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

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Objective: Our objective was to update the guidelines for the evaluation and treatment of androgen deficiency syndromes in adult men published previously in 2006.

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 medical writer. The Task Force received no corporate funding or remuneration.

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 men in whom total testosterone is near the lower limit of normal or in whom SHBG abnormality is suspected by measurement of free or bioavailable testosterone level, using validated assays. We recommend testosterone therapy for men with symptomatic androgen deficiency 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 4 ng/ml or greater than 3 ng/ml in men at high risk for prostate cancer such as African-Americans or men with first-degree relatives with prostate cancer without further urological evaluation, hematocrit greater than 50%, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms with International Prostate Symptom Score above 19, or uncontrolled or poorly controlled 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* **95: 2536–2559, 2010**)

Summary of Recommendations

1.1 Diagnosis and evaluation of patients with suspected androgen deficiency

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 patients report the less specific symptoms and signs listed in Table 1B. (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. (1|⊕⊕◯◯)

We suggest measurement of free or bioavailable testosterone level, using an accurate and reliable assay, in some men in whom total testosterone concentrations are near the lower limit of the normal range and in whom alterations of SHBG are suspected. (2|⊕⊕◯◯)

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

1.1.1 Further evaluation of men deemed androgen deficient

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

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

A. More specific symptoms and signs
    Incomplete or delayed sexual development, eunuchoidism
    Reduced sexual desire (libido) and activity
    Decreased spontaneous erections
    Breast discomfort, gynecomastia
    Loss of body (axillary and pubic) hair, reduced shaving
    Very small (especially <5 ml) or shrinking testes
    Inability to father children, low or zero sperm count
    Height loss, low trauma fracture, low bone mineral density
    Hot flushes, sweats
B. Other less specific symptoms and signs
    Decreased energy, motivation, initiative, and 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)
    Reduced muscle bulk and strength
    Increased body fat, body mass index
    Diminished physical or work performance

In men with secondary hypogonadism, we suggest further evaluation to identify the etiology of hypothalamic and/or pituitary dysfunction. This evaluation may include measurements of serum prolactin and iron saturation, pituitary function testing, and magnetic resonance imaging of the sella turcica. (2|⊕◯◯◯)

In men with primary testicular failure of unknown etiology, we suggest obtaining a karyotype to exclude Klinefelter syndrome, especially in those with testicular volume less than 6 ml. (2|⊕◯◯◯)

We suggest measurement of bone mineral density by using dual-energy x-ray absorptiometry scanning in men with severe androgen deficiency or low trauma fracture. (2|⊕◯◯◯)

1.2 Screening for androgen deficiency (general population)

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

1.2.2 Case finding of androgen deficiency

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|⊕◯◯◯)

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|⊕◯◯◯)

2.0 Treatment of androgen deficiency with testosterone

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. (1|⊕⊕◯◯)

We recommend against testosterone therapy in patients with breast (1|⊕◯◯◯) or prostate cancer. (1|⊕⊕◯◯)

We recommend that clinicians assess prostate cancer risk in men being considered for testosterone therapy. We recommend against testosterone therapy without further urological evaluation in patients with palpable prostate nodule or induration or prostate-specific antigen (PSA) > 4 ng/ml or PSA > 3 ng/ml in men at high risk of prostate cancer, such as African Americans or men with first-degree relatives with prostate cancer. (1|⊕◯◯◯)

We recommend against testosterone therapy in patients with hematocrit above 50%, untreated severe obstructive

sleep apnea, severe lower urinary tract symptoms [American Urological Association (AUA)/International Prostate Symptom Score (IPSS) > 19], or uncontrolled or poorly controlled heart failure, or in those desiring fertility. (1|⊕◯◯◯)

We suggest initiating testosterone therapy 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 1% 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.
- Testosterone pellets implanted sc at intervals of 3 to 6 months; the dose and regimen vary with the formulation used.
- Oral testosterone undecanoate, injectable testosterone undecanoate, testosterone-in-adhesive matrix patch, and testosterone pellets where available.

Monitoring strategies and schedule

We recommend evaluating the patient 3 to 6 months after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering any adverse effects, and to check compliance. (1|⊕◯◯◯)

We suggest monitoring testosterone levels 3 to 6 months after initiation of testosterone therapy. We suggest aiming at achieving serum testosterone levels during treatment in the mid-normal range. In men receiving testosterone enanthate or cypionate, we suggest aiming for testosterone levels between 400 and 700 ng/dl 1 wk after the injection. (2|⊕⊕◯◯)

We recommend determining hematocrit at baseline, at 3 to 6 months, and then annually. If hematocrit is above 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|⊕◯◯◯)

In men 40 yr of age or older who have a baseline PSA greater than 0.6 ng/ml, we recommend digital examination of the prostate and PSA measurement before initiating treatment, at 3 to 6 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|⊕◯◯◯)

- 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.
- AUA/IPSS score above 19.

