

CLINICAL PRACTICE GUIDELINE

Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline

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Objective: The objective was to provide guidelines for the evaluation and treatment of androgen deficiency syndromes in adult men.

Participants: The Task Force was composed of a chair, selected by the Clinical Guidelines Subcommittee of The Endocrine Society, five additional experts, a methodologist, and a professional writer. The Task Force received no corporate funding or remuneration.

Evidence: The Task Force used systematic reviews of available evidence to inform its key recommendations. The Task Force used consistent language and graphical descriptions of both the strength of recommendation and the quality of evidence, using the recommendations of the Grading of Recommendations, Assessment, Development, and Evaluation group.

Consensus Process: Consensus was guided by systematic reviews of evidence and discussions during three group meetings, several conference calls, and e-mail communications. The drafts prepared by the panelists with the help of a professional writer were reviewed successively by The Endocrine Society's Clinical Guidelines Subcommittee, Clinical Affairs Committee, and Council. The version approved by the Council was placed on The Endocrine Society's web site for comments by members. At each stage of review, the Task Force received written comments and incorporated needed changes.

Summary of Evidence-Based Guidelines for Use of Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes

THE TASK FORCE used systematic reviews of available evidence to inform its key recommendations. The number 1 indicates a strong recommendation and is associated

Conclusions: We recommend making a diagnosis of androgen deficiency only in men with consistent symptoms and signs and unequivocally low serum testosterone levels. We suggest the measurement of morning total testosterone level by a reliable assay as the initial diagnostic test. We recommend confirmation of the diagnosis by repeating the measurement of morning total testosterone and in some patients by measurement of free or bioavailable testosterone level, using accurate assays. We recommend testosterone therapy for symptomatic men with androgen deficiency, who have low testosterone levels, to induce and maintain secondary sex characteristics and to improve their sexual function, sense of well-being, muscle mass and strength, and bone mineral density. We recommend against starting testosterone therapy in patients with breast or prostate cancer, a palpable prostate nodule or induration or prostate-specific antigen greater than 3 ng/ml without further urological evaluation, erythrocytosis (hematocrit > 50%), hyperviscosity, untreated obstructive sleep apnea, severe lower urinary tract symptoms with International Prostate Symptom Score (IPSS) greater than 19, or class III or IV heart failure. When testosterone therapy is instituted, we suggest aiming at achieving testosterone levels during treatment in the mid-normal range with any of the approved formulations, chosen on the basis of the patient's preference, consideration of pharmacokinetics, treatment burden, and cost. Men receiving testosterone therapy should be monitored using a standardized plan. (*J Clin Endocrinol Metab* 91: 1995–2010, 2006)

with the phrase "we recommend"; 2 denotes a weak recommendation and is associated with the phrase "we suggest." Evidence grading: $\oplus\ominus\ominus$ denotes very low quality evidence; $\oplus\ominus\ominus$, low quality; $\oplus\oplus\ominus$, moderate quality; and $\oplus\oplus\oplus$, high quality. Numbers to the left of individual recommendations correspond to numbers in the text. Hence, there may

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Abbreviations: CI, Confidence interval; ED, erectile dysfunction; HPG, hypothalamic-pituitary-gonadal; LBM, lean body mass; MRI, magnetic resonance imaging.

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be duplicate numbers below, and the order may not be strictly numerical.

1. Diagnosis

1.1 We recommend making a diagnosis of androgen deficiency only in men with consistent symptoms and signs and unequivocally low serum testosterone levels. (1|⊕○○○)

1.1 We suggest the measurement of morning total testosterone level by a reliable assay as the initial test for the diagnosis of androgen deficiency in men. (2|⊕○○○)

1.1 We recommend confirmation of the diagnosis by repeating the measurement of morning total testosterone and in some patients by measurement of free or bioavailable testosterone level, using an appropriate assay system. (1|⊕○○○)

1.2.1 We recommend against screening for androgen deficiency in the general population. (1|⊕○○○)

1.2.2 We suggest that clinicians not use the available case-finding instruments for detection of androgen deficiency in men receiving health care for unrelated reasons. (2|⊕○○○)

1.2.2 We suggest that clinicians consider case detection by measurement of total testosterone levels in men with certain clinical disorders, listed in Table 3, in which the prevalence of low testosterone levels is high or for whom testosterone therapy is suggested/recommended in *Section 2.0*. (2|⊕○○○)

2. Treatment

2.1 We recommend testosterone therapy for symptomatic men with the classical androgen deficiency syndromes who have low testosterone levels to induce and maintain secondary sex characteristics and to improve their sexual function, sense of well-being, muscle mass and strength, and bone mineral density. (1|⊕○○○)

2.2 We suggest that clinicians offer testosterone therapy to men with low testosterone levels and low libido to improve libido (2|⊕○○○) and to men with erectile dysfunction (ED) who have unequivocally low testosterone levels, after evaluation of underlying causes of ED and consideration of established therapies for ED. (2|⊕○○○)

2.3 We recommend against a general clinical policy of offering testosterone therapy to *all* older men with low testosterone levels. (1|⊕○○○)

2.3 We suggest that clinicians consider offering testosterone therapy on an individualized basis to older men with consistently low testosterone levels on more than one occasion and significant symptoms of androgen deficiency, after appropriate discussion of the uncertainties of the risks and benefits of testosterone therapy in older men. (2|⊕○○○)

2.4.1 We suggest that clinicians consider short-term testosterone therapy as an adjunctive therapy in HIV-infected men with low testosterone levels and weight loss to promote weight maintenance and gains in lean body mass (LBM) and muscle strength. (2|⊕○○○)

2.4.2 We suggest that clinicians offer short-term testosterone therapy to men receiving high doses of glucocorticoids who have low testosterone levels to promote preservation of LBM and bone mineral density. (2|⊕○○○)

2.1 We recommend against starting testosterone therapy in

patients with breast (1|⊕○○○) or prostate cancer. (1|⊕○○○)

2.1 We recommend against starting testosterone therapy in patients with a palpable prostate nodule or induration, or prostate-specific antigen (PSA) greater than 3 ng/ml without further urological evaluation. (1|⊕○○○)

2.1 We recommend against starting testosterone therapy in patients with erythrocytosis (hematocrit >50%), hyperviscosity, untreated obstructive sleep apnea, severe untreated benign prostatic hypertrophy with IPSS symptom score >19, or uncontrolled severe heart failure. (1|⊕○○○)

2.1.D Administration

When testosterone therapy is recommended, we suggest aiming at achieving serum testosterone levels during treatment in the mid-normal range with any of the following regimens, chosen on the basis of the patient's preference, consideration of pharmacokinetics, treatment burden, and cost: (2|⊕○○○)

- 75–100 mg of testosterone enanthate or cypionate administered im weekly, or 150–200 mg administered every 2 wk.
- One or two 5-mg nongenital, testosterone patches applied nightly over the skin of the back, thigh, or upper arm, away from pressure areas.
- 5–10 g of a testosterone gel applied daily over a covered area of nongenital skin (patients should wash hands after application).
- 30 mg of a bioadhesive buccal testosterone tablet applied to buccal mucosa every 12 h.
- Oral testosterone undecanoate, injectable testosterone undecanoate, and testosterone pellets where available.

2.1.D Monitoring strategies and schedule

- We recommend evaluating the patient 3 months after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering any adverse effects. (1|⊕○○○)
- We suggest monitoring testosterone levels 3 months after initiation of testosterone therapy. (2|⊕○○○)

- Therapy should restore serum testosterone levels to the mid-normal range.
- Testosterone cypionate or enanthate: measure serum testosterone levels midway between injections. If serum testosterone level is greater than 700 ng/dl (24.5 nmol/liter) or less than 350 ng/dl (12.3 nmol/liter), adjust dose or frequency.
- Transdermal patch: assess testosterone levels 3 to 12 h after application of the patch.
- Buccal tablet: assess levels immediately before application of fresh system.
- Transdermal gel: assess testosterone level after patient has been on treatment for 1 to 2 wk.

