Testosterone Therapy in Men With Hypogonadism: An Endocrine Society* Clinical Practice Guideline

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***Cosponsoring Organizations:** European Society of Endocrinology.

***Endorsing Organizations:** European Academy of Andrology.

Objective: To update the "Testosterone Therapy in Men With Androgen Deficiency Syndromes" guideline published in 2010.

Participants: The participants include an Endocrine Society–appointed task force of 10 medical content experts and a clinical practice guideline methodologist.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation approach to describe the strength of recommendations and the quality of evidence. The task force commissioned two systematic reviews and used the best available evidence from other published systematic reviews and individual studies.

Consensus Process: One group meeting, several conference calls, and e-mail communications facilitated consensus development. Endocrine Society committees and members and the cosponsoring organization were invited to review and comment on preliminary drafts of the guideline.

Conclusions: We recommend making a diagnosis of hypogonadism only in men with symptoms and signs consistent with testosterone (T) deficiency and unequivocally and consistently low serum T concentrations. We recommend measuring fasting morning total T concentrations using an accurate and reliable assay as the initial diagnostic test. We recommend confirming the diagnosis by repeating the measurement of morning fasting total T concentrations. In men whose total T is near the lower limit of normal or who have a condition that alters sex hormone–binding globulin, we recommend obtaining a free T concentration using either equilibrium dialysis or estimating it using an accurate formula. In men determined to have androgen deficiency, we recommend additional diagnostic evaluation to ascertain the cause of androgen deficiency. We recommend T therapy for men with symptomatic T deficiency to induce and maintain secondary sex characteristics and correct symptoms of hypogonadism after discussing the potential benefits and risks of therapy and of

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Abbreviations: AAS, androgenic–anabolic steroid; BMD, bone mineral density; CDC, Centers for Disease Control and Prevention; CI, confidence interval; DRE, digital rectal examination; FDA, US Food and Drug Administration; FT, free testosterone, FSH, follicle-stimulating hormone; HbA1c, hemoglobin A1c; KS, Klinefelter syndrome; LBM, lean body mass; LH, luteinizing hormone; LUTS, lower urinary tract symptoms; MACE, major adverse cardiovascular events; OSA, obstructive sleep apnea; PSA, prostate-specific antigen; RCT, randomized controlled trial; SHBG, sex hormone–binding globulin; SMD, standardized mean difference; T, testosterone; TT, total testosterone; TTrials, Testosterone Trials; T2DM, type 2 diabetes mellitus; VTE, venous thromboembolism.

monitoring therapy and involving the patient in decision making. We recommend against starting T therapy in patients who are planning fertility in the near term or have any of the following conditions: breast or prostate cancer, a palpable prostate nodule or induration, prostate-specific antigen level > 4 ng/mL, prostate-specific antigen > 3 ng/mL in men at increased risk of prostate cancer (*e.g.,* African Americans and men with a first-degree relative with diagnosed prostate cancer) without further urological 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. We suggest that when clinicians institute T therapy, they aim at achieving T concentrations in the mid-normal range during treatment with any of the approved formulations, taking into consideration patient preference, pharmacokinetics, formulation-specific adverse effects, treatment burden, and cost. Clinicians should monitor men receiving T therapy using a standardized plan that includes: evaluating symptoms, adverse effects, and compliance; measuring serum T and hematocrit concentrations; and evaluating prostate cancer risk during the first year after initiating T therapy. (***J Clin Endocrinol Metab* 103: 1715–1744, 2018**)

Summary of Recommendations

1.0 Diagnosis of hypogonadism in men

Diagnosis of men with suspected hypogonadism

1.1 We recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency and unequivocally and consistently low serum total testosterone and/or free testosterone concentrations (when indicated). (1|⊕⊕⊕O)

Screening and case detection for hypogonadism

1.2 We recommend against routine screening of men in the general population for hypogonadism. (1|⊕⊕OO)

Distinguishing between primary or secondary hypogonadism

1.3 In men who have hypogonadism, we recommend distinguishing between primary (testicular) and secondary (pituitary–hypothalamic) hypogonadism by measuring serum luteinizing hormone and follicle-stimulating hormone concentrations. (1|⊕⊕⊕O)

Evaluation for determining the etiology of hypogonadism

1.4 In men with hypogonadism, we suggest further evaluation to identify the etiology of hypothalamic, pituitary, and/or testicular dysfunction. (2|⊕⊕OO)

2.0 Treatment of hypogonadism with testosterone

2.1 We recommend testosterone therapy in hypogonadal men to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency. (1|⊕⊕⊕O)

2.2 We recommend against testosterone therapy in men planning fertility in the near term or in men with breast or prostate cancer, a palpable prostate nodule or induration, a prostate-specific antigen level > 4 ng/mL, a prostate-specific antigen level > 3 ng/mL combined with a high risk of prostate cancer (without further urological 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. (1|⊕⊕OO)

2.3 In hypogonadal men 55 to 69 years old, who are being considered for testosterone therapy and have a life expectancy > 10 years, we suggest discussing the potential benefits and risks of evaluating prostate cancer risk and prostate monitoring and engaging the patient in shared decision making regarding prostate cancer monitoring. For patients who choose monitoring, clinicians should assess prostate cancer risk before starting testosterone treatment and 3 to 12 months after starting testosterone (2|⊕OOO). In hypogonadal men being considered for testosterone therapy who are 40 to 69 years old and at increased risk of prostate cancer (*e.g.,* African Americans and men with a first-degree relative with diagnosed prostate cancer), we suggest discussing prostate cancer risk with the patient and offering monitoring options. (2|⊕OOO)

Older men with age-related decline in testosterone concentration

2.4 We suggest against routinely prescribing testosterone therapy to all men 65 years or older with low testosterone concentrations (1|⊕⊕OO). In men >65 years who have symptoms or conditions suggestive of testosterone deficiency (such as low libido or unexplained anemia) and consistently and unequivocally low morning testosterone

concentrations, we suggest that clinicians offer testosterone therapy on an individualized basis after explicit discussion of the potential risks and benefits. (2|⊕⊕OO)

HIV-infected men with weight loss

2.5 We suggest that clinicians consider short-term testosterone therapy in HIV-infected men with low testosterone concentrations and weight loss (when other causes of weight loss have been excluded) to induce and maintain body weight and lean mass gain. (2|⊕⊕OO)

Men with type 2 diabetes mellitus

2.6 In men with type 2 diabetes mellitus who have low testosterone concentrations, we recommend against testosterone therapy as a means of improving glycemic control. (1|⊕⊕OO)

3.0 Monitoring of testosterone replacement therapy

3.1 In hypogonadal men who have started testosterone therapy, we recommend evaluating the patient after treatment initiation to assess whether the patient has responded to treatment, is suffering any adverse effects, and is complying with the treatment regimen. (Ungraded Good Practice Statement)

3.2 We recommend a urological consultation for hypogonadal men receiving testosterone treatment if during the first 12 months of testosterone treatment there is a confirmed increase in prostate-specific antigen concentration $>$ 1.4 ng/mL above baseline, a confirmed prostate-specific antigen $>$ 4.0 ng/mL, or a prostatic abnormality detected on digital rectal examination. After 1 year, prostate monitoring should conform to standard guidelines for prostate cancer screening based on the race and age of the patient. (2|⊕⊕OO)

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee of the Endocrine Society deemed testosterone (T) therapy in men with hypogonadism a priority area and appointed a task force to update the "Testosterone Therapy in Men with Androgen Deficiency Syndromes" guideline published in 2010. The task force formulated evidence-based recommendations following the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation Group, an international committee with expertise in the development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The task force used the best available research evidence to develop the recommendations. The task force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of a recommendation, strong recommendations use the phrase "we recommend" and the number 1, and conditional recommendations use the phrase "we suggest" and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕OOO denotes very low-quality evidence; ⊕⊕OO, low quality; ⊕⊕⊕O, moderate quality; and ⊕⊕⊕⊕, high quality. The task force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Conditional recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the values that the task force considered in making the recommendation; in some instances, there are remarks, a section in which the task force offers technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the task force and their values and preferences; therefore, one should consider these remarks as suggestions.

In this guideline, the task force made several statements to emphasize the importance of: informing the patient regarding potential benefits and risks of testosterone treatment and of monitoring treatment; shared decision making; general preventive care measures; and basic principles of androgen deficiency screening, diagnosis, and treatment. They labeled these "Ungraded Good Practice Statement." Direct evidence for these statements was either unavailable or not systematically appraised. The intention of these statements is to draw attention and remind providers of these principles (3).

The Endocrine Society maintains a rigorous conflict-of-interest review process for developing clinical practice guidelines. All task force members must declare any potential conflicts of interest by completing a conflict-of-interest form. The Clinical Guidelines Subcommittee reviews all conflicts of interest before the Society's Council approves the members to participate on the task force and periodically during the development of the guideline. All others participating in the guideline's development must also disclose any conflicts of interest in the matter under study, and most of these participants must be without any conflicts of interest.

Conflicts of interest are defined as remuneration in any amount from commercial interests; grants; research support; consulting fees; salary; ownership interests [*e.g.*, stocks and stock options (excluding diversified mutual funds)]; honoraria and other payments for participation in speakers' bureaus, advisory boards, or boards of directors; and all other financial benefits. Completed forms are available through the Endocrine Society office. The Endocrine Society provided all funding for this guideline; the task force received no funding or remuneration from commercial or other entities.

The Endocrine Society's clinical practice guidelines are developed to be of assistance to endocrinologists by providing guidance and recommendations for specific areas of practice. The guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The guidelines

cannot guarantee any specific outcome, nor do they establish a standard of care. The guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of health care providers and each patient's individual circumstances.

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Commissioned Systematic Review

The guideline task force commissioned two systematic reviews to assist with summarizing the evidence base for this guideline. The first review determined whether T-replacement therapy improves sexual function, physical function, fatigue, mood, cognition, anemia, and bone mineral density in men with hypogonadism (4). The review included placebo-controlled trials that allocated subjects either using randomization or minimization with concealed subject allocation and that recruited hypogonadal men who had symptoms, a screening total testosterone level < 300 ng/dL, and for whom the intervention raised serum testosterone concentrations into the normal range. The review only included trials that used testosterone or its esters. The review identified 11 reports of four trials with 1779 participants. All included trials tested transdermal therapy with a duration of therapy that ranged from 12 to 52 weeks. The mean baseline total testosterone concentrations ranged from 201 to 239 ng/dL. All studies were placebo-controlled trials that used randomization or allocation-by-minimization with a low risk of bias.

The meta-analysis suggested that testosterone treatment was associated with a small but statistically significant improvement in libido [standardized mean difference (SMD), 0.17; 95% confidence interval (CI), 0.01, 0.34], erectile function (SMD, 0.16; 95% CI, 0.06, 0.27), sexual activity (SMD, 0.23; 95% CI, 0.13, 0.33), and sexual satisfaction (SMD, 0.16; 95% CI, 0.01, 0.31), as compared with participants receiving placebo. SMD of 0.2 is considered a small treatment effect, 0.5 a medium treatment effect, and 0.8 a large treatment effect. Researchers observed no statistically significant difference in energy or mood. Data about cognition and bone mineral density were only available in one trial, which reported no significant improvement in measures of cognition but did report improvements in areal and volumetric bone mineral density and bone strength in the spine and hip.

