chronic infection, or inflammatory disorder; body image and eating disorders; excessive physical exercise; or the use of medications, such as opioids, glucocorticoids, androgenic anabolic steroids, or other medications that inhibit testosterone's production, action, or bioavailability (Fig.). The second step is to measure total testosterone concentration and, if indicated, free testosterone concentration using reliable assays of blood samples obtained in the morning after an overnight fast. If the total testosterone levels are low, they should be confirmed by repeating the measurement and, if indicated, by measuring free testosterone concentration. In men deemed testosterone deficient, serum luteinizing hormone (LH) and follicular-stimulating hormone (FSH) levels should be measured to determine the underlying cause of testosterone deficiency.

Sources of Diagnostic Inaccuracy

Although the diagnostic evaluation of testosterone deficiency in men is conceptually uncomplicated, in practice, the risk of misclassification is high, especially in men whose testosterone levels are within 2 standard deviations (SDs) of the threshold used to define testosterone deficiency (Table 1). Nonspecificity of symptoms and signs, variations in testosterone levels over time due to biologic factors, imprecision and inaccuracy in the measurement of total and free testosterone concentrations, variations in binding protein concentrations, and suboptimal reference ranges contribute to diagnostic inaccuracies.

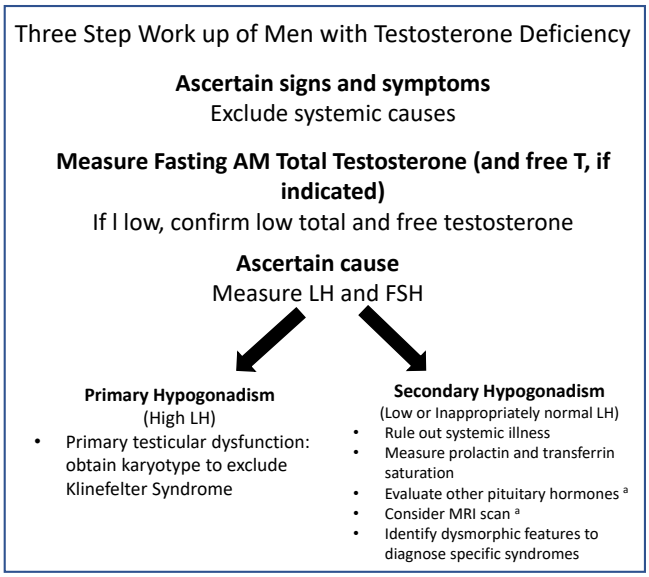

Fig. Three-step diagnostic evaluation of men with testosterone deficiency. *AM* = ante meridiem; *IGF-1* = insulin-like growth factor-1; *FSH* = follicle-stimulating hormone; *LH* = luteinizing hormone; *MRI* = magnetic resonance imaging; *TSH* = thyroid-stimulating hormone; *T* = testosterone; *T4* = thyroxine.
*The need for magnetic resonance imaging and a detailed pituitary workup in men deemed to have secondary hypogonadism should be guided by the severity of testosterone deficiency and the level of suspicion of a pituitary space-occupying lesion. Diagnostic yield can be improved by performing a more detailed search for a pituitary lesion in men with a baseline total testosterone level of <160 ng/dL, hyperprolactinemia, or the evidence of a mass effect (eg, headaches or visual field impairment). The evaluation of other pituitary hormones should include measurements of serum IGF-1, TSH, and free T4 levels and screening for hypercortisolism if Cushing syndrome is suspected.

Nonspecificity of Symptoms and Signs

There is substantial overlap between age-related symptoms and those due to testosterone deficiency. Sexual symptoms, such as low libido, loss of morning erections, and erectile dysfunction, were the most consistently associated with low testosterone levels in the European Male Aging Study.[3] The clinical features with higher levels of specificity include delayed or absent pubertal development, very small testes (<6 mL), loss of body hair, and sexual symptoms (reduced sexual desire and activity, decreased spontaneous erections, and erectile dysfunction). Gynecomastia is more likely to occur in patients with primary hypogonadism than in patients with secondary hypogonadism but is commonly present in middle-aged and older men, even in those without testosterone deficiency.[17] Many questionnaires have been developed to aid in the diagnosis of hypogonadism, but their specificity is low; therefore, their use is not recommended.[18–20]