We recommend evaluation for symptoms and signs of formulation-specific adverse events at each visit: (1|⊕◯◯◯)

- Injectable testosterone esters: inquire about fluctuations in mood or libido, and cough after injection, 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.
- Buccal testosterone tablets: inquire about alterations in taste and examine gums and oral mucosa for irritation.

2.2 Testosterone therapy in men with sexual dysfunction

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 low testosterone levels after evaluation of underlying causes of ED and consideration of established therapies for ED. (2|⊕◯◯◯)

2.3 Older men with low serum testosterone concentration

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

We suggest that clinicians consider offering testosterone therapy on an individualized basis to older men with low testosterone levels on more than one occasion and clinically significant symptoms of androgen deficiency, af-

ter explicit discussion of the uncertainty about the risks and benefits of testosterone therapy. (2|⊕○○○)

2.4 Patients with chronic illness and low testosterone levels

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 Glucocorticoid-treated men

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

Method of Development of Evidence-Based Clinical Practice Guidelines

Consensus of this guideline was guided by systematic reviews of evidence and discussions during three in-person group meetings, several conference calls, and e-mail communications. The drafts prepared by the Task Force were reviewed successively by The Endocrine Society's Clinical Guidelines Subcommittee, Clinical Affairs Committee, and Council. At each stage of review, the Task Force received written comments and incorporated needed changes.

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 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 (GRADE) work group, an international group with expertise in development and implementation of evidence-based guidelines (1).

The Task Force used systematic reviews of available evidence and two commissioned systematic reviews (2–4) to inform its key recommendations and consistent language. The Task Force also used 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. The Task Force

has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak 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*, *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.

Diagnosis of Hypogonadism

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 a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-testicular axis.

Classification of hypogonadism: Abnormalities of the hypothalamic-pituitary-testicular axis at the testicular level cause primary testicular failure, whereas central defects of the hypothalamus or pituitary cause secondary testicular failure. Hypogonadism also can reflect dual defects that affect both the testis and the pituitary.

- Primary testicular failure results in low testosterone levels, impairment of spermatogenesis, and elevated gonadotropin levels.
- Secondary testicular failure results in low testosterone levels, impairment of spermatogenesis, and low or low-normal gonadotropin levels.
- Combined primary and secondary testicular failure results in low testosterone levels, impairment of spermatogenesis, and variable gonadotropin levels, depending on whether primary or secondary testicular failure predominates.

This classification has therapeutic implications because fertility can be restored with appropriate hormonal stimulation in patients with secondary hypogonadism, but not in most 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. Also, further evaluation of secondary hypogonadism may uncover a pituitary tumor or systemic illness.

Combined primary and secondary hypogonadism occurs with hemochromatosis, sickle cell disease, thalassemia, glucocorticoid treatment, alcoholism, and DAX-1 mutations, and in older men (5, 6).

The age-related decline in testosterone levels, confirmed in several cross-sectional and longitudinal studies (7–9), results from defects in both testicular and hypothalamic-pituitary function. The average decline in serum testosterone levels with aging in men is 1–2% per year (7, 8). A significant fraction of older men have levels below the lower limit of the normal range for healthy, young men (8, 9).

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 1. We suggest that clinicians also consider measuring serum testosterone level when patients report the less specific symptoms and signs listed in Table 1. (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. (1|⊕⊕○○)

We suggest measurement of free or bioavailable testosterone level, using an accurate and reliable assay, in some men in whom total testosterone concentrations are near the lower limit of the normal range and in whom alterations of SHBG are suspected. (2|⊕⊕○○)

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

1.1.B Evidence

The clinical presentation of hypogonadism in men 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. In contrast to men whose hypogonadism is of postpubertal onset, men whose hypogonadism is of prepubertal onset and who were not adequately treated will exhibit eunuchoid proportions, delayed development of secondary sex characteristics, and high pitched voice.

Diagnosis of androgen deficiency in men poses several 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 of symptoms and signs in men with classical androgen deficiency have not been conducted.