- We recommend determining hematocrit at baseline, at 3 months, and then annually. If hematocrit is greater than

54%, stop therapy until hematocrit decreases to a safe level, evaluate the patient for hypoxia and sleep apnea, and reinitiate therapy at a reduced dose. (1|⊕○○○)

- We suggest repeating bone mineral density of the lumbar spine, femoral neck, and hip after 1 to 2 yr of testosterone therapy in hypogonadal men with osteoporosis or low trauma fracture. (2|⊕○○○)
- We recommend digital examination of the prostate and PSA measurement before initiating treatment, at 3 months, and then in accordance with evidence-based guidelines for prostate cancer screening, depending on the age and race of the patient. (1|⊕○○○)
- We recommend that clinicians obtain urological consultation if there is: (1|⊕○○○)
 - Verified serum or plasma PSA concentration greater than 4.0 ng/ml.
 - An increase in serum or plasma PSA concentration greater than 1.4 ng/ml within any 12-month period of testosterone treatment.
 - A PSA velocity of more than 0.4 ng/ml·yr using the PSA level after 6 months of testosterone administration as the reference. PSA velocity should be used only if there are longitudinal PSA data for more than 2 yr.
 - Detection of a prostatic abnormality on digital rectal examination.
 - An American Urological Association (AUA) prostate symptom score of more than 19.
- We recommend evaluation for symptoms and signs of formulation-specific adverse events at each visit: (1|⊕○○○)
 - Buccal testosterone tablets: inquire about alterations in taste and examine gums and oral mucosa for irritation.
 - Injectable testosterone esters: inquire about fluctuations in mood or libido and evaluate hematocrit to detect excessive erythrocytosis, especially in older patients.
 - Testosterone patch: look for signs of skin reaction at the application site.
 - Testosterone gels: advise patients to cover the application site with clothing and wash the skin before having skin-to-skin contact, because gels leave a residue of testosterone on the skin that can be transferred to a woman or child who comes in close contact.

METHOD OF DEVELOPMENT OF EVIDENCE-BASED GUIDELINES

The Clinical Guidelines Subcommittee of The Endocrine Society deemed testosterone therapy in androgen-deficient men a priority area in need of practice guidelines and appointed a six-member Task Force to formulate evidence-based recommendations. The Task Force elected to use the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation group, an international group with expertise in development and implementation of evidence-based guidelines (1).

The Task Force used systematic reviews of available evidence to inform its key recommendations and consistent language and graphical descriptions of both the strength of

a recommendation and the quality of evidence. The strength of a recommendation is indicated by the number 1 (strong recommendation, associated with the phrase "we recommend") or 2 (weak recommendation, associated with the phrase "we suggest"). The quality of the evidence is indicated by cross-filled circles, such that ⊕○○○ denotes very low quality evidence; ⊕⊕○○, low quality; ⊕⊕⊕○, moderate quality; and ⊕⊕⊕⊕, high quality.

Each *recommendation* is followed by a description of the *evidence*, *values* that panelists considered in making the recommendation, and in some instances *remarks*, a section in which panelists offer technical suggestions for dosing and monitoring. These technical comments reflect the best available evidence applied to a typical patient. Often, this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions.

GUIDELINES

1.0 Diagnosis of Hypogonadism

1.0.1 Definition of hypogonadism. Hypogonadism in men is a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and the normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-gonadal (HPG) axis.

1.0.2 Classification of hypogonadism. Abnormalities of the HPG axis at the testicular level cause primary testicular failure, whereas central defects of the hypothalamus or pituitary cause secondary testicular failure.

- Primary testicular failure results in low testosterone levels, impairment of spermatogenesis, and elevated gonadotropin levels.
- Secondary testicular failure is associated with low or low-normal gonadotropin levels and low testosterone levels.

This classification has therapeutic implications because fertility can be restored with appropriate hormonal stimulation in patients with secondary hypogonadism, but not primary hypogonadism. Fertility options for men with primary testicular failure are limited to the use of donor sperm, adoption, or, in some patients, intracytoplasmic sperm injection. Also, further evaluation of secondary hypogonadism may uncover a pituitary tumor or systemic illness.

Less commonly, hypogonadism can reflect dual defects in the HPG axis in men with DAX-1 mutations, hemochromatosis, sickle cell disease, thalassemia, glucocorticoid treatment, and alcoholism, and in older men (2).

The age-related decline in testosterone levels, confirmed in several cross-sectional and longitudinal studies (3, 4), results from defects in both testicular and hypothalamic-pituitary function. Because the average decline in serum testosterone levels with aging in men is 1–2% per year (3, 4), only a subset of aging men has levels clearly below the lower limit of the normal range for healthy, young men (5).

1.1 Diagnosis and Evaluation of Patients with Suspected Androgen Deficiency

1.1.A RECOMMENDATIONS

We recommend making a diagnosis of androgen deficiency only in men with consistent symptoms and signs and unequivocally low serum testosterone levels. (1|⊕○○○)

We suggest that clinicians measure serum testosterone level in patients with clinical manifestations shown in Table 1A. We suggest that clinicians also consider measuring serum testosterone level when the less specific symptoms and signs listed in Table 1B occur in conjunction with those listed in Table 1A. (2|⊕○○○)

We suggest the measurement of morning total testosterone level by a reliable assay as the initial diagnostic test. (2|⊕○○○)

We recommend confirmation of the diagnosis by repeating measurement of total testosterone and in some patients by measurement of free or bioavailable testosterone level, using an appropriate assay. (1|⊕○○○)

We suggest that a diagnosis of androgen deficiency should not be made during an acute or subacute illness. (2|⊕⊕○○)

1.1.B EVIDENCE

The clinical presentation of male hypogonadism depends on the age of onset of androgen deficiency. Onset in adulthood leads to a clinical syndrome substantially different from that resulting from onset in the fetal or prepubertal period.

Diagnosis of androgen deficiency in men poses challenges. Symptoms and signs are nonspecific and modified by age, comorbid illness, severity and duration of androgen deficiency, variation in androgen sensitivity, and previous testosterone therapy. The signs and symptoms listed in Table 1 are based on the panelists' experience in clinic-based populations of androgen-deficient men who are likely to have more severe androgen deficiency; population-based surveys in men with classical androgen deficiency have not been conducted. In one cross-sectional survey of middle-aged and older men, the presence of diabetes mellitus and coronary

TABLE 1A. Symptoms and signs suggestive of androgen deficiency in men

- Incomplete sexual development, eunuchoidism, aspermia
- Reduced sexual desire (libido) and activity
- Decreased spontaneous erections
- Breast discomfort, gynecomastia
- Loss of body (axillary and pubic) hair, reduced shaving
- Very small or shrinking testes (especially < 5 ml)
- Inability to father children, low or zero sperm counts
- Height loss, low trauma fracture, low bone mineral density
- Reduced muscle bulk and strength
- Hot flushes, sweats

TABLE 1B. Other symptoms and signs associated with androgen deficiency that are less specific than those in Table 1A

- Decreased energy, motivation, initiative, aggressiveness, self-confidence
- Feeling sad or blue, depressed mood, dysthymia
- Poor concentration and memory
- Sleep disturbance, increased sleepiness
- Mild anemia (normochromic, normocytic, in the female range)
- Increased body fat, body mass index
- Diminished physical or work performance

artery disease was a good predictor of low testosterone levels (6).