Biologic Factors Contributing to Variation in Testosterone Concentrations

Testosterone concentrations vary greatly among men and within the same person over time.[21–23] In the Boston Area Community Health Study, 21% of men with an initial testosterone

Table 1
Strategies to Reduce Diagnostic Inaccuracy in the Evaluation of Men Suspected of Having Testosterone Deficiency

Sources of diagnostic inaccuracy	Steps to minimize diagnostic inaccuracy
Nonspecificity of symptoms and signs	Consider that some of the following clinical features are more strongly associated with testosterone deficiency: Incomplete or delayed sexual development Loss of body hair (axillary and pubic) Very small testes (<6 mL each) Sexual symptoms (reduced sexual desire, decreased spontaneous erections, and erectile dysfunction)
Biologic variation	Measure early-morning testosterone level on ≥2 d. Obtain blood sample in a fasting state Avoid evaluating testosterone deficiency during an acute illness. Avoid making a diagnosis based on 1 value.
Imprecision and inaccuracy of total testosterone assays	Chose an accurate assay: Choose an LC-MS/MS assay, if available, because LC-MS/MS assays have the highest precision and accuracy in the low range. Choose a laboratory that is certified by an accuracy-based benchmark, such as the CDC's HoST program.
Alterations in binding proteins	Measure the free testosterone level when a binding protein abnormality is suspected or when the total testosterone levels are in the borderline zone. Use the equilibrium dialysis method for the measurement of free testosterone level in a reliable laboratory.

Abbreviations: CDC = Center for Disease Control and Prevention; HoST = hormone standardization program for testosterone; LC-MS/MS = liquid chromatography-tandem mass spectrometry.

concentration of <300 ng/dL had a normal testosterone concentration upon subsequent testing.[21]

Diurnal, circadian, and circannual rhythms and episodic secretion contribute to a variation in testosterone concentrations.[21,23,24] Testosterone concentrations exhibit a diurnal variation, with peak values in the morning; this diurnal rhythm is dampened in older men.[23] Testosterone concentrations are suppressed by food intake[25,26] and during an acute illness. Therefore, testosterone concentrations should be measured after an overnight fast, typically within 4 to 5 hours after waking up in the morning. A substantial fraction of the population-level variation in total and free testosterone concentrations is due to heritable factors.[27,28] Genome-wide association studies have identified a large number of loci associated with total and free testosterone concentrations.[27,29,30]

Influence of Alterations in Binding Protein Concentrations

Circulating testosterone is bound largely to sex hormone-binding globulin (SHBG) and albumin and to a lesser degree to orosomucoid and cortisol-binding globulin; only 1% to 4% of the circulating testosterone is unbound or free.[31] The circulating concentrations of the binding proteins, particularly SHBG, affect the levels of the bound fraction and, thereby, the total testosterone concentration. The free hormone hypothesis states that the intracellular concentrations and biologic activity of a hormone are dependent on the concentrations of the free rather than the protein-bound hormone in the plasma.[31] Therefore, the measurement of free testosterone concentration is recommended in men suspected of having alterations in the SHBG concentration.[1] SHBG concentrations increase with age, hyperthyroidism, inflammatory disorders, hepatitis, HIV infection, some SHBG polymorphisms, and medications (eg, estrogens, thyroid hormones, and anticonvulsants) and are decreased in men with obesity, type 2 diabetes, metabolic syndrome, hypothyroidism, acromegaly, nephrotic syndrome, some SHBG polymorphisms, and medications (androgens, glucocorticoids, and progestins).[31] Men with low SHBG concentrations have lower total testosterone concentrations, sometimes even below the normal range, but free testosterone concentrations may remain within the normal range.[32] The measurement of free testosterone should also be performed in men whose total testosterone concentration is modestly above or below the lower limit of the normal range (eg, 200-400 ng/dL).[33,34]