The second review determined whether T-replacement therapy is associated with an increased risk of lower urinary tract symptoms and erythrocytosis in men with hypogonadism. The review identified nine studies of three trials with 1581 patients. Studies were placebo-controlled trials that used randomization or allocation-by-minimization with low-to-moderate risk of bias. All included trials tested transdermal therapy with a duration of therapy that ranged from 12 to 52 weeks. The mean baseline total testosterone concentrations ranged from 201 to 236 ng/dL. Meta-analysis suggested that testosterone treatment was associated with significantly higher frequency of erythrocytosis (hematocrit $> 54\%$) (relative risk, 8.14; 95% CI, 1.87, 35.40). There was no significant difference in the change in lower urinary tract symptoms (mean difference, 0.38, 95% CI, -0.67, 1.43) between the testosterone and placebo groups. The evidence from these trials warranted moderate and high certainty, respectively, in the provided estimates.

1.0 Diagnosis of Hypogonadism in Men

Hypogonadism is a clinical syndrome that results from failure of the testis to produce physiological concentrations of testosterone (T) (T deficiency) and/or a normal number of spermatozoa due to pathology at one or more concentrations of the hypothalamic–pituitary–testicular axis (5, 6). Abnormalities at the testicular level cause primary hypogonadism, whereas defects of the hypothalamus or the pituitary cause secondary hypogonadism. Hypogonadism also can result from defects that affect both the testis and the hypothalamus–pituitary unit. This guideline describes the diagnosis, treatment, and monitoring of T deficiency and does not address isolated defects of spermatogenesis.

Primary hypogonadism results in low T concentrations, impairment of spermatogenesis, and elevated gonadotropin levels. Causes of primary hypogonadism include Klinefelter syndrome (KS), cryptorchidism, some types of cancer chemotherapy, radiation to the testes, trauma, torsion, infectious orchitis, HIV infection, anorchia syndrome, and myotonic dystrophy (5).

Secondary hypogonadism results in low T concentrations, impairment of spermatogenesis, and low or inappropriately normal gonadotropin levels. Causes of secondary hypogonadism include hyperprolactinemia; severe obesity; iron overload syndromes; the use of opioids, glucocorticoids, or androgen-deprivation therapy with gonadotropin-releasing hormone agonists; androgenic–anabolic steroid (AAS) withdrawal syndrome; idiopathic hypogonadotropic hypogonadism; hypothalamic or pituitary tumors or infiltrative disease; head trauma; and pituitary surgery or radiation.

Combined primary and secondary hypogonadism results in low T concentrations, impairment of spermatogenesis,

and variable gonadotropin levels, depending on whether primary or secondary hypogonadism predominates.

Causes of hypogonadism may be organic or functional, a distinction that has important clinical implications (Table 1). Organic hypogonadism (also referred to as "classical" hypogonadism) is caused by a congenital, structural, or destructive disorder that results in permanent hypothalamic, pituitary, or testicular dysfunction (primary or secondary hypogonadism). In contrast, functional hypogonadism is caused by conditions that suppress gonadotropin and T concentrations but that are potentially reversible with treatment of the underlying etiology.

The classification of hypogonadism as primary or secondary has therapeutic implications. Spermatogenesis can be stimulated and fertility can be restored with appropriate gonadotropin therapy in patients with secondary hypogonadism but not in patients with primary hypogonadism. Fertility options for men with primary testicular failure are limited to the use of donor sperm, adoption, or (in some patients) assisted reproductive technologies, such as intracytoplasmic sperm injection using sperm in the ejaculate or following testicular sperm extraction. Additionally, the process of evaluating secondary hypogonadism may uncover a deficiency/excess of other pituitary hormones or a hypothalamic or pituitary tumor that may require management in addition to treating hypogonadism. Secondary hypogonadism can result from functional causes (*e.g.*, obesity, opioids, or systemic illness) that might be reversible by treating the underlying condition or discontinuing the offending medication. Managing the underlying conditions, such as obesity, may have additional health benefits. In some instances, educating patients that obesity or opioids may be contributing to hypogonadism could motivate them to lose weight or discontinue narcotic pain medications.

Table 1. Classification of Hypogonadism and Causes of Primary and Secondary Hypogonadism

Primary Hypogonadism	Secondary Hypogonadism
ORGANIC	
KS	Hypothalamic/pituitary tumor
Cryptorchidism, myotonic dystrophy, anorchia	Iron overload syndromes
Some types of cancer chemotherapy, testicular irradiation/damage, orchidectomy	Infiltrative/destructive disease of hypothalamus/pituitary
Orchitis	Idiopathic hypogonadotropic hypogonadism
Testicular trauma, torsion	
Advanced age	
FUNCTIONAL	
Medications (androgen synthesis inhibitors)	Hyperprolactinemia
End-stage renal disease[a]	Opioids, anabolic steroid use, glucocorticoids
	Alcohol and marijuana abuse[a]
	Systemic illness[a]
	Nutritional deficiency/excessive exercise
	Severe obesity, some sleep disorders
	Organ failure (liver, heart, and lung)[a]
	Comorbid illness associated with aging[a]

[a]Combined primary and secondary hypogonadism, but classified to usual predominant hormonal pattern. Adapted with permission from Bhasin *et al.* (7).

Diagnosis of men with suspected hypogonadism

1.1 We recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency and unequivocally and consistently low serum total testosterone and/or free testosterone concentrations (when indicated). (1|⊕⊕⊕O)

Technical remark

- Testosterone concentrations exhibit significant diurnal and day-to-day variations and may be suppressed by food intake or glucose. Therefore, clinicians should measure total testosterone concentrations on two separate mornings when the patient is fasting. Clinicians should use an accurate and reliable method, optimally, an assay that has been certified by an accuracy-based standardization or quality control program [e.g., Centers for Disease Control and Prevention (CDC) Hormone Standardization Program for Testosterone].
- In men who have conditions that alter sex hormone–binding globulin (SHBG) (Table 2), or whose initial total testosterone concentrations are at or near the lower limit of the normal range (Fig. 1), clinicians should determine free testosterone concentrations either directly from equilibrium dialysis assays or by calculations that use total testosterone, SHBG, and albumin concentrations. Clinicians should not use direct analog-based free testosterone immunoassays, as they are inaccurate.
- Clinicians should not test men for testosterone deficiency who have or are recovering from an acute illness or are engaged in short-term use of medications (e.g., opioids) that suppress testosterone concentrations.

Evidence

The diagnosis of hypogonadism in men poses several challenges:

1. The clinical presentation of hypogonadism in men depends on the age of onset of T deficiency. Men

Table 2. Conditions in Which Measurement of FT Concentration Is Recommended

1. Conditions that are associated with decreased SHBG concentrations
Obesity
Diabetes mellitus
Use of glucocorticoids, some progestins, and androgenic steroids
Nephrotic syndrome
Hypothyroidism
Acromegaly
Polymorphisms in the SHBG gene
2. Conditions associated with increased SHBG concentrations
Aging
HIV disease
Cirrhosis and hepatitis
Hyperthyroidism
Use of some anticonvulsants
Use of estrogens
Polymorphisms in the SHBG gene
3. Total testosterone concentrations in the borderline zone around the lower limit of the normal range (*e.g.*, 200-400 ng/dL)

Adapted with permission from Bhasin *et al.* (8).

who have prepubertal onset of hypogonadism that is not adequately treated will exhibit eunuchoidal proportions, lack of development of secondary sex characteristics, and high-pitched voice (eunuchodism) (5, 6).

2. The symptoms and signs of T deficiency are nonspecific and modified by age, comorbid illness, severity and duration of T deficiency, variations in androgen sensitivity, and previous T therapy. Table 3 lists signs and symptoms based on the clinical experience of severely T-deficient men and their response to T-replacement therapy (5, 6); there are no population-based surveys of symptoms and signs in men with the full spectrum of severity of hypogonadism. Incomplete or delayed sexual development, loss of secondary sex characteristics (such as body hair), and very small testes are specific manifestations of hypogonadism (Table 3).
3. In surveys of community-dwelling middle-aged and older men, low libido, erectile dysfunction, and less specific symptoms (such as fatigue, irritability, depressed mood, poor concentration, reduced physical performance, and sleep disturbance) are associated with low T concentrations (10, 11). In the European Male Aging Study (a cohort study of community-dwelling middle-aged and older men in Europe), only sexual symptoms (poor morning erections, decreased libido, and erectile dysfunction) had a syndromic association with total T (TT) concentrations < 320 ng/dL (11 nmol/L) and free T (FT) < 64 pg/mL (220 pmol/L) (after adjusting for age) (12). T alone is required to maintain lean mass and muscle size and strength; estradiol is required to prevent increases in fat mass and vasomotor symptoms, and both T and estradiol are required to maintain sexual function and bone mineral density (BMD) (13, 14). The conversion of T to dihydrotestosterone is not obligatory for mediating its effects on erythropoiesis or muscle mass and strength (15).
4. T concentrations may be affected by acute illness, nutritional deficiency, and by certain medications (*e.g.*, opioids and glucocorticoids). T concentrations also are affected by age, obesity, diabetes, sleep disorders including obstructive sleep apnea (OSA), and health status (10, 16). Therefore, assessing men for T deficiency should include a general health evaluation to exclude systemic illness, eating disorders, excessive exercise, sleep disorders, and use of recreational drugs and certain medications (*e.g.*, opioids or high-dose glucocorticoid therapy) that affect T production or metabolism (5, 6).
5. Heritability can explain a substantial fraction of population-level variations in T concentrations among men (17).
6. Serum T concentrations vary significantly as a result of diurnal, circadian, and circannual rhythms, episodic secretion, and assay variations (18, 19). Serum T concentrations exhibit a diurnal variation with peak values in the morning; aging reduces the magnitude of this diurnal variation (18). Despite this attenuation of the diurnal rhythm in older men, a substantial fraction of 65- to 80-year-old men who have low serum T concentrations in the afternoon will have normal T concentrations in the morning (9). Glucose and food intake suppress T concentrations (20, 21). Therefore, clinicians should measure T concentrations in the morning after an overnight fast.
7. It is important to confirm low T concentrations, because 30% of men with an initial T concentration in the hypogonadal range have a normal T concentration on repeat measurement (19). Also, a small fraction of healthy young men have a T concentration below the normal range during a 24-hour period (22). Day-to-day variations in serum T concentrations in a community-based, multiethnic cohort of middle-aged to older men were sufficiently large such that single T