Serum testosterone levels vary significantly as a result of circadian and circannual rhythms, episodic secretion, and measurement variations. Testosterone concentrations may be affected by illness and certain medications (e.g. opiates and glucocorticoids). Testosterone measurements are also influenced by alterations in SHBG concentrations.

The threshold testosterone level below which symptoms of androgen deficiency and adverse health outcomes occur is not known and may be age-dependent. Furthermore, the testosterone concentration below which testosterone administration improves outcomes is unknown and may vary among individuals and among target organs (7–9). Therefore, the available evidence does not support use of an arbitrary threshold for testosterone level below which clinical androgen deficiency occurs and that confirms the diagnosis of hypogonadism in all patients.

It is important to confirm low testosterone concentrations in men with an initial testosterone level in the mildly hypogonadal range, because 30% of such patients may have a normal testosterone level on repeat measurement (10). Also, 15% of healthy young men may have a testosterone level below the normal range in a 24-h period (11).

Serum total testosterone concentrations, representing the sum of unbound and protein-bound testosterone in circulation, are measured by RIA, immunometric assays, or liquid chromatography tandem mass spectrometry. Most of the circulating testosterone is bound to SHBG and to albumin (2); only 0.5–3% of circulating testosterone is unbound or "free." The free fraction can be measured by equilibrium dialysis. The term "bioavailable testosterone" refers to unbound testosterone plus testosterone bound loosely to albumin; this term reflects the view that in addition to the unbound testosterone, albumin-bound testosterone is readily dissociable and thus bioavailable. Bioavailable testosterone levels can be measured by the ammonium sulfate precipitation method. Free and bioavailable testosterone concentrations can also be calculated from total testosterone and SHBG concentrations using published algorithms (2).

Automated assays for total testosterone are available in most hospital laboratories and usually are sufficiently accurate to distinguish eugonadal from hypogonadal men (12). Total testosterone levels are affected by alterations in SHBG

TABLE 2. Conditions associated with alterations in SHBG concentrations

Conditions associated with decreased SHBG concentrations

- Moderate obesity^a
- Nephrotic syndrome^a
- Hypothyroidism
- Use of glucocorticoids, progestins, and androgenic steroids^a

Conditions associated with increased SHBG concentrations

- Aging^a
- Hepatic cirrhosis^a
- Hyperthyroidism
- Use of anticonvulsants^a
- Use of estrogens
- HIV infection

^a Particularly common conditions associated with alterations in SHBG concentrations.

that occur in obese men; older men; men with comorbid illness, hyper- and hypothyroidism, and acromegaly; and men taking certain medications (Table 2).

Accurate and reliable assays for free or bioavailable testosterone measurements usually are not available in local laboratories and should be performed in a reliable reference laboratory. Free testosterone measurements by analog methods frequently are available in local laboratories, but these measurements are affected by alterations in SHBG and are inaccurate (13). Free testosterone level can be measured accurately by equilibrium dialysis or calculated from total testosterone, SHBG, and albumin. Bioavailable testosterone is measured by ammonium sulfate precipitation or calculated from total testosterone and SHBG.

The normative ranges for total and free testosterone levels in healthy young men vary among laboratories and assays. In some laboratories, the lower limit of the normal range for total testosterone level in healthy young men is 300 ng/dl (10.4 nmol/liter). Similarly, in some reference laboratories, the lower limit of the normal range for serum free testosterone level, measured by the equilibrium dialysis method, is 50 pg/ml (0.17 nmol/liter). The clinicians should use the lower limit of normal range for healthy young men established in their reference laboratory.

The assessment of men for androgen deficiency should include a general health evaluation to exclude systemic ill-

ness, use of certain medications (e.g. opiates or high-dose glucocorticoid therapy) and recreational drugs that affect testosterone production or metabolism, eating disorders, and excessive exercise (2) because these conditions can lower testosterone levels transiently. The diagnosis of androgen deficiency should not be made during an acute illness.

1.1.C VALUES

Our proposed diagnostic strategy places higher value on avoiding the labeling of men with low testosterone levels due to SHBG abnormalities, natural variations in testosterone levels, or transient disorders, and lower value on treatment of men without unequivocally low testosterone levels and symptoms in whom the benefits and risks of testosterone therapy are unclear.

1.1.1 Further evaluation of men deemed androgen deficient (Fig. 1)

1.1.1.A RECOMMENDATIONS

We recommend measurement of serum LH and FSH levels to distinguish between primary (testicular) and secondary (pituitary-hypothalamic) hypogonadism. (1|⊕⊕○○)

In men with secondary hypogonadism, we suggest further evaluation on an individualized basis to identify the etiology of hypothalamic and/or pituitary dysfunction. This evaluation may in-

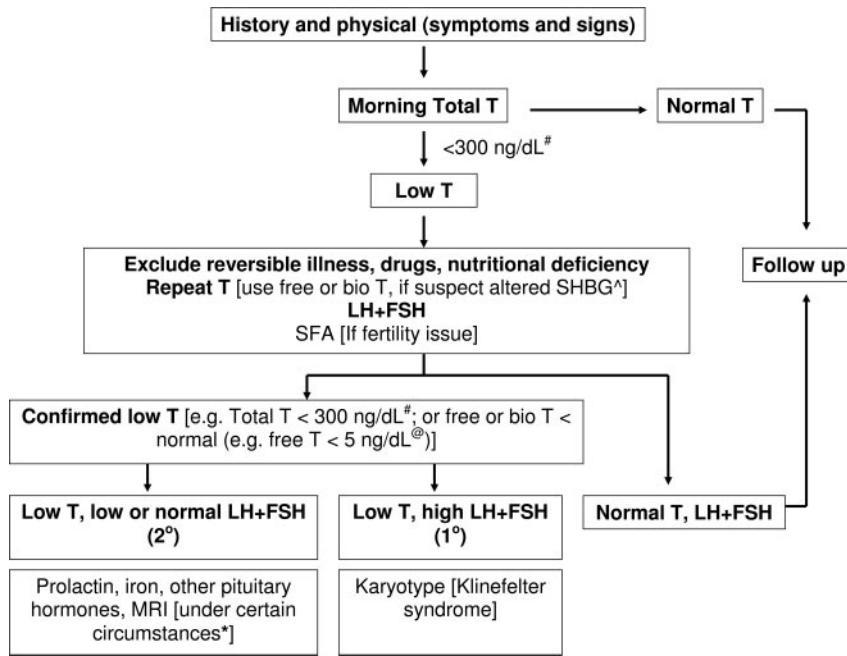


FIG. 1. An approach for the diagnostic evaluation of adult men suspected of having androgen deficiency. T, Testosterone; bio T, bioavailable T; SFA, seminal fluid analysis; 1°, primary testicular failure; 2°, secondary hypogonadism. #, In some laboratories, the lower limit of the normal testosterone range in healthy young men is approximately 300 ng/dl (10.4 nmol/liter); however, this range may vary in different laboratories. Use the lower limit of the range established in your reference laboratory. ^, Refer to Table 2 for a list of conditions that alter SHBG concentrations. @, In some reference laboratories, the lower limit of the normal free testosterone range in healthy young men is approximately 5 ng/dl (0.17 nmol/liter) (approximate lower limit of normal in three major commercial laboratories) using equilibrium dialysis or calculated from total testosterone and SHBG; however, this range may vary in different laboratories [approximate lower limits of normal ranging from 4 to 9 ng/dl (0.14 to 0.31 nmol/liter) in major commercial laboratories] using equilibrium dialysis or calculated from total testosterone and SHBG and the reference population used. Use the lower limit of the range established in your reference laboratory. *, Perform pituitary imaging (MRI) to exclude pituitary and/or hypothalamic tumor or infiltrative disease, if severe secondary hypogonadism (serum T < 150 ng/dl), panhypopituitarism, persistent hyperprolactinemia, or symptoms or signs of tumor mass effect, such as headache, visual impairment, or visual field defect, are present.