In population-based surveys of community-dwelling, middle-aged and older men, low libido, ED and hot flushes, as well as less specific symptoms such as fatigue or loss of vigor, irritability or depressed mood, poor concentration, reduced physical performance, or sleep disturbance, were associated with low testosterone levels (10–12). In these surveys, the crude prevalence of symptomatic androgen deficiency was approximately 6% in the population of middle-aged to older men and increased with age, waist circumference, and poor self-reported health status, but was unrelated to race and ethnicity (12). In other population-based studies, the prevalence of low testosterone irrespective of symptoms was associated with age, obesity, diabetes, and comorbidities or health status (9, 12, 13). The overall prevalence of low testosterone was found to be higher in a primary care practice-based population of patients than that reported in populations of community-dwelling men (14).

The threshold testosterone level below which symptoms of androgen deficiency and adverse health outcomes occur and testosterone administration improves outcomes in the general population is not known. However, in healthy men as well as in referral patient populations, the threshold of testosterone levels varied for various symptoms of androgen deficiency and target organs, and among individuals (11, 12, 15). For most symptoms, the average testosterone threshold corresponded to the lower limit of the normal range for young men, *i.e.* approximately 300 ng/dl (10.4 nmol/liter), with a greater likelihood of having symptoms below this threshold than above it (11, 15).

Serum testosterone levels vary significantly as a result of circadian and circannual rhythms, episodic secretion, and measurement variations (16–19). Testosterone concentrations may be affected by illness and certain medications (*e.g.* opiates and glucocorticoids). Total testosterone concentrations are also influenced by alterations in SHBG concentrations.

Serum testosterone levels exhibit a circadian variation with peak values in the morning; this circadian rhythm is blunted with aging (16). Because of this circadian variation in testosterone levels and the fact that normal ranges for serum testosterone are usually established using morning blood samples, testosterone measurement for the diagnosis of androgen deficiency should be performed in the morning. It has been argued that morning testosterone measurements are not needed in older men in whom the

circadian rhythm is blunted. However, a substantial fraction of older men, 65 to 80 yr of age, who have low serum testosterone levels in the afternoon will have normal testosterone concentrations in the morning (17).

It is important to confirm low testosterone concentrations in men with an initial testosterone level in the mildly hypogonadal range because 30% of such men may have a normal testosterone level on repeat measurement (17). Also, 15% of healthy young men may have a testosterone level below the normal range in a 24-h period. In a community-based, multiethnic cohort of middle-aged to older men, day-to-day variations in serum testosterone concentrations were found to be sufficiently large that single testosterone measurements were inadequate to characterize an individual's levels, and at least two testosterone measurements were needed to diagnose androgen deficiency with greater confidence (17).

Serum total testosterone concentration represents the sum of unbound and protein-bound testosterone in circulation. Most of the circulating testosterone is bound to SHBG and to albumin (18, 19); only 0.5–3% of circulating testosterone is unbound or "free." The term "bioavailable testosterone" refers to unbound testosterone plus testosterone bound loosely to albumin; this term reflects the hypothesis that in addition to the unbound testosterone, albumin-bound testosterone is readily dissociable and thus bioavailable. Free or bioavailable testosterone concentrations should be measured when total testosterone concentrations are close to the lower limit of the normal range and when altered SHBG levels are suspected, *e.g.* in older men and in men with obesity, diabetes mellitus, chronic illness, or thyroid disease (conditions listed in Table 2).

Total testosterone concentrations are measured by RIA, immunometric assays, or liquid chromatography tandem mass spectrometry. Automated assays for total testosterone are available in most hospital laboratories and usually are sufficiently accurate to distinguish eugonadal from hypogo-

nadal men (18, 19). Total testosterone levels are affected by alterations in SHBG that occur in obesity, old age, diabetes mellitus, hyper- and hypothyroidism, and acromegaly, and in men taking certain medications (Table 2). Accurate and reliable assays for free or bioavailable testosterone measurements usually are not available in local laboratories, and these tests should be performed in a reliable reference laboratory. Free testosterone measurements by analog methods are frequently available in local laboratories, but these measurements are affected by alterations in SHBG and are inaccurate (19). Their use is not recommended. Free testosterone level can be measured accurately by equilibrium dialysis or calculated from total testosterone, SHBG, and albumin (20). The calculated free testosterone concentrations are dependent on the quality of total testosterone and SHBG assays. The calculated free testosterone concentrations differ systematically from those measured by equilibrium dialysis and vary with the algorithm used for calculating free testosterone (21). 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 (18). In some laboratories, the lower limit of the normal range for total testosterone level in healthy young men is 280–300 ng/dl (9.8–10.4 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 5–9 pg/ml (0.17–0.31 nmol/liter). The clinicians should use the lower limit of normal range for healthy young men established in their laboratory.