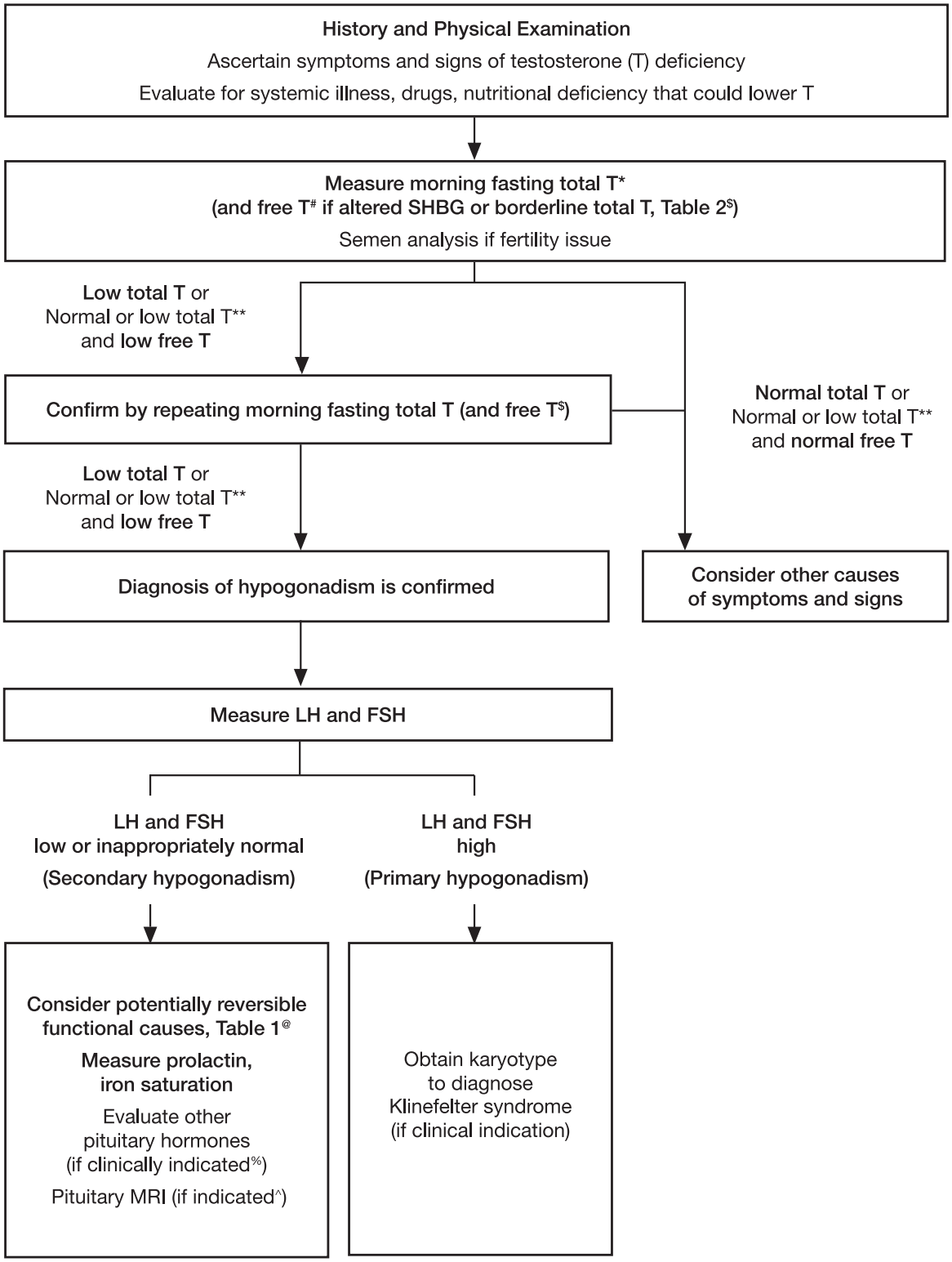

Figure 1. An approach for the diagnostic evaluation of adult men suspected of having T deficiency. *The lower limit of the normal total testosterone (TT) harmonized to the CDC standard in healthy nonobese young men is 264 ng/dL (9.2 nmol/L) (9); this limit could be used for TT assays that are CDC certified. For laboratories that are not CDC certified and do not participate in an accuracy-based quality control program, the reference range may vary considerably depending on the assay and reference population used. Using the lower limit of the range established in local laboratories may not accurately identify men with hypogonadism. #free testosterone (FT) should be measured by an equilibrium dialysis method or estimated from total testosterone, SHBG, and albumin using a formula that accurately reflects FT by equilibrium dialysis. A harmonized reference range for FT has not been established, so reference ranges may vary considerably depending on the specific equilibrium dialysis method or the algorithm used to calculate FT. Therefore, until a harmonized reference range is established, the lower limits established by the laboratory may be used. $Conditions in which measurement of FT concentration is recommended, including those conditions that alter SHBG levels, are listed in Table 3. **TT may also be high in some conditions in which SHBG levels are high, such as HIV

Table 3. Symptoms and Signs Suggestive of T Deficiency in Men

Specific symptoms and signs
Incomplete or delayed sexual development
Loss of body (axillary and pubic) hair
Very small testes (<6 mL)
Suggestive symptoms and signs
Reduced sexual desire (libido) and activity
Decreased spontaneous erections, erectile dysfunction
Breast discomfort, gynecomastia
Eunuchoidal body proportions
Inability to father children, low sperm count
Height loss, low-trauma fracture, low BMD
Hot flushes, sweats
Nonspecific symptoms and signs associated with testosterone deficiency
Decreased energy, motivation, initiative, and self-confidence
Feeling sad or blue, depressed mood, persistent low-grade depressive disorder
Poor concentration and memory
Sleep disturbance, increased sleepiness
Mild unexplained anemia (normochromic, normocytic)
Reduced muscle bulk and strength
Increased body fat, body mass index

Adapted with permission from Bhasin *et al.* (7).

measurements were inadequate to characterize an individual's concentrations. At least two T measurements were needed to diagnose T deficiency with confidence (9, 19).

8. TT concentrations are measured using radioimmunoassay, immunometric assays, or liquid chromatography–tandem mass spectrometry. There is considerable interassay and interlaboratory variability in TT measurements. When 1133 laboratories using 14 different assays measured TT concentrations using the same College of American Pathologists quality control sample from a single hypogonadal man, the measured values ranged from 45 to 365 ng/dL (1.6 to 12.7 nmol/L) (23). Similar large interassay and interlaboratory variability occurs with FT measurements. The variability in T measurements is partly due to calibrator differences and to biotin interference in some immunoassays. Since 2010, the CDC has provided an accuracy-based standardization program for T (CDC Hormone Standardization Program for Testosterone). Although several commercial laboratories, some assay manufacturers, and some academic laboratories are now CDC certified, most T immunoassay kit manufacturers and local hospital-based laboratories have not been certified. Liquid chromatography–tandem mass spectrometry assays for TT generally offer higher concentrations of specificity, sensitivity, and precision (especially in the low range) than do most immunoassays. Clinicians should ideally measure TT using a CDC-certified assay or an assay verified by an accuracy-based external quality control program.
9. Serum TT concentration represents the sum of unbound and protein-bound T in circulation. Most of the circulating T is bound to SHBG and albumin and, to a lesser extent, to cortisol-binding globulin and orosomucoid; only 2.0% to 4.0% of circulating T is unbound or free (24). The term "bioavailable T" refers to unbound T plus T bound with low affinity to albumin, reflecting the view that albumin-bound T is dissociable at the capillary level, especially in tissues with relatively long blood transit times (such as the liver and brain), and is biologically available for action in those tissues (24). The free hormone hypothesis states that intracellular concentrations and biologic activity of a hormone are dependent upon the concentrations of the free rather than protein-bound hormone in plasma (24). Support for the free hormone hypothesis has come from a recent analysis of the European Male Aging Study data, which showed that (compared to middle-aged and older men who had normal TT and FT concentrations) men with low FT concentrations had sexual and physical symptoms consistent with T deficiency, regardless of their TT concentrations (25). Importantly, men with low TT but normal FT concentrations were more obese (and presumably had lower SHBG levels) and did not have associated sexual or physical symptoms (25). Also, a man with a missense mutation of the SHBG gene who had complete deficiency of SHBG and very low TT concentrations was reported to have normal FT and gonadotropin levels, normal male reproductive development, and normal testes size and spermatogenesis, suggesting a limited role of SHBG in

Figure 1. (Continued). disease or use of some anticonvulsants. @Potentially reversible functional causes of secondary hypogonadism are listed in Table 1. %If there is clinical indication of hypopituitarism or sella abnormality on imaging, evaluation of other pituitary hormones (*e.g.*, free thyroxine, morning cortisol and ACTH stimulation test if clinical hypocortisolism is suspected) should be performed. ^Perform pituitary imaging (magnetic resonance imaging) to exclude pituitary and/or hypothalamic tumor or infiltrative disease when severe secondary hypogonadism [*e.g.*, serum T < 150 ng/dL (5.2 nmol/L)], panhypopituitarism, persistent hyperprolactinemia, or symptoms or signs of tumor mass effect (such as new-onset headache, visual impairment, or visual field defect) are present. CT scan may be sufficient if macroadenoma is suspected or to assess parasellar bone involvement. FSH, follicle-stimulating hormone; LH, leutinizing hormone.

male sexual development and spermatogenesis (26). Clinicians should measure FT in men who have conditions that alter SHBG levels (Table 2) (24). Conditions that lower SHBG [*e.g.*, obesity, type 2 diabetes mellitus (T2DM), or androgen use] can lower TT concentrations to below the normal range, although FT concentrations might remain within the normal range. Conditions that increase SHBG (*e.g.*, advanced age, some anticonvulsants, or HIV infection) can raise TT concentrations to well above 400 ng/dL and sometimes into the high-normal range or even above the normal range, even though FT concentrations might be low. Clinicians should also measure FT in men whose serum TT concentration is modestly above or below the lower limit of normal (*e.g.*, 200 to 400 ng/dL) (27). In men whose TT concentrations are far below the lower limit of the normal range (*e.g.*, <150 ng/dL), the probability of FT concentration being within the normal range is low. So, in such circumstance, measuring FT is generally not necessary (27). Local laboratories usually do not have accurate and reliable assays for FT measurement. Therefore, clinicians should use a reliable reference laboratory for these tests.

Clinicians should measure FT using the equilibrium dialysis method performed under standardized conditions. If equilibrium dialysis is not available for measuring FT, clinicians should estimate FT concentrations using a formula that accurately calculates FT concentrations using TT, SHBG, and albumin concentrations. The estimates of FT, regardless of the formula used, are predicated upon accurate measurements of TT, SHBG, and albumin. Several different algorithms are available for calculating FT concentrations based on the binding characteristics of T to SHBG and albumin (28–30). Recent studies using modern biophysical techniques suggest that SHBG circulates as a dimer (24, 28) and that binding of T to SHBG is a multistep process that involves an allosteric interaction between the two binding sites on the SHBG dimer, such that the affinities of the two sites are not equivalent (28). Estimates of FT that use an allosteric model provide close approximations of levels measured using equilibrium dialysis. Further investigation is needed to determine the preferred method for routinely estimating FT concentrations in clinical populations (28). FT measurements by direct tracer analog immunoassays are frequently available in local and some reference laboratories, but these direct immunoassays are inaccurate and should not be used (23, 24). Bioavailable T concentrations are measured by ammonium sulfate precipitation or calculated from TT, SHBG, and albumin levels (23, 24). Measuring bioavailable T concentrations using ammonium sulfate precipitation is technically challenging. Furthermore, there are no detailed studies (similar to those described previously that relate FT concentrations to manifestations of T deficiency) that use bioavailable T concentrations (24).

The reported reference ranges for TT and FT concentrations in healthy young men vary considerably among laboratories and assays (31). A substantial amount of the variation in reference ranges is due to the lack of standardization of T assays, calibrator differences, and differences in the reference populations used to generate ranges. Recently, the Endocrine Society and the Partnership for the Accurate Testing of Hormones supported a project to develop a harmonized reference range based on data from community-dwelling men from four large cohorts in the United States and Europe. The project cross-calibrated the assays used for each cohort against a higher order method and calibrator developed by the CDC and then harmonized the local values to the CDC-standardized measurements (31). The harmonized reference range for TT in healthy, *nonobese* young men (aged 19 to 39 years) was 264 to 916 ng/dL (9.2 to 31.8 nmol/L) using the 2.5th and 97.5th percentile, and 303 to 852 ng/dL (10.5 to 29.5 nmol/L) using the 5th and 95th percentile (31). Clinicians can use this range for all CDC-certified TT assays.