clude measurements of serum prolactin and iron saturation, pituitary function testing, and magnetic resonance imaging (MRI) scanning. (2|⊕○○○)

In men with primary testicular failure of unknown etiology, we suggest obtaining a karyotype to exclude Klinefelter's syndrome. (2|⊕○○○)

In men being evaluated for infertility, we recommend obtaining seminal fluid analysis. (1|⊕⊕○○)

We suggest measurement of bone mineral density by using DXA scanning in men with severe androgen deficiency or low trauma fracture. (2|⊕○○○)

1.1.1.B EVIDENCE

In men deemed to have secondary hypogonadism, additional diagnostic evaluation may be needed to exclude pituitary neoplasia, hyperprolactinemia, hemochromatosis and other infiltrative diseases, obstructive sleep apnea, and genetic disorders associated with gonadotropin deficiency. The measurement of serum prolactin and iron saturation can help determine the presence of hyperprolactinemia and hemochromatosis, respectively. Assessment of anterior pituitary function, if clinically indicated or in the presence of severe secondary hypogonadism (testosterone level < 150 ng/dl), can uncover other pituitary hormone deficiencies. A diagnosis of idiopathic hypogonadotropic hypogonadism is made after excluding other causes of hypogonadotropic hypogonadism. Patients with idiopathic hypogonadotropic hypogonadism should be examined for dysmorphic features—such as extreme obesity, polydactyly, anosmia, short stature, or kidney abnormalities—to facilitate recognition of specific syndromes by pattern recognition.

The cost-effectiveness of pituitary imaging (MRI) to exclude pituitary and/or hypothalamic tumor is unknown. One survey of men with sexual dysfunction revealed a low prevalence of hypothalamic-pituitary abnormalities (14). The diagnostic yield of pituitary imaging to exclude pituitary and/or hypothalamic tumor can be improved by performing this procedure in men with serum testosterone below 150 ng/dl, panhypopituitarism, persistent hyperprolactinemia, or symptoms of tumor mass effect (headache, visual impairment, or visual field defect) (15).

Klinefelter's syndrome, a common identifiable cause of primary testicular failure, can be diagnosed by obtaining a karyotype. These patients can benefit from genetic counseling.

Testosterone stimulates bone formation and inhibits bone resorption through multiple mechanisms that involve both androgen and estrogen receptor-mediated processes (16). However, the cost-effectiveness of measuring bone mineral density and the frequency at which it should be performed are still being debated.

The cost-effectiveness of these diagnostic strategies has not been evaluated in clinical trials.

1.1.1.C VALUES

Recommendations in favor of performing additional tests to diagnose primary etiologic disorders place a higher value on detecting the presence of pituitary neoplasia or other treatable pituitary disorders and on ascer-

taining the need for additional treatment or counseling and a lower value on avoiding the burden and cost of tests with unknown yield.

1.2 Screening for Androgen Deficiency

1.2.1 Screening in the general population

1.2.1.A RECOMMENDATION

We recommend against screening for androgen deficiency in the general population. (1|⊕○○○)

1.2.1.B EVIDENCE

Because of the lack of consensus on a case definition and the extent to which androgen deficiency is an important health problem, as well as the lack of data on the performance characteristics of candidate screening tools, the usefulness of population screening cannot be evaluated at present. The long-term health consequences of low testosterone levels are unknown in the two largest subsets of men with low testosterone levels—older men and men with chronic illness. The impact of untreated androgen deficiency on mortality is unclear (17). The benefits and adverse consequences of long-term testosterone therapy on patient-important outcomes in asymptomatic men with presumed hypogonadism remain unclear (5, 18). Therefore, screening for androgen deficiency does not fulfill any of the necessary criteria to justify it. No clinical trials have assessed the effectiveness of screening strategies. (Quality of evidence: ⊕○○○)

1.2.1.C VALUES

The recommendation not to screen men in the general population places a high value on avoiding labeling and medicalization of otherwise healthy men for whom testing, treatment, and monitoring would represent a burden with unclear benefit. 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 androgen deficiency in men who have not sought medical attention.

TABLE 3. Conditions in which there is a high prevalence of low testosterone levels and in which we suggest measurement of serum testosterone levels

- Sellar mass, radiation to the sellar region, or other diseases of the sellar region
- Treatment with medications that affect testosterone production or metabolism, such as glucocorticoids, ketoconazole, and opioids
- HIV-associated weight loss
- End-stage renal disease and maintenance hemodialysis
- Moderate to severe chronic obstructive lung disease
- Infertility
- Osteoporosis or low trauma fracture, especially in a young man
- Type 2 diabetes mellitus

A high prevalence of low testosterone levels has been reported in men with several chronic disorders. This list is not exhaustive. Most surveys of men with chronic illness included relatively small, convenience samples. The information about the benefits and risks of testosterone therapy in these conditions is either limited or not available.

1.2.2 Case finding of androgen deficiency

1.2.2.A RECOMMENDATIONS

We suggest that clinicians not use the available case-finding instruments for detection of androgen deficiency in men receiving health care for unrelated reasons. (21⊕○○○)

We suggest that clinicians consider case detection by measurement of total testosterone levels in men with certain clinical disorders, listed in Table 3, in which the prevalence of low testosterone levels is high or for whom testosterone therapy is suggested/recommended in Section 2.0. (21⊕○○○)

1.2.2.B EVIDENCE

Ideally, case detection should identify from the clinic population patients who present with medical problems apparently unrelated to androgen deficiency, but who are likely to benefit from testosterone therapy. Candidate groups in whom there is high prevalence of low testosterone levels and in whom we suggest measurement of serum testosterone level are listed in Table 3; these include men with chronic illness, such as those with HIV-associated weight loss, end-stage renal disease on dialysis, chronic obstructive pulmonary disease, osteoporosis or fracture after low trauma at a young age, type 2 diabetes mellitus, and men receiving chronic glucocorticoid and opioids (2, 22–25). Most surveys of men with chronic illness included relatively small, convenience samples. The information about the benefits and risks of testosterone therapy in these conditions is either limited or not available.

There is limited information about the performance properties of case-detection instruments that rely on self-report, namely, Androgen Deficiency in Aging Males (ADAM) (19), the Aging Males' Symptoms (AMS) Rating Scale (20), and the Massachusetts Male Aging Study Questionnaire (21). There are no trials of case-detection strategies in these patient populations, and the cost-effectiveness of the use of case-finding instruments over measurement of serum testosterone levels is unknown. (Quality of evidence: ⊕○○○)

1.2.2.C VALUES

Our recommendation in favor of case detection by measurement of testosterone levels places a relatively high value on the potential benefits and a relatively low value on the burden of testosterone therapy and uncertainty about its long-term safety.

2.0 Treatment of Androgen Deficiency with Testosterone

2.1 Testosterone Therapy in Adult Men with Classical Androgen Deficiency

2.1.A RECOMMENDATIONS

We recommend testosterone therapy for symptomatic men with classical androgen deficiency syndromes aimed at inducing and maintaining secondary sex characteristics and at improving their sexual function, sense of well-being, and bone mineral density. (11⊕○○○)

We recommend against testosterone therapy in patients with breast (11⊕○○○) or prostate cancer. (11⊕○○○)

We recommend against testosterone therapy in patients with

palpable prostate nodule or induration or PSA below 3 ng/ml without further urological evaluation. (11⊕○○○)

We recommend against testosterone therapy in patients with erythrocytosis, hyperviscosity, untreated obstructive sleep apnea, severe benign prostatic hyperplasia symptoms (AUA prostate symptom score > 19), or uncontrolled severe heart failure. (11⊕○○○)

We suggest that when clinicians prescribe testosterone therapy, the therapeutic target should be to raise serum testosterone levels into a range that is mid-normal for healthy, young men. (21⊕○○○)

2.1.B EVIDENCE

2.1.1 Non-placebo-controlled studies. Lowering of testosterone concentrations in adult men by surgical orchiectomy or by GnRH agonist or antagonist administration is associated with rapid and marked loss of bone mineral density (16), increase in fat mass (26), and a loss of muscle mass and strength (26). Lowering of testosterone concentrations also results in hot flushes and a decrease in overall sexual activity, thoughts, and fantasies.