The assessment of men for androgen deficiency should include a general health evaluation to exclude systemic illness, 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 because these conditions can lower testosterone levels transiently (5). Long-acting opioid analgesics suppress the hypothalamic-pituitary-gonadal axis in men, produce symptomatic androgen deficiency, and are associated with increased risk of osteoporosis (22, 23). The suppression of testosterone is particularly profound in men on methadone maintenance therapy because of its long duration of action; buprenorphine suppresses plasma testosterone to a lesser extent than methadone (24). Androgen deprivation therapy using GnRH analogs in men with prostate cancer has emerged as an important cause of therapeutically induced androgen deficiency that is associated with increased risk of sexual dysfunction, fatigue, fractures, cardiovascular disease, and diabetes (25). The diagnosis of androgen deficiency should not be made during an acute illness.

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]
　Acromegaly
　Diabetes mellitus[a]
Conditions associated with increased SHBG concentrations
　Aging[a]
　Hepatic cirrhosis and hepatitis[a]
　Hyperthyroidism
　Use of anticonvulsants[a]
　Use of estrogens
　HIV disease

[a] Particularly common conditions associated with alterations in SHBG concentrations.

1.1.C Values

Our proposed diagnostic strategy reflects our preference to avoid labeling men with low testosterone levels due to SHBG abnormalities, natural variations in testosterone levels, or transient disorders as requiring testosterone therapy. Our strategy also reflects our preference to avoid treatment in men without unequivocally low testosterone levels and symptoms in whom the benefits and risks of testosterone therapy remain 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 to identify the etiology of hypothalamic and/or pituitary dysfunction. This evaluation may include measurements of serum prolactin and iron saturation, pi-

FIG. 1. An approach for the diagnostic evaluation of adult men suspected of having androgen deficiency. #, In some laboratories, the lower limit of the normal testosterone range in healthy young men is approximately 280–300 ng/dl (9.8–10.4 nmol/liter); however, this range may vary in different laboratories. Use the lower limit of the range established in your reference laboratory. @, In some reference laboratories, the lower limit of the normal free testosterone range in healthy young men is approximately 5–9 ng/dl (0.17–0.31 nmol/liter) using equilibrium dialysis or calculated from total testosterone and SHBG; however, this range may vary in different laboratories, depending on the specific equilibrium dialysis or calculated from total testosterone and SHBG assays and the reference population used. Use the lower limit of the range established in your reference laboratory. ^, Conditions in which SHBG levels may be altered are listed in Table 2. *, 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. SFA, Seminal fluid analysis; T, testosterone; MRI, magnetic resonance imaging.

tuitary function testing, and magnetic resonance imaging of the sella turcica. (2|⊕○○○)

In men with primary testicular failure of unknown etiology, we suggest obtaining a karyotype to exclude Klinefelter syndrome, especially in those with testicular volume less than 6 ml. (2|⊕○○○)
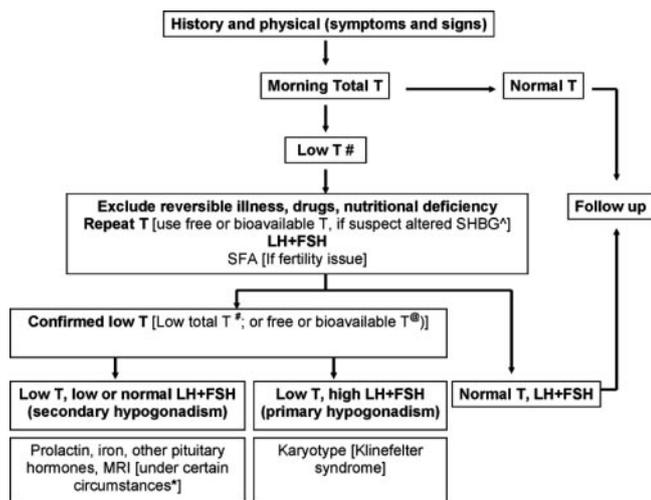
In men being evaluated for infertility, we recommend obtaining at least two seminal fluid analyses. (1|⊕⊕○○)

We suggest measurement of bone mineral density by using dual-energy x-ray absorptiometry scanning in men with severe androgen deficiency or low trauma fracture. (2|⊕○○○)

1.1.1.B Evidence

Measurement of LH and FSH concentrations can help distinguish between primary and secondary hypogonadism. Men with primary hypogonadism have low testosterone levels in association with elevated LH and FSH levels, whereas men with secondary hypogonadism have low testosterone levels in association with low or inappropriately normal LH levels. Because LH is secreted in a pulsatile manner by the pituitary, serum LH levels in men with secondary hypogonadism may be below the normal range or in low-normal range, but clearly inappropriate in relation to the low testosterone concentrations. In individuals with complete idiopathic hypogonadotropic hypogonadism (*e.g.* Kallmann syndrome) and severe gonadotropin suppression or deficiency, LH pulsatility may be absent or markedly suppressed, and these men usually have very low testosterone and LH levels. In most clinical laboratories, LH levels are measured using nonradioactive immunometric assays that have sufficient sensitivity to distinguish between normal and low levels.