A major difficulty in interpreting FT concentrations is the lack of standardization regarding FT assays, resulting in variability in the lower limit of the reference ranges quoted by different laboratories. Given the uncertainties in the methods of calculations and variations in reference intervals, laboratories are encouraged to establish their own specific reference ranges for FT measured by equilibrium dialysis and calculated FT (preferably calibrated against the equilibrium dialysis method).

Values and preferences

Our diagnostic strategy reflects our preference to avoid labeling men as having hypogonadism and requiring T therapy based on low T concentrations due to transient medical disorders, biological variations in T concentrations, technical variations and inaccuracy in T measurements, or SHBG abnormalities. Our strategy also reflects our preference to avoid treating men without symptoms and signs of T deficiency or without unequivocally low T concentrations when the benefits and risks of T therapy remain unclear.

Screening and case detection for hypogonadism

1.2 We recommend against routine screening of men in the general population for hypogonadism. (1|⊕⊕OO)

Technical remark

- Low T concentrations occur frequently without symptoms or signs of testosterone deficiency, and these low levels (alone) do not establish a diagnosis of hypogonadism. Current case-finding instruments for detecting testosterone deficiency lack sufficient sensitivity and specificity to be useful for screening men who are receiving health care for unrelated reasons.

Evidence

Because of the lack of consensus on the extent to which hypogonadism is an important public health problem, as well as the lack of data on the performance characteristics of candidate screening tools, we do not recommend population screening. The impact of untreated T deficiency on mortality is unclear, although several, but not all, epidemiological studies have reported an association of low T concentrations with higher all-cause mortality (particularly mortality due to cardiovascular disease) (32).

The benefits and adverse consequences of long-term T therapy on patient-important outcomes in asymptomatic men with low T concentrations remain unclear. Therefore, screening for hypogonadism does not fulfill the necessary criteria to justify population-level screening (33, 34). No clinical trials have assessed the effectiveness of screening strategies.

Ideally, case detection should identify those patients who seek medical attention for one or more medical problems who are at increased risk of having hypogonadism and likely to benefit from T therapy. Table 4 lists candidate groups that have a high prevalence of low T concentrations and for whom we suggest measuring T concentrations; these include men with low libido, erectile dysfunction, infertility, HIV-associated weight loss, osteoporosis or low-trauma fracture, a history of AAS use, and men receiving opioids or other drugs or substances that affect T production or metabolism (5, 6, 35–41).

There is limited information about the performance properties of case-detection questionnaires that rely on self-reports, namely Androgen Deficiency in Aging Males (42), the Aging Males' Symptoms Rating Scale (43), and the Massachusetts Male Aging Study Questionnaire (44). Two recent scales have been designed to assess hypogonadism symptoms: the Hypogonadism Impact of Symptoms Questionnaire (45) and the Sexual Arousal, Interest, and Drive Scale (46). Although these new scales are psychometrically more robust than previous instruments, clinical experience with them is limited. There are no trials of case-detection strategies in the patient populations described above. As such, the positive and negative predictive value and the cost-effectiveness of the use of case-finding questionnaires over measuring serum T concentrations is unknown. Therefore, we suggest that clinicians not use the available case-finding questionnaires for detecting T deficiency in men receiving health care for unrelated reasons. We suggest that clinicians consider using TT concentration measurements for case detection in men with certain clinical disorders (Table 4) in whom the prevalence of hypogonadism is high and T treatment might be indicated.

Values and preferences

The recommendation not to routinely screen men in the general population places a high value on avoiding labeling, testing, treating, and monitoring healthy men for whom the benefits and risks are unclear. This recommendation also places a high value on avoiding interventions with unclear outcomes. It places a low value on the potential benefits of early detection and treatment of T deficiency in men who have not sought medical attention.

Table 4. Conditions in Which There Is a High prevalence of Low T Concentrations and for Which We Suggest Measurement of Serum T Concentrations

Pituitary mass, radiation to the pituitary region, or other diseases of the sellar region
Treatment with medications that affect T production or metabolism, such as opioids and glucocorticoids
Withdrawal from long-term AAS use
HIV-associated weight loss
Infertility
Osteoporosis or low trauma fracture
Low libido or erectile dysfunction

Adapted with permission from Bhasin *et al.* (7).

Distinguishing between primary or secondary hypogonadism

1.3 In men who have hypogonadism, we recommend distinguishing between primary (testicular) and secondary (pituitary-hypothalamic) hypogonadism by measuring serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations (Fig. 1). (1|⊕⊕⊕O)

Evidence

Measuring LH and FSH concentrations can help distinguish between primary and secondary hypogonadism (Fig. 1). Most clinical laboratories measure LH and FSH levels using immunometric assays that have sufficient sensitivity to distinguish between normal and

low levels. LH and FSH assays are susceptible to biotin interference (47) that can cause falsely high or low values; accordingly, clinicians should stop biotin supplements for at least 72 hours before testing.

Values and preferences

This recommendation places high value on identifying men with secondary hypogonadism who might have disorders of the pituitary gland or hypothalamus that require management in addition to T treatment.

Evaluation for determining the etiology of hypogonadism

1.4 In men with hypogonadism, we suggest further evaluation to identify the etiology of hypothalamic, pituitary, and/or testicular dysfunction. (2|⊕⊕OO)

Technical remark

- In men with secondary hypogonadism, clinicians should perform serum prolactin and iron saturation measurements, and in certain cases, pituitary function testing and magnetic resonance imaging of the sella turcica to determine the cause of gonadotropin deficiency.
- In men with primary hypogonadism of unknown etiology, especially in those with testicular volume < 6 mL, clinicians should obtain a karyotype to diagnose KS.

Evidence

In men deemed to have secondary hypogonadism, additional diagnostic evaluations may be needed to exclude hyperprolactinemia, head trauma, iron overload syndromes, hypothalamic or pituitary tumors, and other infiltrative or destructive hypothalamic–pituitary diseases, as well as genetic disorders associated with gonadotropin deficiency. Measuring serum prolactin and iron saturation and/or serum ferritin can help determine the presence of hyperprolactinemia and iron overload syndromes, respectively. Assessing anterior pituitary function, if clinically indicated, can uncover other pituitary hormone deficiencies. Clinicians can make a diagnosis of congenital (also referred to as idiopathic) hypogonadotropic hypogonadism after excluding other causes of secondary hypogonadism in men with prepubertal or less commonly adult onset T deficiency. In patients with hypogonadotropic hypogonadism, phenotypic features—such as hyperphagia or extreme obesity (*e.g.*, Prader–Willi syndrome), polydactyly, syndactyly, synkinesia, anosmia, kidney abnormalities (*e.g.*, Kallmann syndrome), or short stature (*e.g.*, contiguous gene deletions of chromosome X)—can help clinicians identify specific syndromes via pattern recognition (48).

When evaluating middle-aged and older men with secondary hypogonadism, the cost-effectiveness of pituitary imaging (magnetic resonance imaging) to exclude pituitary and/or hypothalamic disease is unknown. Surveys of middle-aged and older men with secondary hypogonadism and sexual dysfunction have revealed a low prevalence of hypothalamic–pituitary abnormalities (49). Clinicians can improve the diagnostic yield of pituitary imaging to exclude pituitary and/or hypothalamic tumors by performing this procedure in men with panhypopituitarism, persistent hyperprolactinemia, serum TT < 150 ng/dL (5.2 nmol/L) (49), or symptoms of tumor mass effect (*e.g.*, visual impairment, visual field defect, or new onset headache).

Many men with secondary hypogonadism have potentially reversible or treatable causes of gonadotropin suppression and low T concentrations or functional secondary hypogonadism [*e.g.*, due to obesity, opioid use, or comorbid illness (Table 1)] that may be managed without need for testosterone treatment.

Karyotype can be useful in diagnosing KS (47 XXY), a common identifiable cause of primary testicular failure, characterized by infertility, gynecomastia, very small testes (testicular volume < 6 mL; although men with mosaic KS may have larger testes), and elevated gonadotropin levels. The karyotype obtained from peripheral blood lymphocytes may be normal (46 XY) in some men with KS who have mosaicism (46 XY/47 XXY). Men with KS can benefit from genetic counseling and need surveillance for certain disorders, such as breast cancer and autoimmune disorders, for which they are at increased risk (50).

T directly stimulates bone formation and inhibits bone resorption through multiple mechanisms that involve estrogen receptor– and androgen receptor–mediated processes (14, 41). Additionally, T may increase skeletal muscle mass and strength, which may indirectly increase BMD and potentially reduce fall propensity and fracture risk; however, there are no randomized trials that assess the effect of T on fall and fracture prevention. The cost-effectiveness of measuring BMD and the frequency at which it should be performed are not known.

If fertility is a concern to a patient and his partner, clinicians should perform at least two semen analyses separated by an interval of several weeks on semen samples collected within 1 hour of ejaculation after at least 48 hours of abstinence.

Values and preferences

Our recommended diagnostic strategy places a relatively higher value on detecting potentially reversible

functional or organic conditions (*e.g.*, pituitary tumors or other treatable pituitary disorders) for which effective treatment or counseling is available. This strategy places a relatively lower value on avoiding the burden and cost of tests with unknown yield.

2. Treatment of Hypogonadism With Testosterone

2.1 We recommend testosterone therapy in hypogonadal men to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency. (1|⊕⊕⊕O)

Technical remark

- Clinicians can initiate testosterone therapy with any of the therapeutic regimens described in Tables 5 and 6, based on the patient's preference, consideration of pharmacokinetics, treatment burden, and cost.
- Clomiphene citrate has been used empirically in men with hypogonadotropic hypogonadism; however, neither its efficacy nor its safety has been demonstrated in randomized trials.

2.2 We recommend against testosterone therapy in men planning fertility in the near term or in men with breast or prostate cancer, a palpable prostate nodule or induration, a prostate-specific antigen (PSA) level $>$ 4 ng/mL, a PSA level $>$ 3 ng/mL combined with a high risk of prostate cancer (without further urological evaluation), elevated hematocrit, untreated severe OSA, severe lower urinary tract symptoms, uncontrolled heart failure, myocardial infarction or stroke within the last 6 months, or thrombophilia (Table 7). (1|⊕⊕OO)

Technical remark

- Men who have a prostate nodule or induration require a urological evaluation. Clinicians should not administer testosterone therapy to men with baseline hematocrit above the upper limit of normal for the laboratory without discussing the potential for an increased risk of erythrocytosis and the need to monitor hematocrit assiduously.

2.3 In hypogonadal men 55 to 69 years old, who are being considered for testosterone therapy and have a life expectancy $>$ 10 years, we suggest discussing the potential benefits and risks of evaluating prostate cancer risk and prostate monitoring and engaging the patient in shared decision making regarding prostate cancer monitoring. For patients who choose monitoring, clinicians should assess prostate cancer risk before starting testosterone treatment and 3 to 12 months after starting testosterone (2|⊕OOO). In hypogonadal men being considered for testosterone therapy who are 40 to 69 years old and at increased risk of prostate cancer (*e.g.*, African Americans and men with a first-degree relative with diagnosed prostate cancer), we suggest discussing prostate cancer risk with the patient and offering monitoring options. (2|⊕OOO)

Technical remark

- We suggest that clinicians offer evaluation of prostate cancer risk beginning at age 40 in hypogonadal men who are being considered for testosterone therapy and are at high risk of prostate cancer (e.g., African Americans and men with a first-degree relative with prostate cancer). In patients who agree to prostate cancer monitoring, clinicians should evaluate PSA levels and perform a digital prostate examination at baseline and at 3 to 12 months after starting testosterone treatment. After 1 year of testosterone-replacement therapy, we suggest clinicians follow the guidelines for prostate cancer screening based on the age and race of the patient.