Free testosterone concentration is ideally measured using the equilibrium dialysis method, performed under standardized conditions.[1,31] Direct tracer analog methods for measuring free testosterone concentrations are inaccurate, and therefore, their use is not recommended.[35] Although several equations to estimate free testosterone concentration from total testosterone, SHBG, and albumin concentrations have been published,[36–38] the estimation of free testosterone concentration performed using these equations are predicated upon accurate measurements of total testosterone, SHBG, and albumin concentrations.[31,35] Furthermore, equations that are based on a linear model of testosterone's binding to SHBG assume a fixed binding affinity (approximately 1 nM)[31] and ignore the competing presence of other sex steroids, such as dihydrotestosterone and estradiol. Recent studies using modern biophysical techniques have suggested that the binding of testosterone and estradiol to an SHBG dimer is a dynamic process that involves allosteric interactions between binding sites on each of the 2 SHBG monomers such that the binding affinities of the 2 sites are not equivalent.[36,39] The binding of a ligand to the first monomer influences the conformational and energetic states of both the monomers.[39] The estimation of free testosterone concentration based on an ensemble allosteric model provides a close approximation of concentrations measured using equilibrium dialysis[36]; the computations of free testosterone concentrations using the ensemble allostery model can be obtained at https://tru-t.org. Because of dynamic changes in the binding affinity of SHBG upon ligand binding, depending on the ligand and SHBG concentrations, no equation can accurately estimate free testosterone concentration under all conditions.[39]

The term "bioavailable testosterone" refers to non-SHBG–bound testosterone and is based on the assumption that testosterone is bound to albumin with low affinity and can dissociate from it in tissue capillaries, especially in organs with a long transit time, such as the liver and brain. Bioavailable testosterone concentrations are measured by ammonium sulfate precipitation or calculated from total testosterone, SHBG, and albumin concentrations.[31,35] Measurements of bioavailable testosterone concentrations are technically challenging and associated with high imprecision.[31]

There are multiple, allosterically coupled binding sites for testosterone on albumin.[40] Testosterone shares these binding sites

with free fatty acids and commonly used drugs, such as aspirin, ibuprofen, and coumadin,[40] which can displace testosterone from albumin, affecting its bioavailability.

Methodologic Factors That Contribute to Diagnostic Inaccuracy

Total testosterone concentration can be measured using immunoassays, immunometric assays, and liquid chromatography-tandem mass spectrometry.[35] Platform-based immunoassays offer convenience and rapid throughput but suffer from inaccuracy, especially for a low range of testosterone concentration, which is prevalent in hypogonadal men.[35,41] Liquid chromatography-tandem mass spectrometry assays have emerged as the method of choice, with the highest accuracy and precision for the measurement of total testosterone concentration, and are now widely available. With the establishment of a process for accuracy-based certification of laboratories by the Center for Disease Control and Prevention's (CDC) hormone standardization program for testosterone, interlaboratory variation in CDC-certified laboratories has decreased substantially.[42,43]

Reference Ranges for Total and Free Testosterone

Reference ranges for total testosterone reported by commercial laboratories vary substantially because of the lack of standardization of testosterone assays, calibrator differences, and differences in the reference populations included. A harmonized reference range for total testosterone was generated based on analyses of data from 4 cohorts of community-dwelling men in the United States and Europe.[44] The assays used in these 4 cohorts were cross-calibrated against a higher order method by the CDC, and the values from each cohort were harmonized to the CDC-standardized measurements using Deming regression. The harmonized reference range for the total testosterone concentration in healthy nonobese men, aged 19 to 39 years, was 264 to 916 ng/dL using the 2.5th and 97.5th percentiles and 303 to 852 ng/dL using the 5th and 95th percentiles[44]; the age-specific 2.5th, 5th, 95th, and 97.5th percentile reference values are shown in Table 2. These reference values can be used for all testosterone assays and laboratories that are certified by the CDC's hormone standardization program for testosterone.

Table 2
Model-Based Estimates of Population Percentiles for Harmonized Total Testosterone Concentrations (ng/dL) Based on the Data of Nonobese Men ($n = 6933$) and in all Men ($n = 9054$) in 4 Cohorts From the United States and Europe[a]

Percentile	Nonobese men: Age (y)					
	19-39	40-49	20-39	60-69	70-79	80-99
2.5	267	235	219	218	218	157
5.0	304	273	256	254	252	218
95.0	850	839	839	839	839	839
97.5	929	929	929	929	926	913
Percentile	All men: Age (y)					
	19-39	40-49	50-59	60-69	70-79	80-99
2.5	229	208	192	190	190	119
5.0	273	243	222	221	220	203
95.0	834	813	812	812	812	812
97.5	902	902	902	902	902	902

Adapted with permission from the study by Travison et al.[44]

[a] The harmonized reference ranges for total testosterone were derived from 9054 community-dwelling men in 4 cohort studies in the United States and Europe: Framingham Heart Study, European Male Aging Study, Osteoporotic Fractures in Men Study, and Male Sibling Study of Osteoporosis. The testosterone concentrations in 100 participants in each of the 4 cohorts were measured using a reference method at the Center for Disease Control and Prevention and using normalizing equations; Passing-Bablok regression was used to generate harmonized values, which were used to derive standardized, age-specific reference ranges.