Testosterone therapy of young, hypogonadal men is associated with improvements in overall sexual activity scores, frequency of sexual thoughts and fantasies, an increase in attentiveness to erotic stimuli, and an increase in the frequency and duration of nighttime erections (27–29). Testosterone therapy increases hair growth in several androgen-sensitive areas. Testosterone therapy of healthy, hypogonadal men also increases fat-free mass (29–38) and muscle strength (30) and decreases fat mass (29, 33, 35, 37). Testosterone administration in hypogonadal men is associated with a dose-dependent increase in hemoglobin levels (39); the increase in hemoglobin is greater in older men than in young hypogonadal men (40).

Although testosterone therapy of healthy, hypogonadal men increases bone mineral density, the effects of testosterone on fracture risk are unknown (33, 41).

Testosterone therapy improves the positive and reduces the negative aspects of mood (29). Uncontrolled studies report improvements in energy and sense of well-being after testosterone therapy (42). The effects of testosterone on cognitive function are poorly understood; some studies report small effects on visuospatial cognition and verbal memory and fluency (43, 44).

Previous studies have reported conflicting effects of testosterone therapy on insulin sensitivity (45, 46).

TABLE 4. Conditions in which testosterone administration is associated with a high risk of adverse outcome and in which testosterone should not be administered

Very high risk of serious adverse outcomes

- Metastatic prostate cancer
- Breast cancer

Moderate to high risk of adverse outcomes

- Undiagnosed prostate nodule or induration
- Unexplained PSA elevation
- Erythrocytosis (hematocrit > 50%)
- Severe lower urinary tract symptoms associated with benign prostatic hypertrophy as indicated by AUA/IPSS > 19
- Unstable severe congestive heart failure (class III or IV)

Testosterone therapy may be associated with increased risk of serious adverse effects in men with some types of disorders (Table 4). Metastatic prostate cancer and breast cancer are hormone-dependent cancers that may be stimulated to grow during testosterone treatment (47); testosterone should not be administered to men with these cancers. Although some have suggested that patients with low testosterone levels who have been disease-free 2 or more years after radical prostatectomy and who have undetectable PSA levels may be considered for testosterone replacement on an individualized basis (48, 49), the lack of randomized trials data precluded a general recommendation.

A prostate nodule or induration or an elevated PSA may indicate previously unrecognized prostate cancer. Furthermore, in men with erythrocytosis, untreated obstructive sleep apnea, severe lower urinary tract symptoms, or severe congestive heart failure, testosterone may worsen these conditions (5, 50).

Open-label studies in young, hypogonadal men have found a low frequency of adverse events with replacement doses of testosterone (50). Common drug-related adverse events include increase in hematocrit, acne, oiliness of skin, and breast tenderness (Table 5). The frequency of breast enlargement, sleep apnea, and prostate events is low in trials of young, hypogonadal men.

2.1.2 Placebo-controlled, randomized trials. Our systematic review found no randomized, placebo-controlled trials of the effect of testosterone therapy on depression, cognition, fra-

TABLE 5. Potential adverse effects of testosterone replacement

- A. Adverse events for which there is evidence of association with testosterone administration
 - Erythrocytosis
 - Acne and oily skin
 - Detection of subclinical prostate cancer
 - Growth of metastatic prostate cancer
 - Reduced sperm production and fertility
- B. Uncommon adverse events for which there is weak evidence of association with testosterone administration
 - Gynecomastia
 - Male pattern balding (familial)
 - Worsening of BPH symptoms
 - Growth of breast cancer
 - Induction or worsening of obstructive sleep apnea
- C. Formulation-specific adverse effects
 - Oral tablets
 - Effects on liver and cholesterol (methyltestosterone)
 - Pellet implants
 - Infection, expulsion of pellet
 - Intramuscular injections of testosterone enanthate or cypionate
 - Fluctuation in mood or libido
 - Pain at injection site
 - Excessive erythrocytosis (especially in older patients)
 - Transdermal patches
 - Skin reactions at application site
 - Transdermal gel
 - Potential risk for testosterone transference to partner (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)
 - Buccal testosterone tablets
 - Alterations in taste
 - Irritation of gums

gility fractures, quality of life, or cardiovascular outcomes in young, hypogonadal men. In trials that reported the effect of testosterone on libido (36, 51–53) and erectile function (36, 51, 54, 55) in hypogonadal men, testosterone therapy was associated with greater improvements in libido [1.2; 95% confidence interval (CI), 0.3, 2.2] and nonsignificant improvements in self-reported erectile function (0.8; 95% CI, −0.05, 1.6) than placebo. The inconsistency across trials and imprecision of pooled estimates weaken these inferences.

Most studies of testosterone therapy in young, hypogonadal men have been open-label and did not include a placebo group. The observations in these open-label studies are consistent with the sparse data from randomized trials and with the experience of the panelists. (Quality of evidence: $\oplus\ominus\ominus\ominus$)

2.1.C VALUES

The recommendation to offer testosterone therapy to healthy, hypogonadal men with classical androgen deficiency syndromes places a relatively higher value on alleviating hypogonadal symptoms and other benefits of testosterone therapy and a relatively lower value on avoiding the potential burden of long-term treatment, monitoring, cost, and its unclear long-term safety.

2.1.D REMARKS

Table 6 summarizes the clinical pharmacology of the available testosterone formulations. When clinicians recommend testosterone therapy, we suggest aiming at achieving testosterone levels in a range that is mid-normal for healthy, young men. Testosterone therapy can be initiated with any of the suggested regimens, in accord with considerations of the patient's preference, pharmacokinetics of testosterone formulation, treatment burden, and cost (Table 7).

Monitoring of androgen-deficient men receiving testosterone therapy. Androgen-deficient men receiving testosterone therapy should be followed according to a standardized, monitoring plan (Table 8) to facilitate early detection of adverse events and to prevent unnecessary prostate biopsies that might lead to detection of subclinical prostate cancer.