Evidence

Tables 5 and 6 summarize the clinical pharmacology of T formulations. Patients can begin T therapy using any of the suggested regimens based on their preference, the pharmacokinetics of the formulation, the treatment burden, and the cost (Table 6). Outside the United States, oral T undecanoate and a matrix transdermal T patch are available for clinical use in many countries; physicians should follow the drug regimens approved in those countries. See Tables 5 and 6 for additional safety and pharmacokinetics information.

When the goal of treatment is to replace T, treating men with prepubertal onset of hypogonadism is similar to treating men with postpubertal onset hypogonadism, although some practitioners and patients may elect to start T treatment at a lower dosage initially and gradually increase the dose over many months to avoid sexually disturbing thoughts. In contrast, when the goal of treatment is to induce or restore fertility, men with prepubertal onset hypogonadism are more likely to require both FSH and LH (human chorionic gonadotropin or recombinant LH) replacement, whereas men with postpubertal onset hypogonadism are more likely to require LH replacement only (51).

Efficacy

Most studies of T therapy in young, hypogonadal men were open label and did not include a placebo group. The observations from these open-label studies are consistent with the data from a small number of randomized trials.

Secondary sexual characteristics. In men who have not undergone complete pubertal development, T therapy induces the development of secondary sex characteristics, including facial and body hair growth, deepening of the voice, muscle and bone accretion, penile enlargement, and pigmentation of the scrotum (52).

Sexual function. The commissioned systematic review and meta-analysis showed that T treatment in hypogonadal men with low libido is associated with significantly greater improvement in libido, erectile function, and sexual activity vs placebo (53–55). T does not significantly improve sexual function and activity in men who do not have low T concentrations in the hypogonadal range (56).

Phosphodiesterase 5 inhibitors can improve erectile function in eugonadal (57) and hypogonadal men (58). However, randomized controlled trials (RCTs) have failed to demonstrate further improvements in erectile function with the addition of T to an optimized regimen of phosphodiesterase 5 inhibitors (58, 59). T therapy does not improve ejaculatory function in men with low T concentrations and ejaculatory dysfunction (60).

Well-being and depressive symptoms. T therapy improves the positive and reduces the negative aspects of mood, but the magnitude of the effect of T on mood in older men is small (61, 62). T therapy does not improve depressive symptoms in men with clinical depression (63). Epidemiological studies have reported an association between lower T concentrations and late-onset, low-grade, persistent depressive disorder (previously referred to as dysthymia) (64, 65). There is limited evidence that T improves depressive symptoms in middle-aged and elderly men with late-onset, low-grade, persistent depressive disorder and low T concentrations (66, 67).

In the Testosterone Trials (TTrials) (which we describe in greater detail later in this article), no statistically significant improvement was observed in fatigue with T treatment vs placebo (68); this was confirmed in the commissioned systematic review and meta-analysis.

Bone mineral density. T therapy in healthy hypogonadal men increases areal and volumetric vertebral and femoral BMD and vertebral and femoral bone strength (69–71), but there are no studies on the effects of T on fracture risk. T is not an approved treatment for osteoporosis or for reducing fracture risk. Clinicians should not prescribe T for treating osteoporosis in men who have normal T concentrations or as monotherapy to prevent bone fracture in men who are at high risk of bone fracture, regardless of T concentrations (clinicians can assess fracture risk using a fracture risk assessment instrument, such as FRAX®). In hypogonadal men receiving T replacement, clinicians should treat osteoporosis in patients at high risk of bone fracture with a pharmacologic agent that has been approved for the treatment of osteoporosis (72). In hypogonadal men who have osteoporosis, are not at high risk of bone fracture, and are being started on T-replacement therapy, clinicians may consider deferring treatment with approved osteoporosis drugs until they have evaluated the response to T replacement by repeating BMD tests of the lumbar spine, femoral neck, and hip after 1 to 2 years of T therapy.

Body composition, muscle strength, and physical function. T therapy in healthy men with hypogonadism increases fat-free mass (73, 74) and muscle strength (73, 75). T administration reduces whole body, intraabdominal, and intermuscular fat (75). The effects of T on muscle/fat mass and muscle strength are related to the administered dose and increase in circulating T concentrations (75–77). Estrogen predominantly mediates the effects of T on body fat (13, 78). In placebo-controlled trials in healthy and mobility-limited older men, T therapy resulted in greater gains in lean body mass (LBM), maximal voluntary strength, muscle power, and some performance-based measures of physical function vs placebo (79–83). However, these studies have not shown consistent improvements in gait speed or measures of disability (68, 79–81).

Cognitive function. Two RCTs in community-dwelling older men did not find significant improvements in memory or multiple other domains of cognitive function with T treatment (84, 85). There are no studies on the effects of T on men with dementia or on the progression from mild cognitive impairment to dementia.

Adverse events associated with testosterone therapy

Randomized and open-label trials in young men with hypogonadism report a low frequency of serious adverse events with replacement doses of T (86–88). Common drug-related adverse events include acne, oiliness of skin, and breast tenderness (Table 8). The frequency of breast enlargement, sleep apnea, and prostate events has been low in trials of young men with hypogonadism. Erythrocytosis is the most frequent adverse event reported in RCTs of T. T therapy is associated with a significant but

Table 5. Clinical Pharmacology of T Formulations Approved in the United States and Europe

Formulation	Typical Starting Doses	Pharmacokinetic Profile	Advantages	Disadvantages
T enanthate or cypionate	150–200 mg IM every 2 wk or 75–100 mg/wk	After a single IM injection, serum T concentrations rise into the supraphysiological range, then decline gradually into the hypogonadal range by the end of the dosing interval	Relatively inexpensive, if self-administered; flexibility of dosing	Requires IM injection; peaks and valleys in serum T concentrations that may be associated with fluctuations in symptoms
T transdermal gels: 1%, 1.62%, or 2%	50–100 mg of 1% transdermal gel; 20.25–81 mg of 1.62% gel or 40–70 mg of 2% transdermal gel applied to skin; check package insert for application site and instructions	With appropriate dose, restores serum T and E2 concentrations to the physiological male range; less fluctuation of T concentrations than T enanthate or cypionate	Provides flexibility of dosing, ease of application, good skin tolerability; less erythrocytosis than injectable T	Potential of transfer to a female partner or child by direct skin-to-skin contact; T concentrations may be variable from application to application; skin irritation in a small proportion of treated men; moderately high DHT concentrations (of unknown significance)
T Axillary Solution	60 mg of T solution applied in the axillae	Restores serum T and E2 concentrations to the physiological male range	Provides, good skin tolerability	Potential of transfer to a female partner or child by direct skin-to-skin contact; T concentrations may be variable from application to application; skin irritation in a small proportion of treated men; moderately high DHT concentrations (of unknown significance)
Transdermal T patch	One or two patches, designed to nominally deliver 2–4 mg of T during 24 h applied every day on nonpressure areas	Restores serum T, DHT, and E2 concentrations to the physiological male range	Ease of application	Serum T concentrations in some T-deficient men may be in the low-normal range; these men may need applications of two patches daily; skin irritation at the application site occurs frequently in many patients
Buccal, bioadhesive T tablets	30-mg controlled release, bioadhesive tablets twice daily	Restores serum T, DHT, and E2 concentrations to the physiological male range; absorbed from the buccal mucosa	Convenience and discreet	Gum-related adverse events in 16% of treated men
T pellets	Pellets containing 600–1200 mg T implanted SC; the number of pellets and the regimen may vary with formulation	Serum T peaks at 1 month and then is sustained in normal range for 3–6 mo, depending on formulation	Requires infrequent administration	Requires surgical incision for insertions; pellets may extrude spontaneously; rarely, local hematoma and infection may occur
Injectable long-acting T undecanoate in oil	United States regimen: 750 mg IM, followed by 750 mg at 4 wk, and 750 mg every 10 wk	When administered at a dose of 750 mg IM, serum T concentrations are maintained in the normal range in most treated men	Requires infrequent administration	Requires IM injection of a large volume (3 or 4 mL); coughing episode reported immediately after injection in a small number of men

(*Continued*)

Table 5. Continued

Formulation	Typical Starting Doses	Pharmacokinetic Profile	Advantages	Disadvantages
Nasal T gel	11 mg two or three times daily	Serum T concentrations are maintained in the normal range in most treated men	Rapid absorption and avoidance of first pass metabolism	Multiple daily intranasal dosing required; local nasal side effects, not appropriate for men with nasal disorders

Adapted with permission from Bhasin *et al.* (7).

Abbreviations: DHT, dihydrotestosterone; E2, estradiol; IM, intramuscular(ly); SC, subcutaneous(ly).

small decrease in high-density lipoprotein cholesterol levels (87, 88). T therapy may increase the risk of serious adverse effects in men with some conditions (Table 7); we recommend against using T therapy in patients with these disorders.

Erythrocytosis. T administration increases hemoglobin and hematocrit (88, 89); these effects are related to T doses and circulating concentrations (89). In some men with hypogonadism, T therapy can cause erythrocytosis (hematocrit > 54%). The increase in hematocrit during T administration and the frequency of erythrocytosis is higher in older men than in young men (87). The commissioned meta-analysis showed that T treatment was associated with a significantly higher frequency of erythrocytosis vs placebo. The hematocrit level at which the risk of neuro-occlusive or cardiovascular events increases is not known. The frequency of neuro-occlusive events in men with hypogonadism enrolled in RCTs of T who developed erythrocytosis has been very low.

Clinicians should evaluate men who develop erythrocytosis during T-replacement therapy and withhold T therapy until hematocrit has returned to the normal range and then resume T therapy at a lower dose. Using therapeutic phlebotomy to lower hematocrit is also effective in managing T treatment–induced erythrocytosis.

Cardiovascular. There have been no RCTs that were large enough or long enough to determine the effects of T-replacement therapy on major adverse cardiovascular events (MACE). Additionally, there is no conclusive evidence that T supplementation is associated with increased cardiovascular risk in hypogonadal men.

The relationship of endogenous T concentrations and coronary artery disease in cross-sectional and prospective cohort studies has been inconsistent (90). The relationship between T concentrations and cardiovascular events in prospective epidemiologic studies is also inconsistent (91, 92). A small number of epidemiologic studies have reported a negative relationship between T concentrations and measures of subclinical atherosclerosis, such as common carotid artery intima–media thickness (92, 93).

The relationship of T and mortality has been heterogeneous across studies (32). A meta-analysis by Araujo *et al.* (32) associated lower T concentrations with higher risk for all-cause mortality, especially cardiovascular mortality. It is possible that T is a marker of health, and those who are at higher risk of dying have lower T concentrations. Epidemiological studies can only show association but cannot prove causality, and we cannot exclude reverse causality. Other studies suggest that men with erectile dysfunction and low T may have an increased risk of cardiovascular disease and all-cause mortality, but we cannot infer a causal association (94).

There are no adequately powered RCTs on the effects of T replacement on MACE. The few RCTs that have reported cardiovascular events were limited by their small

Table 6. Testosterone Formulations Available Outside the United States, but Not Approved by the FDA

Formulation	Regimen	Pharmacokinetic profile	Advantages	Disadvantages
Oral T undecanoate	40–80 mg oral, two or three times daily with meals	When administered in castor oil, T undecanoate is absorbed hrough the lymphatics, bypassing the portal system; considerable variability in the same individual on different days and among individuals	Convenience of oral administration	Variable clinical responses; administration with fatty meal is required; fat content of meals affects bioavailability; variable serum T concentrations, high DHT:T ratio
T-in-adhesive matrix patch	Two 60-cm^2 patches delivering ~4.8 mg	Restores serum T, DHT, and E2 to the physiological range	Lasts 2 d	Some skin irritation

Abbreviations: DHT, dihydrotestosterone; E2, estradiol.