The lack of standardization of the equilibrium dialysis procedures for the measurement of free testosterone has retarded efforts at generating harmonized reference ranges.[35] A reference range for free testosterone, using an ensemble allostery method that was validated against the equilibrium dialysis method using data from the Framingham Heart Study and the European Male Aging Study, has been published.[36]

The lower limit of the normal range should not be viewed as an absolute cut point; moreover, the assay's imprecision should be taken into consideration, especially when the reported testosterone concentration is within 2 SDs of the cut point. Multiple measured concentrations below the lower limit of the normal range increase the likelihood that the patient has testosterone deficiency but do not completely eliminate the risk of misclassification.

Additional Clinical and Laboratory Data Can Improve Diagnostic Accuracy

Testicular volume, secondary sex characteristics, and LH and FSH levels can be valuable in improving diagnostic accuracy, especially when the total testosterone levels are within 2 SDs of the lower limit of the normal range. For instance, in a young man presenting with sexual dysfunction with a total testosterone level of 300 ng/dL, elevated serum LH and FSH levels can strengthen the diagnosis of primary hypogonadism. A testicular volume of 2 mL would point toward a diagnosis of Klinefelter syndrome. The presence of unexplained mild normocytic anemia, loss of body hair, and unexplained osteoporosis can offer additional support for the diagnosis.

Evaluation to Determine the Cause of Testosterone Deficiency

In men deemed to have testosterone deficiency, the measurement of serum LH and FSH levels is recommended to determine whether the patient has primary or secondary hypogonadism.[1] Biotin supplements can interfere with some LH and FSH assays; therefore, these supplements should be stopped at least 3 days before the blood test depending on how much biotin the patient is taking. Men with elevated LH and FSH levels in association with low testosterone levels have primary testicular dysfunction. Karyotyping should be performed in these men to confirm whether they have Klinefelter syndrome, a common cause of primary testicular dysfunction. The other causes of primary testicular dysfunction include cancer chemotherapy, radiation to the testes, cryptorchidism, trauma, torsion, infectious orchitis, HIV infection, anorchia syndrome, and myotonic dystrophy.

Low or inappropriately normal LH and FSH levels in association with low testosterone levels suggest secondary hypogonadism due to disorders of the pituitary or hypothalamus. The causes of secondary hypogonadism include severe obesity; hyperprolactinemia; hemochromatosis; the use of opioids, glucocorticoids, androgenic-anabolic steroids, or androgen deprivation therapy with gonadotropin-releasing hormone (GnRH) agonists or antagonists; body image and eating disorders; idiopathic hypogonadotropic hypogonadism (IHH); head trauma; pituitary tumors or infiltrative disease; acromegaly and hypercortisolism; and pituitary surgery or radiation. Conditions such as aging, heavy alcohol use, hemochromatosis, and some genetic disorders may be associated with dual defects in the testes and pituitary.

In men with secondary hypogonadism, serum prolactin and ferritin levels should be measured, and other pituitary hormones should be evaluated. An imaging study, such as magnetic resonance imaging of the pituitary and hypothalamus, may be indicated to rule out the possibility of a space-occupying lesion, but the cost effectiveness of an imaging study in the evaluation of middle-aged men with sexual dysfunction has been debated upon because the

incidence of pituitary space-occupying lesions among such men is low. Diagnostic yield can be improved by performing imaging studies in men whose total testosterone level is <150 ng/dL or those who have hyperprolactinemia, panhypopituitarism, or symptoms of tumor mass effect, such as new-onset headache or a visual field defect.