A difficult issue in the follow-up of hypogonadal men receiving testosterone therapy relates to the criteria that should be used to guide the decision to perform prostate biopsy. PSA measurements have considerable test-retest variability (56). The 90% confidence limit for the change in PSA levels between two tests performed 3 to 6 months apart in a study of men with benign prostatic hyperplasia was 1.4 ng/ml (57). In a systematic review, the average PSA increase after initiation of testosterone therapy was 0.3 ng/ml in young, hypogonadal men and 0.44 ng/ml in older men (58). The increases in PSA levels after testosterone therapy in androgen-deficient men in excess of 1.4 ng/ml over a 3- to 6-month period are unusual. These considerations led us to suggest urological consultation for evaluation of confirmed PSA increments greater than 1.4 ng/ml during any 1-yr period after starting testosterone therapy. In men for whom sequential PSA measurements are available for more than 2 yr, Carter (59) has proposed the use of PSA velocity to iden-

TABLE 6. Clinical pharmacology of some testosterone formulations

Formulation	Regimen	Pharmacokinetic profile	DHT and E2	Advantages	Disadvantages
T enanthate or cypionate	100 mg/wk im or 200 mg every 2 wk im	After a single im injection, serum T levels rise into the supraphysiological range, then decline gradually into the hypogonadal range by the end of the dosing interval.	DHT and E2 levels rise in proportion to the increase in T levels. T:DHT and T:E2 ratios do not change.	Corrects symptoms of androgen deficiency. Relatively inexpensive, if self-administered. Flexibility of dosing.	Requires im injection. Peaks and valleys in serum T levels
Scrotal T patch ^a	One scrotal patch designed to nominally deliver 6 mg over 24 h applied daily	Normalizes serum T levels in many but not all androgen-deficient men	Serum E2 levels are in the physiological male range, but DHT levels rise into the supraphysiological range. T:DHT ratio is significantly lower than in healthy men.	Corrects symptoms of androgen-deficiency	To promote optimum adherence of the patch, scrotal skin needs to be shaved. High DHT levels
Nongenital transdermal system	1 or 2 patches, designed to nominally deliver 5–10 mg T over 24 h applied daily on nonpressure areas	Restores serum T, DHT, and E2 levels into the physiological male range	T:DHT and T:E2 levels are in the physiological male range	Ease of application, corrects symptoms of androgen deficiency and mimics the normal diurnal rhythm of T secretion. Lesser increase in hemoglobin than injectable esters	Serum T levels in some androgen-deficient men may be in the low-normal range; these men may need application of 2 patches daily. Skin irritation at the application site may be a problem for some patients.
T gel	5–10 g T gel containing 50–100 mg T should be applied daily.	Restores serum T and E2 levels into the physiological male range	Serum DHT levels are higher and T:DHT ratios are lower in hypogonadal men treated with the T gel than in healthy eugonadal men.	Corrects symptoms of androgen deficiency, provides flexibility of dosing, ease of application, good skin tolerability	Potential of transfer to a female partner or child by direct skin-to-skin contact; moderately high DHT levels
17- α -methyl T	This 17- α -alkylated compound should not be used because of potential for liver toxicity	Orally active			Clinical responses are variable; potential for liver toxicity. Should not be used for treatment of androgen deficiency
Buccal, bioadhesive, T tablets	30 mg controlled release, bioadhesive tablets used twice daily	Absorbed from the buccal mucosa	Normalizes serum T and DHT levels in hypogonadal men	Corrects symptoms of androgen deficiency in healthy, hypogonadal men	Gum-related adverse events in 16% of treated men
Oral T undecanoate ^b	40 to 80 mg orally 2 or 3 times daily with meals	When administered in oleic acid, T undecanoate is absorbed through the lymphatics, bypassing the portal system. Considerable variability in the same individual on different days and among individuals	High DHT to T ratio	Convenience of oral administration	Not approved in the United States. Variable clinical responses, variable serum T levels, high DHT:T ratio
Injectable long-acting T undecanoate in oil ^b	1000 mg injected im, followed by 1000 mg at 6 wk, and 1000 mg every 12 wk	When administered at a dose of 1000 mg im, serum T levels are maintained in the normal range in a majority of treated men.	DHT and E2 levels rise in proportion to the increase in T levels; T:DHT and T:E2 ratios do not change.	Corrects symptoms of androgen deficiency. Requires infrequent administration	Requires im injection of a large volume (4 ml)
T pellets	Four to six 200-mg pellets implanted sc	Serum T peaks at 1 month and then sustained in normal range for 4–6 months	T:DHT and T:E2 ratios do not change	Corrects symptoms of androgen deficiency	Requires surgical incision for insertions; pellets may extrude spontaneously

T, Testosterone; DHT, dihydrotestosterone; E2, estradiol.

^a Not available in the United States currently.^b Formulation available outside the United States, but not approved currently by the U.S. Food and Drug Administration.

TABLE 7. Some recommended regimens^a for testosterone replacement therapy

- 75–100 mg of testosterone enanthate or cypionate administered im weekly, or 150 to 200 mg administered every 2 wk.
- One or two 5-mg nongenital, testosterone patches applied nightly over the skin of the back, thigh, or upper arm, away from pressure areas.
- 5 to 10 g of testosterone gel applied daily over a covered area of skin.
- 30 mg of a bioadhesive, buccal testosterone tablet applied to buccal mucosa twice daily.

Outside the United States, oral testosterone undecanoate (typically used at a dose of 40 to 80 mg orally two or three times daily with meals), injectable formulation of testosterone undecanoate (typically used at a dose of 1000 mg im initially and at 6 wk followed by 1000 mg im every 12 wk), and testosterone pellets (typically, four to six 200-mg pellets implanted every 4 to 6 months) are available for clinical use in many countries; physicians in those countries who wish to use these formulations should follow the drug regimens approved in those countries. See Tables 6 and 8 for additional safety and pharmacokinetics information.

^aThese regimens should be viewed as suggestions for initiation of testosterone replacement therapy; dose and regimen should be adjusted on the basis of measurement of serum testosterone levels.

tify men at higher risk for prostate cancer. For periods of less than 3 yr, PSA velocity above 0.4 ng/ml·yr should warrant a urological evaluation and more intensive future surveillance for prostate cancer (58).

2.2. Testosterone Therapy in Men with Sexual Dysfunction

2.2.A RECOMMENDATION

We suggest that clinicians offer testosterone therapy to men with low testosterone levels and low libido to improve libido (2 | ⊕⊕○○) and to men with ED who have unequivocally low testosterone levels after evaluation of underlying causes of ED and consideration of established therapies for ED. (2 | ⊕○○○)

2.2.B EVIDENCE

Spontaneous and experimentally induced androgen deficiency is associated with a decreased frequency of sexual thoughts and fantasies, nighttime erections, and overall sexual activity and decreased attentiveness to erotic stimuli (9, 28, 29, 52, 60, 61). Androgen deficiency is an important cause of hypoactive sexual desire disorder. However, androgen deficiency and ED are two independently distributed clinical disorders with distinct pathophysiology; the two disorders may coexist in middle-aged and older men (62).

Libido. Among randomized trials that enrolled patients with total testosterone levels below 300 ng/dl (10.4 nmol/liter), we found two parallel trials (36, 63) and three crossover trials (51, 53, 64) reporting effects on libido; the longest trial followed participants for 6 months. The results of these trials were inconsistent but revealed a large improvement in libido (1.2 SD units; 95% CI, 0.3, 2.2). (Quality of evidence: ⊕⊕○○)

Among trials that enrolled men with total testosterone levels above 300 ng/dl (10.4 nmol/liter), we found four trials in men with ED or low libido that reported effects on libido (54, 65, 66). The pooled effect of testosterone on libido was not significant (0.4 SD units; 95% CI, -0.1, 0.9). Lack of pre-

cision around this estimate weakens this inference. (Quality of evidence: ⊕⊕○○)

Erectile dysfunction. A meta-analysis by Jain et al. (67) evaluated the effects of testosterone therapy in men with ED. Among 16 published studies (67), 57% of subjects experienced an improvement in erectile function. In our systematic review of randomized placebo-controlled trials that enrolled patients with total testosterone less than 300 ng/dl (10.4 nmol/liter), two parallel trials (36, 63) and two crossover trials (54, 55) reported effects on erectile function. The results were inconsistent across trials, and the pooled estimate was not significant (0.8 SD units; 95% CI, -0.05, 1.6). (Quality of evidence: ⊕○○○)