Table 7. Conditions in Which T Administration Is Associated With a High Risk of Adverse Outcomes and for Which We Recommend Against Using T

Very high risk of serious adverse outcomes
Metastatic prostate cancer
Breast cancer
Moderate to high risk of adverse outcomes
Unevaluated prostate nodule or induration
Unevaluated PSA > 4 ng/mL (>3 ng/mL in individuals at high risk for prostate cancer, such as African Americans or men with first-degree relatives who have prostate cancer)
Hematocrit > 48% (>50% for men living at high altitude)
Severe LUTS associated with benign prostatic hypertrophy as indicated by AUA/IPSS > 19
Uncontrolled or poorly controlled congestive heart failure
Desire for fertility in the near term

Adapted with permission from Bhasin *et al.* (7).

Abbreviations: AUA, America Urological Association; IPSS, International Prostate Symptom Score.

Table 8. Potential Adverse Effects of T Replacement

Adverse events for which there is evidence of association with T administration
Erythrocytosis
Acne and oily skin
Detection of subclinical prostate cancer
Growth of metastatic prostate cancer
Reduced sperm production and fertility
Uncommon adverse events for which there is weak evidence of association with T administration
Gynecomastia
Male pattern balding (familial)
Growth of breast cancer
Induction or worsening of obstructive sleep apnea
Formulation-specific adverse effects
Intramuscular injections of T enanthate, cypionate, or undecanoate
Fluctuation in mood or libido
Pain at injection site
Coughing episodes immediately after the intramuscular injection[a]
Transdermal patches
Frequent skin reactions at application site
Transdermal gels and solutions
Potential risk for T transfer to partner or another person who is in close contact (need to remind patient to cover application sites with clothing and to wash skin and hands with soap before having skin-to-skin contact with another person)
Skin irritation and odor at application site
Stickiness, slow drying, dripping
Buccal T tablets
Alterations in taste
Irritation of gums
Pellet implants
Infection, expulsion of pellet
T nasal gel
Rhinorrhea, epistaxis, nasal discomfort, nasal congestion, parosmia
Oral tablets (methylT)—not recommended
Effects on liver and cholesterol[b]

Adapted with permission from Bhasin *et al.* (7).

[a]The mechanism of cough, which has been reported rarely after intramuscular injections of T undecanoate and even more rarely after T enanthate and cypionate, is unknown, but it has been attributed to pulmonary oil microembolization.

[b]Liver toxicity has been reported mostly with oral 17α-alkylated androgens.

size, short intervention durations, variable quality of adverse event reporting, and failure to prespecify and adjudicate cardiovascular events (79–82, 84, 95). Retrospective analyses of data using electronic medical records have also been inconclusive and are similarly constrained by the lack of randomized allocation and prospective adjudication of cardiovascular events, confounding by indication, and heterogeneity of patient populations, T doses, and intervention durations (96–101). A number of meta-analyses have examined the association between T-replacement therapy and cardiovascular events, MACE, and death in RCTs (101, 102). Many of these meta-analyses show point estimates > 1. However, most meta-analyses have not shown a statistically significant association between T treatment and cardiovascular events, MACE, or deaths. The trials included in these meta-analyses suffered from various limitations, including heterogeneity of eligibility criteria, dosing, formulations, and intervention durations; variability in the quality of adverse event recording; lack of large trial cohorts; failure to prespecify and adjudicate cardiovascular outcomes; and lack of a sufficient number of MACE. Thus, there are insufficient data to establish a causal link between T therapy and cardiovascular events.

In response to a citizen petition to add a "black box" warning about the potential cardiovascular dangers of T, the United States Food and Drug Administration (FDA) conducted an extensive review and concluded "the studies presented in the petition have significant limitations that weaken their evidentiary value for confirming a causal relationship between T and adverse cardiovascular outcomes" (103). Nevertheless, the FDA mandated pharmaceutical companies to add labeling information about a possible increased risk of cardiovascular events with the use of T. The European Medicines Agency concluded that there is no consistent evidence of an increased risk of coronary heart disease associated with T therapy in hypogonadal men (104).

Venous thromboembolism. Case-control and pharmacoepidemiologic studies have not shown a consistent increase in the risk of venous thromboembolism (VTE) with

T treatment (105, 106). However, there are too few T-associated VTE events in RCTs to draw meaningful inferences. Some case reports have suggested that the risk for VTE may be increased in the presence of thrombophilia even without a raised hematocrit, especially within the first 6 months after starting T therapy (105–107). The FDA has required manufacturers to include a warning about the risk of VTE for T products.

Prostate. The relationship between T administration and the risk of prostate cancer remains poorly understood (106). No RCT has been long enough or large enough to have adequate statistical power to determine whether T administration increases the risk of prostate cancer.

There is no strong evidence for the association between prostate cancer risk and T concentrations or polymorphisms in genes that encode for proteins involved in androgen action or metabolism (108–112). Meta-analyses of prospective epidemiologic studies found no significant association between T concentrations and the risk of prostate cancer, but there are some inconsistencies among studies (109, 112). However, androgen receptor signaling plays a central role in the biology of prostate cancer, T administration promotes the growth of metastatic prostate cancer, and androgen ablation can provide benefits for aggressive prostate cancer (113, 114). Therefore, we recommend against T supplementation in men with prostate cancer and suggest assessing prostate cancer risk prior to treatment initiation.

Many older men harbor small foci of subclinical cancer in their prostate (108); we do not know whether T replacement might cause these subclinical cancers to grow and become clinically overt.

T therapy increases the risk of detecting subclinical prostate cancer because of increased surveillance and T-induced increase in PSA levels, which may lead to increased risk of prostate biopsy (108). Because of the high prevalence of subclinical prostate cancer in older men, more prostate biopsies in men receiving T therapy would lead to the detection of a greater number of subclinical prostate cancers. In a meta-analysis of RCTs, a greater proportion of men randomized to T had prostate biopsies than those assigned to placebo (88). Prostate biopsy may be associated with adverse effects such as pain, fever, bleeding, infection, transient urinary difficulties, the psychological harm of false-positive test results, and overdiagnosis (115). Prostate cancer treatment can result in erectile dysfunction, urinary incontinence, bowel dysfunction, and a small risk of premature death. Because of the current inability to reliably distinguish tumors that will remain indolent from those destined to be lethal, many men are being subjected to the harms of treatment of prostate cancer that might never become symptomatic. Longer term follow-up of the participants of the European Randomized Study of Screening for Prostate Cancer (116) found that PSA-based screening for prostate cancer prevents one to two men from dying of prostate cancer for every 1000 men screened, and that screening 1000 men 55 to 69 years of age may prevent approximately three men from developing metastatic prostate cancer. Therefore, it is important to establish a standardized monitoring process and criteria for referring patients receiving T treatment for possible prostate biopsies to minimize the risks and expense of unnecessary testing.

Metastatic prostate cancer and breast cancer are hormone-dependent cancers that T treatment may stimulate to grow (114); T should not be administered to men with these cancers.

Although some clinicians have suggested considering patients with a history of organ-confined prostate cancer for T replacement on an individualized basis—if they have undergone radical prostatectomy, have undetectable PSA, and no detectable residual disease 2 or more years after surgery (117)—the lack of data from RCTs precludes a general recommendation.

An important objective of the baseline evaluation in men being considered for T-replacement therapy is to identify and exclude those who have a history of prostate cancer or are at high risk for developing prostate cancer. As previously noted, screening and monitoring for prostate cancer entails some risk. Most organizations that provide guidelines for prostate cancer screening strongly encourage informing the patient of the potential benefits and risks and engaging him in shared decision making regarding screening with PSA levels and digital rectal examination (DRE) (118). Clinicians should consider screening and monitoring for all men with hypogonadism who are 55 to 69 years of age, being considered for T-replacement therapy, and in excellent health, and who have a life expectancy >10 years. This should start at age 40 in men who are at increased risk for high-grade cancers, such as African Americans and men with a first-degree male relative with diagnosed prostate cancer. Men <40 years do not need prostate monitoring because the risk of prostate cancer is very low. The risk of death due to prostate cancer in men diagnosed when they are >70 years of age is not considered high enough to warrant monitoring. The baseline assessment of prostate cancer risk should consider risk factors, such as age, family history (increased risk in men having a first-degree relative with prostate cancer), race (increased risk in African Americans), prior biopsy history, elevated PSA levels, and positive prostate examination results. Clinicians can estimate the prostate cancer risk using the prostate cancer risk calculator (119), which considers

age, race, PSA levels, prostate examination results, family history, use of a 5-α-reductase inhibitor, and prior biopsy history. However, clinicians should only use the prostate cancer risk calculator for men 55 to 95 years old; furthermore, clinical experience with this tool is limited (especially in men with hypogonadism) and criteria for urological referral have not been established. The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial found that abnormal PSA and suspicious DRE are independently associated with clinically significant prostate cancer and prostate cancer–specific mortality (120). The predictive value of a suspicious DRE was greater in men who had a PSA level > 3.0 ng/mL (121).

A prostate nodule or induration or a PSA > 4.0 ng/mL may indicate a previously unrecognized prostate cancer. A confirmed PSA > 4.0 ng/mL is a widely accepted indication for urological evaluation for prostate cancer (122, 123).

Lower urinary tract symptoms. T therapy does not worsen lower urinary tract symptoms (LUTS) in men who do not have severe LUTS prior to treatment (124, 125). We do not know whether T worsens LUTS in men who have severe LUTS at baseline, because such men have been excluded from T trials.

Fertility. T therapy suppresses spermatogenesis and is not appropriate in men with hypogonadotropic hypogonadism who desire fertility in the next 6 to 12 months. Men who are not certain about future plans for conceiving children may want to bank their sperm if they are not azoospermic. Uncontrolled studies show that gonadotropin therapy can reinitiate spermatogenesis in men with hypogonadotropic hypogonadism who have been treated previously with T-replacement therapy (126). Not all hypogonadal men are necessarily infertile; a semen analysis may be performed prior to initiating treatment to determine whether contraception is needed.

Formulation-specific adverse effects of testosterone therapy. Table 8 lists the adverse effects associated with the use of specific T formulations.

Miscellaneous. T therapy can cause fluid retention and edema (127) and potentially worsen edema associated with heart failure or other edematous states. Although OSA and sleep disorders are associated with increased risk of low T concentrations, the frequency of OSA in randomized T trials has been very low.

Values and preferences

The recommendation to offer T therapy to healthy hypogonadal men places a higher value on alleviating symptoms of T deficiency and achieving the other benefits of T therapy and a lower value on avoiding the potential burden of long-term treatment, monitoring, cost, and the unclear long-term safety of T therapy.

Older men with age-related decline in testosterone concentration

2.4 We suggest against routinely prescribing testosterone therapy to all men 65 years of age or older with low testosterone concentrations (1|⊕⊕OO). In men > 65 years who have symptoms or conditions suggestive of testosterone deficiency (such as low libido or unexplained anemia) and consistently and unequivocally low morning testosterone concentrations, we suggest that clinicians offer testosterone therapy on an individualized basis after explicit discussion of the potential risks and benefits. (2|⊕⊕OO)

Evidence

TT and FT concentrations fall with increasing age in men (12, 91, 128). Because SHBG levels increase with advancing age, the decline in FT concentrations with age is greater than that in TT. The fall in T concentrations with age is gradual, and varies in different individuals with higher rates of decline in men with adiposity and comorbid diseases (12, 128, 129).