The diagnosis of IHH is made after excluding other known causes of gonadotropin deficiency. IHH is a heterogeneous group of disorders that can be broadly categorized into anosmic and normosmic disorders.[45] Mutations in genes involved in the development and migration of GnRH neurons or in the regulation of GnRH secretion have been shown to be linked to GnRH deficiency, although the genetic defect remains elusive in nearly two-third of cases.[46] The anosmic form of GnRH deficiency, referred to as Kallmann syndrome, can result from mutations in ≥1 neurodevelopmental genes associated with olfactory bulb morphogenesis or the migration of GnRH neurons from their origin in the region of the olfactory placode to their final location in the preoptic region of the hypothalamus. Mutations in the anosmin gene; genes involved in fibroblast growth factor (FGF) signaling (*FGF8*, *FGFR1*, *FGF17, IL17RD, DUSP6, SPRY4,* and *FLRT3);* genes involved in prokineticin *(PROK)* signaling *(PROK2* and *PROK2R*); N-methyl-D-aspartate receptor synaptonuclear signaling and neuronal migration factor (*NSMF*); as well as *NELF, WDR11, SOX10, TUBB3 SEMA3, HS6ST1, CHD7,* and *FEZF1* have been described in patients with Kallmann syndrome.[46] The normosmic form of GnRH deficiency results from defects in pulsatile GnRH secretion, its regulation, or its action and has been shown to be associated with mutations in *GnRHR*, *GNRH1*, *KISS1R*, *TAC3*, *TACR3*, *NROB1 (DAX1)*, gene encoding leptin, or gene encoding leptin receptor. Some mutations, such as those in *PROK2*, *PROKR2*, *NSMF*, *FGFR1*, *FGF8*, *SEMA3A*, *WDR11*, and *CHD7*, have been shown to be associated with both anosmic and normosmic forms of IHH.[46] The presence of dysmorphic features, such as marked obesity, anosmia or hyposmia, defects of the urogenital system, deafness, abnormal movements, mental retardation, visual deficit, skin lesions, or short stature, might point toward specific genetic syndromes.[45]

A Patient-Centric Nonbinary Approach to Treatment Decision Making

The guidelines of the Endocrine Society and the American Urological Association recommend making a diagnosis of hypogonadism in men with symptoms and signs of testosterone deficiency and consistently low total testosterone concentrations and, when indicated, free testosterone concentrations (Table 3).[1,47] Testosterone treatment is indicated for men with testosterone deficiency to induce and maintain secondary sex characteristics and to correct the symptoms of testosterone deficiency.[1,47]

Testosterone therapy is associated with increased risk of harm in patients who have breast or prostate cancer; a palpable prostate nodule or induration; a prostate-specific antigen level of >3ng/mL without further urologic evaluation; elevated hematocrit; untreated severe obstructive sleep apnea; severe lower urinary tract symptoms; uncontrolled heart failure, myocardial infarction, or stroke within the last 6 months; or thrombophilia and should not be given to such patients.[1] Men, aged ≥55 years, with testosterone deficiency who are being considered for testosterone treatment should undergo an evaluation for prostate cancer risk before starting testosterone treatment. In hypogonadal men at high risk of prostate cancer (eg, African Americans and men with a first-degree relative with diagnosed prostate cancer), this evaluation may be performed at a younger age (≥40 years). Prostate cancer screening has some risk; therefore, the decision to perform prostate cancer screening should be a shared decision of the patient and the clinician.

Table 3

Considerations in Making a Shared Decision to Treat With Testosterone

1. Testosterone treatment is indicated for men who have symptomatic testosterone deficiency to induce and maintain secondary sex characteristics and to relieve symptoms of testosterone deficiency.
2. Testosterone treatment should be prescribed only after a discussion of the long-term benefits, risks, and uncertainties of MACE and prostate cancer. The burden of symptoms should be weighed against the potential risks and the cost and burden of long-term treatment and monitoring.
3. Testosterone treatment should be avoided in men who are planning fertility in the near future.
4. Testosterone treatment should be avoided in men with prostate or breast cancer, polycythemia, thrombophilia, uncontrolled heart failure, or untreated severe sleep apnea or in men with increased risk of prostate cancer or severe lower urinary tract symptoms without urologic evaluation.
5. A patient's values and their tolerance of the cost, burden, and uncertainties of long-term benefits and risks should be considered.
6. Testosterone treatment can be instituted with any of the approved testosterone formulations based on the consideration of pharmacokinetics, patient preference, cost, and convenience.