In the trial of older men with low free testosterone levels and borderline low total testosterone levels (63), oral testosterone yielded a moderate treatment effect on sexual function (0.5 SD units; 95% CI, 0.05, 0.9). In two trials of young, hypogonadal men with low total testosterone levels (55, 68), oral testosterone administration was associated with a larger treatment effect (1.8 SD units; 95% CI, 1.0, 2.7). The largest trial (36) that examined the effects of transdermal testosterone on erectile function reported a nonsignificant effect (-0.2 SD units, 95% CI, -0.6, 0.1). The inconsistency across trials and the imprecision of the pooled estimates weaken the inference. (Quality of evidence: ⊕○○○)

Among trials that enrolled men with total testosterone greater than 300 ng/dl (10.4 nmol/liter), we found two parallel trials in men with ED in whom sildenafil had failed (65, 69) and three crossover trials in men with either low libido or ED (66, 70). These trials reported inconsistent and non-significant effects on erectile function (0.4 SD units; 95% CI, -0.1, 0.8). The inconsistency across trials and the imprecision of the pooled estimate weaken our inferences. (Quality of evidence: ⊕○○○)

Other sexual outcomes. Several trials reported on the impact of testosterone therapy on other sexual outcomes, namely, orgasmic and ejaculatory function, intercourse, and overall satisfaction. Generally, the effect of testosterone was positive, but the data came from a few trials with inconsistent findings and incomplete reporting yielding imprecise estimates. (Quality of evidence: ⊕○○○)

2.2.C VALUES

Our recommendation to offer testosterone therapy to men with hypoactive sexual desire or ED who have unequivocally low testosterone levels places a relatively higher value on improving these complaints and a relatively lower value on avoiding the burden of testosterone therapy and its unclear long-term safety. Older patients with a greater potential for adverse effects may opt to avoid testosterone therapy.

2.2.D REMARKS

Diagnostic and treatment recommendations are the same as for patients with classical androgen deficiency (Sections 1.1 and 2.1). Men with sexual dysfunction should be evaluated for the underlying causes, including low testosterone levels.

TABLE 8. Monitoring of men receiving testosterone therapy

- Evaluate the patient 3 months after treatment starts and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects.
- Monitor testosterone levels 2 or 3 months after initiation of testosterone therapy:
 - Therapy should aim to raise serum testosterone levels into the mid-normal range.
 - Injectable testosterone enanthate or cypionate: Measure serum testosterone levels midway between injections. If testosterone is >700 ng/dl (24.5 nmol/liter) or <350 ng/dl (12.3 nmol/liter), adjust dose or frequency.
 - Transdermal patch: Assess testosterone levels 3–12 h after application of the patch; adjust dose to achieve testosterone levels in the mid-normal range.
 - Buccal testosterone bioadhesive tablet: Assess levels immediately before or after application of fresh system.
 - Transdermal gel: Assess testosterone level any time after patient has been on treatment for at least 1 wk; adjust dose to achieve serum testosterone levels in the mid-normal range.
 - Oral testosterone undecanoate^a: monitor serum testosterone levels 3 to 5 h after ingestion.
 - Injectable testosterone undecanoate^a: Measure serum testosterone level just prior to each subsequent injection and adjust the dosing interval to maintain serum testosterone in mid-normal range.
- Check hematocrit at baseline, at 3 months, 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 bone mineral density of lumbar spine and/or femoral neck after 1–2 yr of testosterone therapy in hypogonadal men with osteoporosis or low trauma fracture, consistent with regional standard of care.
- Perform digital rectal examination and check PSA level before initiating treatment, at 3 months, 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:
 - Verified serum PSA concentration >4.0 ng/ml
 - An increase in serum PSA concentration >1.4 ng/ml within any 12-month period of testosterone treatment
 - A PSA velocity of >0.4 ng/ml/yr using the PSA level after 6 months of testosterone administration as the reference (only applicable if PSA data are available for a period exceeding 2 yr)
 - Detection of a prostatic abnormality on digital rectal examination
 - An AUA or IPSS prostate symptom score of >19
- Evaluate formulation-specific adverse effects at each visit:
 - Buccal testosterone tablets: inquire about alterations in taste and examine the gums and oral mucosa for irritation.
 - Injectable testosterone esters (enanthate and cypionate): ask about fluctuations in mood or libido.
 - Testosterone patches: look for skin reaction at the application site.
 - Testosterone gels: Advise patients to cover the application sites with a shirt and to wash the skin with soap and water before having skin-to-skin contact, because testosterone gels leave a testosterone residue on the skin that can be transferred to a woman or child who might come in close contact. Serum testosterone levels are maintained when the application site is washed 4–6 h after application of the testosterone gel.

^a Not approved for clinical use in the United States.

2.3 Older Men with Low Serum Testosterone Concentration

2.3.A RECOMMENDATION

We recommend against a general clinical policy of offering testosterone therapy to all older men with low testosterone levels. (1) \oplus ○○○

We suggest that clinicians consider offering testosterone therapy on an individualized basis to older men with consistently low testosterone levels on more than one occasion and clinically significant symptoms of androgen deficiency, after explicit discussion of the uncertainty about the risks and benefits of testosterone therapy. (2) \oplus ○○○

The panelists disagreed on serum testosterone levels below which testosterone therapy should be offered to older men with symptoms. Depending on the severity of clinical manifestations, some panelists favored treating symptomatic older men with a testosterone level below 300 ng/dl (10.4 nmol/liter); others favored a level below 200 ng/dl (6.9 nmol/liter).

2.3.B EVIDENCE

Several cross-sectional and longitudinal studies (3, 4) demonstrate that serum total and free testosterone concentrations in men fall with increasing age. Although the fall is gradual, by the eighth decade, according to one study (4), 30% of men had total testosterone values in the hypogonadal range, and

50% had low free testosterone values. The rate of age-related decline in serum testosterone levels varies in different individuals and is affected by chronic disease and medications (4, 6).

Testosterone Trials in Older Men

In randomized, placebo-controlled trials of 1- to 3-yr duration in older men with low-normal to low testosterone concentrations (71–73), testosterone administration was associated with sustained increase in testosterone levels. Overall, testosterone trials in older men were characterized by small sample size, inclusion of healthy older men with low or low-normal testosterone levels who were asymptomatic, and the use of surrogate outcomes; these studies did not have sufficient power to detect either meaningful gains in patient-important outcomes or changes in prostate and cardiovascular event rates (72–79).

Bone mineral density. We did not find any trials reporting the effect of testosterone on bone fractures. A systematic review of randomized, placebo-controlled trials of 1- to 3-yr duration that evaluated effects on bone mineral density yielded inconsistent and imprecise results: the trial following patients for 1 yr yielded an insignificant effect (72) (-0.01 SD units; 95% CI, -0.6 , 0.6); two longer trials (71, 80) showed a moderate treatment effect on lumbar bone mineral density (0.4 SD units; 95% CI, 0.1 , 0.7), equivalent to an increase in

lumbar bone density of 2% (95% CI, 0.5, 3.3). These trials ruled out a moderate-to-large testosterone effect on femoral neck bone density (0.0 SD units; 95% CI, -0.3, 0.3).

Body composition. In our systematic review (72–74, 77, 79, 81, 82), testosterone therapy was associated with a significantly greater increase in LBM (2.7 kg; 95% CI, 1.6, 3.7) and a greater reduction in fat mass (-2.0 kg; 95% CI, -3.1, -0.8) than placebo. The body weight change did not differ significantly between groups (-0.6 kg; 95% CI, -2.0, 0.8).

Muscle strength and physical function. Testosterone therapy was associated with a greater improvement in grip strength than placebo (3.3 kg; 95% CI, 0.7, 5.8) (76–78, 82). Changes in lower-extremity muscle strength and measures of physical function were reported in only a few studies and were inconsistent. One study reported no changes in physical function (73), whereas another reported improvement in a composite measure of physical function (77).