TTrials in older men. Initial RCTs of T in older men were characterized by relatively small sample sizes, inclusion of healthy men without symptoms of T deficiency, low-normal rather than frankly low T concentrations, and variable elevations of T in treated men (79–82, 84, 95, 130). In these trials, T treatment consistently increased LBM and vertebral BMD and decreased fat mass, but the effects on muscle strength, physical function, femoral bone density, sexual function, energy, and mood were variable. Additionally, no RCT was of sufficient size to evaluate risk.

The TTrials reported that T treatment of 1 year in symptomatic men ≥65 years of age resulted in moderate improvements in sexual function (sexual activity, sexual desire, and erectile function), a small improvement in walking distance, mood, and depressive symptoms, but no improvements in vitality and cognitive function (68). Also, a greater proportion of men who had anemia at baseline and were assigned to the T arm had hemoglobin increments > 1 g/dL compared with those in the placebo arm (131). T administration was associated with significantly greater increments in hemoglobin and PSA levels vs placebo. T administration significantly increased volumetric and areal BMD and the estimated strength of

trabecular and peripheral bone in the spine as well as hip (69). The increases were greater in trabecular bone than peripheral bone and greater in the spine than the hip.

In another RCT, T treatment in men >60 years who were not selected for sexual symptoms and who had baseline T concentrations >300 ng/dL was not associated with improvements in sexual function (56).

Adverse outcomes associated with testosterone therapy in older men. The TTrials observed men for adverse outcomes during the year of treatment and the year after treatment (68). Only three men treated with T and one treated with placebo were diagnosed with prostate cancer during those 2 years. During the year of treatment, the International Prostate Symptom Score increased to >19 (indicating moderately severe LUTS) in similar numbers of men in the placebo and testosterone arms. Seven men treated with T but none treated with placebo experienced an increase in hemoglobin to ≥17.5 g/dL. Compared with placebo, T treatment was associated with a significantly greater increase in coronary artery noncalcified plaque volume, as measured by coronary computed tomographic angiography (132). Similar numbers of men in both treatment groups experienced MACE during the year of treatment or the subsequent year of observation. Although the differences between the two treatment arms with regard to prostate and cardiovascular adverse outcomes were not statistically significant, the number of participants and the treatment duration in the TTrials were not sufficient to draw conclusions about the effect of T on these adverse outcomes. Another RCT in men ≥ 60 years old reported that the rate of subclinical atherosclerosis progression, assessed using common carotid artery intima–media thickness and multidetector computerized tomography, did not differ between T- and placebo-treated men (56).

Values and preferences

The recommendation not to treat asymptomatic older men with age-related declines in T concentration places a higher value on avoiding unknown long-term risks and a lower value on the limited evidence of the potential benefits of T therapy.

Physicians should recognize that there is considerable disagreement among experts on this issue due to incomplete evidence. Nonspecific age-related symptoms and low T concentrations often coexist in older men without a clear causal link. Although good evidence suggests that T treatment in older men with low T improves sexual function, anemia, vertebral and femoral BMD, and possibly walking distance, the risks of this treatment are unknown. Furthermore, we still do not know the long-term efficacy of T in improving patient-important outcomes, such as disability, falls, fractures, low-grade progressive depressive disorder, and progression to diabetes or dementia.

Patients with chronic illness and low testosterone concentrations

Many chronic disorders are associated with an increased risk of low T concentrations, sexual symptoms, weight loss, muscle atrophy, anemia, and/or osteoporosis. However, the paucity of RCT data on the efficacy or safety of T therapy in these conditions precludes a general recommendation for T therapy in patients with chronic illnesses. Clinicians must individualize the decision to treat or not to treat these men with T based on careful consideration of the severity of symptoms, the degree of T deficiency, confounding influence of the comorbid illness, patient preferences, and the uncertainty of the risks and benefits of T therapy.

HIV-infected men with weight loss

2.5 We suggest that clinicians consider short-term testosterone therapy in HIV-infected men with low testosterone concentrations and weight loss (when other causes of weight loss have been excluded) to induce and maintain body weight and lean mass gain. (2|⊕⊕OO)

Technical remark

- Diagnostic and treatment recommendations are the same as for patients with classical testosterone deficiency. Additionally, clinicians should provide appropriate counseling for safe sex practices.

Evidence

There is a high prevalence of low T concentrations in HIV-infected men (40, 133, 134). Twenty to 25% of HIV-infected men on highly active antiretroviral therapy have low TT or FT concentrations (134). Low T concentrations in HIV-infected men are associated with multimorbidity, HIV-associated non-AIDS conditions, progression to AIDS, frailty, weight loss, wasting, depression, and loss of muscle mass and exercise capacity (40, 133, 134).

In a systematic review of RCTs of T therapy in HIV-infected patients with weight loss (135), 3 to 6 months of T therapy was associated with greater gains in body weight (+1.54 kg; 95% CI, 0.03, 3.10) and LBM (+1.22 kg; 95% CI, 0.2, 2.2) vs placebo. The differences in LBM between placebo and T groups were greater in trials that used T esters (+3.34 kg). A Cochrane review also found greater weight and LBM gains in men assigned to androgens than in those assigned to placebo arms of

RCTs (136). T administration has also been associated with improvements in maximal voluntary strength (137, 138). There are no data on the effects of T on physical function, risk of disability, or long-term safety. In another systematic review of RCTs, T therapy had a moderate effect on depression (−0.6 SD units; 95% CI, −1.0, −0.2) (138, 139). There were no significant T effects on quality of life. Considerable heterogeneity across trials, varying degrees of weight loss and disease severity, variable T regimens and treatment durations, and imprecision all limited the strength of inferences.

The adverse event rates did not differ significantly between placebo and T groups. Changes in $CD4^+$ T lymphocyte counts, HIV viral load, PSA, and plasma high-density lipoprotein cholesterol were not significantly different between groups.

Overall, short-term (3 to 6 months) T use in HIV-infected men with low T concentrations and weight loss can lead to small gains in body weight, LBM, and mood, with minimal change in quality of life.

Values and preferences

The suggestion to offer short-term T therapy to HIV-infected men with low T concentrations and weight loss places a higher value on reversing weight loss and gaining LBM and muscle strength and a lower value on the lack of RCT evidence on the long-term safety of T therapy and the efficacy of T in improving physical function, disability, fracture risk, and other health outcomes. Although the evidence of benefit is limited to 6 months of therapy, shared decision making is needed regarding continuation of therapy beyond 6 months.

Men with type 2 diabetes mellitus

2.6 In men with type 2 diabetes mellitus who have low testosterone concentrations, we recommend against testosterone therapy as a means of improving glycemic control. (1|⊕⊕OO)

Technical remark

- Testosterone therapy in hypogonadal men who have T2DM should follow the same treatment and monitoring plan as hypogonadal men without T2DM.

Evidence

T2DM is associated with a high prevalence of low T concentrations. In cross-sectional studies of men with T2DM (140, 141), about one-third have low T concentrations, and TT concentrations were, on average, 86 ng/dL lower in men with T2DM vs controls (141). In epidemiological studies, TT concentrations are negatively associated with the risk of T2DM. The association of SHBG and TT with the risk of T2DM is stronger than for FT concentrations. Interventional studies designed to address whether low T concentrations contribute to the development of diabetes by modulating insulin resistance have yielded conflicting results. Some studies have demonstrated a favorable effect of T on insulin sensitivity in men with T2DM (142–144), whereas others showed no benefit (145, 146). Trials of the effects of T on glycemic control have also yielded variable results; some show no improvement in hemoglobin A1c (HbA1c), whereas others show a decrease. The discrepancy between studies likely reflects small sample size, differences in baseline HbA1c levels, degrees of insulin resistance, and the extent to which oral hypoglycemic agents were controlled during the study. A meta-analysis of RCTs of men with T2DM and/or the metabolic syndrome found no evidence of an improvement in HbA1c (141).

Values and preferences

The suggestion not to treat asymptomatic men with T2DM places a lower value on the unproven potential benefits of T therapy with regard to glycemic control and a higher value on avoiding the burdens of T administration, monitoring, and cost, as well as the unknown long-term risks of T therapy.

3. Monitoring of Testosterone-Replacement Therapy

3.1 In hypogonadal men who have started testosterone therapy, we recommend evaluating the patient after treatment initiation to assess whether the patient has responded to treatment, is suffering any adverse effects, and is complying with the treatment regimen. (Ungraded Good Practice Statement)

Technical remark

- Clinicians should maintain serum testosterone concentrations during treatment in the mid-normal range for healthy young men (Table 9).
- Clinicians should evaluate symptoms and signs of testosterone deficiency and formulation-specific adverse events at each visit (see Table 9).
- Monitoring includes measuring testosterone and hematocrit at 3 to 6 months (depending upon the formulation) and measuring testosterone and hematocrit at 12 months and annually after initiating testosterone therapy.
- For those who choose prostate monitoring, monitoring should include PSA and DRE 3 to 12 months

Table 9. Monitoring Men Receiving T Therapy

Explain the potential benefits and risks of monitoring for prostate cancer and engage the patient in shared decision making regarding the prostate monitoring plan.
Evaluate the patient at 3–12 mo after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects
Monitor T concentrations 3–6 mo after initiation of T therapy:
Therapy should aim to raise serum T concentrations into the mid-normal range.
Injectable T enanthate or cypionate: measure serum T concentrations midway between injections. If mid-interval T is >600 ng/dL (24.5 nmol/L) or <350 ng/dL (14.1 nmol/L), adjust dose or frequency.
Transdermal gels: assess T concentrations 2–8 h following the gel application, after the patient has been on treatment for at least 1 wk; adjust dose to achieve serum T concentrations in the mid-normal range.
Transdermal patches: assess T concentrations 3–12 h after application; adjust dose to achieve T concentration in the mid-normal range.
Buccal T bioadhesive tablet: assess concentrations immediately before or after application of fresh system.
T pellets: measure T concentrations at the end of the dosing interval. Adjust the number of pellets and/or the dosing interval to maintain serum T concentrations in the mid-normal range.
Oral T undecanoate[a]: monitor serum T concentrations 3–5 h after ingestion with a fat-containing meal.
Injectable T undecanoate: measure serum T levels at the end of the dosing interval just prior to the next injection and aim to achieve nadir levels in low-mid range.
Check hematocrit at baseline, 3–6 mo after starting treatment, and then annually. If hematocrit is >54%, stop therapy until hematocrit decreases to a safe level; evaluate the patient for hypoxia and sleep apnea; reinitiate therapy with a reduced dose.
Measure BMD of lumbar spine and/or femoral neck after 1–2 y of T therapy in hypogonadal men with osteoporosis, consistent with regional standard of care.
For men 55–69 years of age and for men 40–69 years of age who are at increased risk for prostate cancer who choose prostate monitoring, perform digital rectal examination and check PSA level before initiating treatment; check PSA and perform digital rectal examination 3–12 mo after initiating T treatment, and then in accordance with guidelines for prostate cancer screening depending on the age and race of the patient.
Obtain urological consultation if there is:
An increase in serum PSA concentration >1.4 ng/mL within 12 mo of initiating T treatment
A confirmed PSA > 4 ng/mL at any time
Detection of a prostatic abnormality on DRE
Substantial worsening of LUTS
Evaluate formulation-specific adverse effects at each visit as per Table 5.