Abbreviation: MACE = major adverse cardiovascular event.

The clinician should weigh the burden of symptoms and conditions associated with testosterone deficiency (eg, anemia and osteoporosis) against the potential of harm and the cost and burden of treatment and monitoring. This assessment of benefit-to-risk ratio is particularly important in men whose testosterone levels are within 2 SDs of the lower limit of the normal range because the risk of misdiagnosis is high in such patients.

It is important to distinguish organic testosterone deficiency due to known diseases of the testes, pituitary, and hypothalamus from that due to an age-related decline in testosterone levels. Testosterone treatment is not recommended for all older men with age-related decline in testosterone levels.[1] Testosterone treatment may be offered on an individualized basis to older men who experience distressing symptoms or conditions associated with testosterone deficiency (eg, sexual dysfunction or unexplained anemia) after a discussion of the uncertainty of the long-term benefits and risks of testosterone treatment.[1]

A limited amount of data suggests that testosterone treatment is associated with improved pain sensitivity, sexual desire, body composition, and some aspects of the quality of life and lower rates of anemia and bone fractures in men with opioid-associated hypogonadism.[48,49] Clinicians should consider testosterone treatment in men with opioid-associated hypogonadism who have sexual symptoms, unexplained anemia, osteoporosis and in whom the discontinuation of opioid medication seems unlikely.[1]

Potential Benefits and Risks of Testosterone Treatment

Most testosterone efficacy trials in men with hypogonadism have been open-label trials with a duration of 3 to 6 months, and only a small number of randomized trials have been conducted.[50–54] In randomized trials of testosterone that included young and older men with hypogonadism, testosterone treatment was shown to be associated with improvements in sexual desire, erectile function, and overall sexual activity[50–54]; consistent increases in lean body mass and maximal voluntary muscle strength; modest improvements in mobility, stair climbing speed, and aerobic capacity[55–59]; a decrease in whole body and abdominal fat[60–62]; an increase in areal and volumetric bone mineral density (more in the spine than in the hip)[63]; small improvements in depressive symptoms[64,65]; and an increase in hemoglobin level and the correction of anemia (Table 4).[66–68] Testosterone does not

Table 4
Effects of Testosterone Treatment in Men With Testosterone Deficiency—Finding of Randomized Clinical Trials

Outcome/condition	Treatment effect	
	Improves	Does not improve or evidence is absent or inconclusive
Sexual function	Sexual desire Erectile function Overall sexual activity	Ejaculatory dysfunction Orgasmic dysfunction
Muscle performance and physical function	Lean body mass Maximal voluntary muscle strength Stair climbing speed and power Mobility Aerobic capacity	…
Bone health	Areal and volumetric bone mineral density (particularly in the spine) Estimated bone strength	Effects on bone fractures (unknown) Inconclusive data on falls
Anemia	Hemoglobin Correct unexplained anemia due to aging	…
Depressive symptoms	Depressive symptoms Limited evidence of improvement in depressive symptoms in late-onset, low-grade, persistent depressive disorder (dysthymia)	Major depressive disorder Response to antidepressant therapy in patients with major depressive disorder
Fatigue	…	Inconclusive evidence of effect on energy or fatigue
Cognitive function	…	Does not improve cognitive function in men with testosterone deficiency who do not have a cognitive deficit Effects on the prevention or treatment of Alzheimer disease (unknown)
Health-related quality of life	Improves self-reported physical function and mobility	No effect on overall quality of life assessed using the MOS SF-36 scale

Abbreviations: MOS = medical outcomes study; SF-36 = 36-Item Short Form survey.

improve cognitive function in men who do not have cognitive deficit.[69,70] There is some evidence that testosterone treatment improves depressive symptoms in men with late-onset, low-grade, persistent depressive disorder (dysthymia) and low testosterone levels.[71,72] In the Testosterone for Diabetes Mellitus (T4DM) trial, which included randomized middle-aged and older men, aged 50 to 75 years, with newly diagnosed diabetes or impaired glucose tolerance, testosterone treatment administered in conjunction with a lifestyle program for 2 years was associated with a lower proportion of participants with diabetes than those on a placebo in conjunction with lifestyle program; however, the enrolled participants did not meet the criteria for hypogonadism.[73]