Sexual function. Two placebo-controlled trials (63, 73) reported on the effect of testosterone on overall sexual satisfaction, yielding imprecise results (0.2 SD units; 95% CI, -0.02, 0.57).

Quality of life. Four placebo-controlled randomized trials (75, 83–85) reported on testosterone's effect on quality of life. The results were inconsistent across trials and imprecise. There was significant improvement only for the physical function domain (0.5 SD units; 95% CI, 0.03, 0.9).

Depression. Systematic review of three randomized trials (63, 75, 86) found no significant effects of testosterone therapy for 3 months or longer on depression in older men with low or low-normal testosterone levels (-0.5 SD units; 95% CI, -1.0, 0.1). The inconsistent and imprecise results limit the inferential strength.

Cognition. Three placebo-controlled randomized trials (75, 87, 88), one of which studied patients with Alzheimer's dementia and low testosterone levels (88), reported imprecise effects on several dimensions of cognition, none of which was significant after pooling.

Adverse Outcomes Associated with Testosterone Therapy

In a systematic review of 19 randomized trials to determine the risks of adverse events associated with testosterone therapy in older men (50), the combined rate of all prostate events was significantly greater in testosterone-treated men than in placebo-treated men (odds ratio, 1.78; 95% CI, 1.07, 2.95). Rates of prostate cancer, PSA greater than 4 ng/ml, and prostate biopsies were numerically higher in the testosterone group than in the placebo group, although differences between groups were not individually statistically significant. Testosterone-treated men were nearly four times more likely than placebo-treated men to experience hematocrit greater than 50% (odds ratio, 3.69; 95% CI, 1.82, 7.51). The frequency of cardiovascular events, sleep apnea, or death did not differ significantly between groups. Thus, testosterone therapy of older men was associated with a higher risk of detecting prostate events and hematocrit above 50% than placebo (50).

In a systematic review of placebo-controlled trials, studies

(77, 89–91) that enrolled older men with low or low-normal testosterone levels reported insignificant changes in major lipid fractions [total cholesterol, -8 mg/dl (0.2 mmol/liter); 95% CI, -20, 1.2; LDL cholesterol, -4 mg/dl (0.1 mmol/liter); 95% CI, -15, 4; high-density lipoprotein cholesterol, -0.6 mg/dl (0.02 mmol/liter); 95% CI, -4.8, 3.2; and triglycerides, -9 mg/dl (0.1 mmol/liter); 95% CI, -36, 9].

2.3.C VALUES

The recommendation not to treat asymptomatic older men with age-related decline in testosterone level places a lower value on the unproven, potential benefits of testosterone therapy and a higher value on avoiding the burdens of testosterone administration, monitoring, and cost, as well as on unknown long-term risks.

2.3.D REMARKS

Diagnostic and treatment recommendations are the same as for patients with classical androgen deficiency. However, for older men, we suggest that clinicians aim at achieving total testosterone levels in the lower part of the normal range of young men [400–500 ng/dl (14.0–17.5 nmol/liter)]. Physicians should recognize considerable disagreement among experts on this issue (92).

2.4 Patients with Chronic Illness and Low Testosterone Levels

2.4.1 HIV-infected men with weight loss

2.4.1.A RECOMMENDATION

We suggest that clinicians consider short-term testosterone therapy as an adjunctive therapy in HIV-infected men with low testosterone levels and weight loss to promote weight maintenance and gains in LBM and muscle strength. (21⊕○○)

2.4.1.B EVIDENCE

There is a high prevalence of low testosterone levels in HIV-infected men (22, 24): 20 to 25% of HIV-infected men on highly active antiretroviral therapy have low testosterone levels (93). Low testosterone levels are associated with weight loss, progression to AIDS (94), wasting (24), depression, and loss of muscle mass and exercise capacity (95).

Body weight and LBM. In a systematic review (96) of randomized, placebo-controlled trials of testosterone therapy in HIV-infected patients with weight loss that reported body composition (97–102), 3 to 6 months of testosterone 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) than placebo. Difference in LBM between placebo and testosterone groups was greater in trials that used testosterone esters (+3.34 kg) (96).

Muscle strength. In two of three trials that measured muscle strength (98, 99, 102), testosterone administration was associated with significantly greater improvements in maximal voluntary strength than was placebo.

Other outcomes. In a systematic review of placebo-controlled trials, we found four reporting on depression in patients with

HIV infection (103–106). A large loss to follow-up in one trial, inconsistency across trials, incomplete data reporting, and imprecision limit the strength of inferences. Overall, testosterone therapy had a moderate effect on depression (-0.6 SD units; 95% CI, -1.0 , -0.2). There were no significant testosterone effects on quality of life.

Adverse outcomes. The adverse event rates did not differ significantly between placebo and testosterone groups (98–101). Changes in CD4+ T lymphocyte counts, HIV viral load, PSA, and plasma high-density lipoprotein cholesterol were not significantly different between groups.

There was considerable heterogeneity across trials (varying degrees of weight loss, disease severity, testosterone regimens, treatment duration, and methods to assess body composition). There are no data on testosterone's effects on physical function, risk of disability, or long-term safety. Overall, short-term (3- to 6-month) testosterone use in HIV-infected men with low testosterone levels and weight loss can lead to small gains in body weight and LBM with minimal change in quality of life and mood. This inference is weakened by inconsistent results across trials.

2.4.1.C VALUES

The recommendation to offer short-term testosterone therapy to HIV-infected men with low testosterone levels and weight loss places a relatively higher value on gaining LBM and muscle strength and a relatively lower value on avoiding the potential for testosterone-related adverse effects, cost, and unclear long-term safety. Patients with a different value structure may decide to avoid testosterone therapy.

2.4.1.D REMARKS

Diagnostic and treatment recommendations are the same as for patients with classical androgen deficiency (Sections 1.1 and 2.1). Additionally, appropriate counseling for safe sex practices should be provided.

2.4.2 Glucocorticoid-Treated Men

2.4.2.A RECOMMENDATION

We suggest that clinicians offer short-term testosterone therapy to men receiving high doses of glucocorticoids who have low testosterone levels to promote preservation of LBM and bone mineral density. (21⊕○○)

2.4.2.B EVIDENCE

Testosterone levels are lower in glucocorticoid-treated men than in age-matched controls (25). There is a high prevalence of low testosterone levels in glucocorticoid-treated men due to glucocorticoid-induced suppression of all components of the HPG axis. Typically, administration of more than 5–7.5 mg/d of prednisone or its equivalent increases the risk of gonadotropin and testosterone suppression and alterations in muscle and bone mass (107, 108).

In two placebo-controlled trials (107, 109), testosterone therapy of men receiving glucocorticoid treatment for bronchial asthma or chronic obstructive pulmonary disease was associated with a greater gain in LBM (2.3 kg; 95% CI, 2.0, 3.6)

and a greater decrease in fat mass (-3.1 kg; 95% CI, -3.5 , -2.8) than placebo. These two trials reported significant increase in lumbar bone mineral density in association with testosterone therapy (4%; 95% CI, 2%, 7%); the effect on femoral bone mineral density was inconsistent and not significant. There are no bone fracture data in this population.

Testosterone administration was associated with a low frequency of adverse events (107, 109). However, these inferences are weakened by the small size of these studies and their inconsistent results.

2.4.2.C VALUES

Our recommendation to offer testosterone therapy to glucocorticoid-treated men with low testosterone levels places a relatively higher value on the potential benefit of maintaining muscle mass and bone mineral density and a relatively lower value on avoiding the potential for adverse effects, on avoiding the burdens of testosterone administration, monitoring, and cost, and on the unclear long-term safety of the therapy.

2.4.2.D REMARKS

Diagnostic and treatment recommendations are the same as for patients with classical androgen deficiency.

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