Adapted with permission from Bhasin *et al.* (7).

[a]Not available in the United States.

after treatment initiation. After 1 year, prostate monitoring should conform to guidelines for prostate cancer screening, depending on the race and age of the patient.

3.2 We recommend a urological consultation for hypogonadal men receiving testosterone treatment if during the first 12 months of testosterone treatment there is a confirmed increase in PSA concentration > 1.4 ng/mL above baseline, a confirmed PSA > 4.0 ng/mL, or a prostatic abnormality detected on digital rectal examination. After 1 year, prostate monitoring should conform to standard guidelines for prostate cancer screening based on the race and age of the patient. (2|⊕⊕OO)

Technical remark

- Clinicians should confirm PSA elevations by repeating the test to exclude the possibility of transient rises (e.g., due to prostatitis or assay variability).
- In hypogonadal men whose baseline PSA is between 2.6 and 4 ng/mL, an increase >4 ng/mL during testosterone treatment could be due to test–retest variability and/or the testosterone-induced increase in PSA; therefore, in such men, the decision to refer the patient for urological evaluation should be guided by a confirmed increase of >1.4 ng/mL in PSA concentration above baseline as well as the absolute PSA level of >4 ng/mL.

Evidence

There is considerable variation in T concentrations in hypogonadal men who are receiving T therapy (8, 147); this variation is even greater in hypogonadal men being treated with transdermal gels or with oral T undecanoate. Subtherapeutic T concentrations may contribute to poor efficacy and high treatment discontinuation rates. Furthermore, a small fraction of hypogonadal men develop supraphysiologic T concentrations with intramuscular T and may be susceptible to dose-related adverse effects. Therefore, it is important to measure T concentrations in the patient group once a steady-state has been achieved. The pharmacokinetics of the T formulation should guide the timing of therapeutic level monitoring, as shown in Table 9. Multiple dose titrations are usually necessary to maintain T concentrations in the therapeutic range in hypogonadal men who are receiving T therapy.

T administration in hypogonadal men is associated with a dose-dependent increase in hemoglobin concentrations (88); the increase in hemoglobin is greater in older men than in young hypogonadal men (89). Baseline hematocrit > 48% and > 50% for men living at higher altitudes is a relative contraindication to T therapy because these men are more likely to develop a hematocrit

> 54% when treated with T. Men with elevated hematocrit should undergo further evaluation before considering T therapy. Clinicians should measure hematocrit at baseline, 3 to 6 months, and then annually after a patient begins T therapy.

As discussed earlier, T therapy increases the risk of detection of subclinical prostate disease due to increased surveillance and T-induced increases in PSA concentrations, which may lead to increased risk of prostate biopsy. Some men may develop a new prostate cancer unrelated to T treatment. It is also possible that T administration may cause subclinical prostate cancers (which may have been present before but were undetected) to grow during T administration and become clinically overt. An important goal of the monitoring plan is to detect those who develop a prostate cancer during T treatment (regardless of its relationship to T treatment) to evaluate those at increased risk of having a prostate cancer and to minimize the risk of unnecessary prostate biopsy in those who are not at increased risk of prostate cancer.

T-replacement therapy increases PSA concentrations in hypogonadal men. In a systematic review, the average PSA increase after initiating T therapy was 0.3 ng/mL in young hypogonadal men and 0.44 ng/mL in older men (108). The 90% confidence limit was 1.4 ng/mL for the change in PSA concentrations between two PSA tests performed 3 to 6 months apart in men with benign prostatic hyperplasia (148). Increases in PSA concentrations > 1.4 ng/mL during 3 to 6 months after T therapy in hypogonadal men are unusual (148). In the TTrials, PSA increases > 1.4 ng/mL occurred in 2.4% of men at 3 months and 4.7% of men at 12 months in the T group and 1.6% and 0.6%, respectively, in the placebo group (68). A confirmed PSA > 4.0 ng/mL is a widely accepted indication for urological evaluation for prostate cancer (122, 123).

Because of the T-induced increase in PSA and the test–retest variability of PSA measurements, some hypogonadal men with baseline PSA between 2.6 and 4.0 ng/mL will develop PSA concentrations > 4.0 ng/mL after initiating T treatment. Therefore, in hypogonadal men treated with T whose baseline PSA was between 2.6 and 4 ng/mL, we suggest clinicians consider both a confirmed increase of >1.4 ng/mL in PSA concentration above baseline and the absolute PSA level when deciding to refer the patient for further urological evaluation. Transient PSA elevations are common and may be due to test–retest variability (149) or other disorders, such as prostatitis, benign prostatic hyperplasia, prostate trauma, urinary tract infections, or assay variability. If PSA elevation is due to prostatitis, appropriate antibiotic treatment may lower PSA level (150). Therefore, clinicians should confirm PSA elevations by repeating the test.

Similarly, the detection of a prostate nodule or an induration may indicate an unrecognized cancer. Based on these considerations, we recommend that clinicians obtain a urological consultation if a prostatic abnormality is detected on DRE.

Because of the considerable controversy over prostate cancer screening and monitoring, clinicians should discuss the risks and benefits of prostate cancer screening and monitoring and engage the patient in shared decision making prior to starting T treatment (115, 118).

In men with osteoporosis who are not considered to be at high risk for fracture, clinicians should repeat BMD measurements 1 to 2 years after initiating T therapy to determine the response to T and to ascertain whether the patient needs additional therapy with an approved osteoporosis drug.

Other syndromes associated with hypogonadism in men

AAS withdrawal hypogonadism

AAS use suppresses the hypothalamic–pituitary–testicular axis in men. AAS withdrawal after an extended period of high-dose AAS use is associated with marked suppression of endogenous T concentrations and severe symptoms of AAS withdrawal hypogonadism, including sexual dysfunction, fatigue, depressed mood, and sometimes clinical depression and even suicidality (151). The recovery of endogenous T may vary depending on the dose and duration of AAS use. After prolonged use of highly supraphysiologic doses of AAS, the recovery of the hypothalamic–pituitary–testicular axis may take months and even years and may be incomplete. A small minority of these men may never recover normal endogenous T production and require T-replacement therapy (38). In some men's health clinics, a substantial fraction of young men receiving T prescriptions have a history of prior AAS use (37, 39). The distressing symptoms of AAS withdrawal hypogonadism may lead some AAS users to relapse into recurrent AAS abuse resulting in a vicious cycle of AAS dependence (38).

Hypogonadism associated with chronic opioid use

Hypogonadotropic hypogonadism is common in men receiving chronic enteral, parenteral, or intrathecal opioid medications for pain management (152). Nearly all opioids in doses equivalent to 30 mg of methadone suppress endogenous T production, although longer acting opioids induce greater and more sustained suppression of T concentrations. Men receiving methadone maintenance therapy are at high risk of developing opioid-induced hypogonadism, whereas the prevalence of opioid-induced hypogonadism is substantially lower with buprenorphine. Although long-term health

Appendix. Conflict of Interest of Testosterone Therapy in Men with Hypogonadism Guideline Task Force Members

Task Force Member	Employment	Uncompensated Leadership	Personal Financial	Organizational Financial	Spousal/Family Information
Shalender Bhasin, MD (Chair)	Chief, Research Program in Men's Health: Aging and Metabolism; Director, Boston Claude D. Pepper Older Americans Independence Center, Brigham and Women's Hospital	None declared	National Institute on Aging, research support National Institute of Nursing Research, research support PCORI, research support AbbVie, research support and consultant Metro International Biotechnology, research support Alivegen, research support Abbott, research support Transition Therapeutics, research support Function Promoting Therapies, LLC, equity interest (phase II)	None declared	None declared
Juan P. Brito Campana, MD	Senior Associate Consultant, Division of Endocrinology, Diabetes, Metabolism, Nutrition; Principal Investigator, Knowledge and Evaluation Research Unit, Mayo Clinic	None declared	None declared	None declared	None declared
Glenn R. Cunningham, MD	Distinguished Professor Emeritus, Department of Medicine, Baylor College of Medicine	None declared	AbbVie, consultant Clarus Therapeutics, consultant Ferring Pharmaceuticals, consultant Eli Lilly, consultant Lipocine, consultant Repros Therapeutics, expert witness Merck, expert witness	None declared	None declared
Frances J. Hayes, MD	Clinical Director, Reproductive Endocrine Associates; Co-Director Turner Syndrome Clinic; Clinical Director Endocrine Division, Massachusetts General Hospital	None declared	None declared	None declared	None declared
Howard N. Hodis, MD	Director, Atherosclerosis Research Unit, Keck School of Medicine of USC	None declared	None declared	None declared	None declared

(*Continued*)

Appendix. Continued

Task Force Member	Employment	Uncompensated Leadership	Personal Financial	Organizational Financial	Spousal/Family Information
Alvin M. Matsumoto, MD	Associate Director, Geriatric Research, Education and Clinical Center; Director, Clinical Research Unit, Veterans Affairs Puget Sound Health Care System	American Society for Bone and Mineral Research, Partnership for the Accurate Testing of Hormones	AbbVie, research support GlaxoSmithKline, research support AbbVie, consultant AYTU, consultant Endo, consultant Lipocine, consultant UpToDate, editor U.S. Anti-Doping Agency, TUE Committee Partnership for Clean Competition, Scientific Advisory Board	None declared	None declared
Peter J. Snyder, MD	Medical Director, Penn Pituitary Center, University of Pennsylvania Professor of Medicine, Perelman School of Medicine at the University of Pennsylvania	None declared	UpToDate, Co-Editor-in-Chief AbbVie, research support	None declared	None declared
Ronald S. Swerdloff, MD	Chief of Division of Endocrinology, Harbor UCLA Medical Center; Chief of Endocrinology, Los Angeles Biomedical Research Institute	None declared	Novartis, consultant and investigator Axon, consultant advisory board Clarus, consultant and investigator Merck, consultant Abbott, consultant Antares, consultant AEZ, consultant Chiasma, advisory board Quest Diagnostics, consultant	None declared	Spouse: Novartis, consultant and onvestigator Axon, consultant advisory board Clarus, consultant and investigator Merck, consultant Abbott, consultant Antares, consultant AEZ, consultant Chiasma, advisory board Quest Diagnostics, consultant
Frederick C. Wu, MD	Professor of Medicine and Endocrinology, University of Manchester	None declared	Bayer-Schering, advisory board Eli Lilly, advisory Board Besins Health Care, advisory board, research support Repros Therapeutics, consultant Merck Serono, research support Mereo Biopharma, research support	None declared	None declared
Maria A. Yialamas, MD	Associate Program Director, Harvard Medical School Associate Program Director, Internal Medicine Residency Program, Brigham and Women's Hospital	None declared	None declared	None declared	None declared

consequences of chronic opioid use are not completely understood, opioid-induced suppression of the endogenous hypothalamic–pituitary–testicular axis is associated with sexual dysfunction, low mood, osteoporosis, and increased risk of fracture (152–154). Chronic opioid use has emerged as a common antecedent of T prescription use in some health care systems (155).

Only limited clinical trials data are available on the benefits of T therapy in men with opioid-induced hypogonadism (156). In one RCT in men with opioid-induced T deficiency, T administration improved pain sensitivity, sexual desire, body composition, and some aspects of quality of life (156). Clinicians should consider T-replacement therapy in men with opioid-induced hypogonadism who are experiencing sexual symptoms and in whom discontinuation of opioid medication seems unlikely.

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Disclosure Summary: See Appendix.

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