Adverse Events Associated With Testosterone Treatment

The testosterone treatment of carefully selected men with testosterone deficiency in randomized trials has been shown to be associated with a low frequency of adverse events.[52,53,74] The adverse effects associated with testosterone treatment include erythrocytosis, acne, breast tenderness, leg edema, suppression of spermatogenesis; and formulation-specific adverse effects, such as injection site pain and pulmonary oil microembolism reactions with intramuscular testosterone esters, local skin reactions, and the risk of transfer with transdermal gel formulations. Erythrocytosis is the most frequent adverse event associated with testosterone treatment, but the frequency of neuro-occlusive events was very low in the randomized trials. Testosterone treatment can cause transient salt and water retention and may exacerbate heart failure in patients with heart failure. Testosterone treatment does not worsen lower urinary tract symptoms in men with testosterone deficiency who do not have severe lower urinary tract symptoms prior to treatment.[53,75] Testosterone treatment did not affect the rate of atherosclerosis progression, assessed using common carotid artery intima media thickness or coronary calcium scores; in the Cardiovascular Trial of the TTrials,[76] which enrolled men with hypogonadism, aged ≥65 years, or in the Testosterone Effects on Atherosclerosis in Aging Men trial, which enrolled men, aged ≥60 years, with low or low-to-normal testosterone levels.[77] In the Cardiovascular Trial of the TTrials,[76] testosterone treatment was associated with a significantly greater increase in noncalcified plaque volume in the coronary arteries from baseline to 12 months, measured using computed tomography angiography; however, the clinical significance of the increase in the noncalcified plaque volume remains unclear. No trial has been long enough or large enough to determine the long-term risk of major adverse cardiovascular events or prostate cancer during testosterone treatment.[66] There is no clear evidence that testosterone increases the risk of venous thromboembolism; most case reports of venous thrombosis associated with testosterone treatment have occurred in men with thrombophilia.[78] An ongoing large cardiovascular safety trial (TRAVERSE trial, NCT NCT03518034) is evaluating the effects of testosterone treatment on major adverse cardiovascular events for up to 5 years in men, aged 45 to 80 years, with hypogonadism.

The initiation of testosterone treatment should be accompanied by a standardized monitoring plan that includes follow-up at 3 to 6 months, 12 months, and then annually thereafter (Table 5).[1] The monitoring plan should include the ascertainment of symptom resolution and adverse effects, lower urinary tract symptoms, serum testosterone levels, hemoglobin and hematocrit levels, and prostate-specific antigen levels in men aged ≥55 years (or ≥40 years if they are at a high risk of prostate cancer).[1]

Conclusion

Nonspecificity of symptoms, substantial variations in testosterone levels over time due to biologic factors, methodologic problems in the measurement of total and free testosterone levels, and suboptimally derived reference ranges contribute to diagnostic inaccuracy in the evaluation of men suspected of having testosterone deficiency. To reduce the risk of misdiagnosis, the specificity of symptoms and examination findings should be weighed, an accurate assay should be used for the measurement of total testosterone levels, free testosterone levels should be measured using the equilibrium dialysis method when a binding protein alteration is suspected, and a rigorously derived reference range should be applied. The benefit-to-risk ratio can be optimized by treating men

Table 5
Monitoring of Testosterone Replacement Therapy

Outcome measure	Baseline	3-6 mo	12 mo	Annually
Symptoms	X	X	X	X
Adverse events	X	X	X	X
Testosterone level	X	X	X	X
Hemoglobin or hematocrit	X	X	X	X
PSA or DRE[a]	X	X	X	X[a]

Abbreviations: DRE = digital rectal examination; PSA = prostate-specific antigen.
[a] Standardized plan for the monitoring of testosterone replacement therapy. Because prostate monitoring has the potential for harm, the decision to screen patients for prostate cancer risk and to institute PSA monitoring should be made jointly by the clinician and the patient. Expert opinions and local practices on PSA screening and monitoring vary. After 1 year of testosterone treatment, prostate monitoring should conform to the guidelines for prostate cancer screening, depending on the race and age of the patient.

with only ≥1 symptoms of testosterone deficiency and consistently low testosterone levels, maintaining on-treatment testosterone levels in the midnormal range, and using a standardized monitoring plan.

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