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 (<5.2 nmol/liter)], can uncover other pituitary hormone deficiencies. A diagnosis of idiopathic hypogonadotropic hypogonadism is made after excluding other causes of hypogonadotropic hypogonadism. Patients with hypogonadotropic hypogonadism should be examined for dysmorphic features—such as extreme obesity (*e.g.* Prader-Willi syndrome), polydactyly, anosmia (*e.g.* Kallmann syn-

drome), short stature (*e.g.* contiguous gene deletions of chromosome X), or kidney abnormalities (*e.g.* Kallmann syndrome)—to facilitate recognition of specific syndromes by pattern recognition.

In the evaluation of men with secondary hypogonadism, the cost-effectiveness of pituitary imaging (magnetic resonance imaging) to exclude pituitary and/or hypothalamic tumor is unknown. Surveys of men with secondary hypogonadism and sexual dysfunction have revealed a low prevalence of hypothalamic-pituitary abnormalities (26, 27). 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 less than 150 ng/dl (26), panhypopituitarism, persistent hyperprolactinemia, or symptoms of tumor mass effect (headache, visual impairment, or visual field defect).

Karyotype can be useful in excluding Klinefelter syndrome—a common identifiable cause of primary testicular failure—in men with primary testicular failure, especially in those with testicular volume less than 6 ml, although men with mosaic Klinefelter syndrome may have larger testicular volumes. The karyotype obtained from peripheral blood lymphocytes may be normal (46, XY) in men with Klinefelter syndrome who have mosaicism (46, XY/47, XXY). Men with Klinefelter syndrome can benefit from genetic counseling and need surveillance for certain disorders for which they are at increased risk (28).

Testosterone stimulates bone formation and inhibits bone resorption through multiple mechanisms that involve both androgen and estrogen receptor-mediated processes (29, 30). However, the cost-effectiveness of measuring bone mineral density and the frequency at which it should be performed are still being debated.

If fertility is a pressing clinical issue to patients and their partners, at least two seminal fluid analyses separated by an interval of several weeks should be performed on semen samples collected within 1 h of ejaculation after at least 48 h of abstinence.

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

1.1.1.C Values

Our recommended diagnostic strategy places a relatively higher value on detecting conditions (*e.g.* pituitary neoplasia 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.

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, although several, but not all, epidemiological studies have reported an association of low testosterone levels with higher all-cause mortality, particularly mortality due to cardiovascular disease (31–34). The benefits and adverse consequences of long-term testosterone therapy on patient-important outcomes in asymptomatic men with presumed hypogonadism remain unclear (35, 36). 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.

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.

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. (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|⊕○○○)

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

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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 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

In men with chronic diseases such as diabetes mellitus, end-stage renal disease, and chronic obstructive lung disease, measurement of testosterone may be indicated by symptoms such as sexual dysfunction, unexplained weight loss, weakness, or mobility limitation. In men with some other conditions, such as a pituitary mass, HIV-associated weight loss, low trauma fracture, or treatment with medications that affect testosterone production, measurement of testosterone may be indicated regardless of symptoms.

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 (5, 6, 37–40). 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 (41), the Aging Males' Symptoms Rating Scale (42), and the Massachusetts Male Aging Study Questionnaire (43). There are no trials of case-detection strategies in these patient populations; the cost-effectiveness of the use of case-finding instruments over measurement of serum testosterone levels is unknown, and their specificity is poor (44).

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. (1|⊕⊕○○)

We recommend against testosterone therapy in patients with breast (1|⊕○○○) or prostate cancer. (1|⊕⊕○○)

We recommend that clinicians assess prostate cancer risk in men being considered for testosterone therapy. We recommend against testosterone therapy without further urological evaluation in patients with palpable prostate nodule or induration or PSA greater than 4 ng/ml or PSA greater than 3 ng/ml in men at high risk of prostate cancer, such as African-Americans or men with first-degree relatives with prostate cancer. (1|⊕○○○)

We recommend against testosterone therapy in patients with hematocrit above 50%, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms (AUA/IPSS > 19), or uncontrolled or poorly controlled heart failure, or in those desiring fertility. (1|⊕○○○)

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. (2|⊕○○○)

In men receiving testosterone enanthate or cypionate, serum testosterone levels vary during the dosing interval; we suggest aiming for testosterone levels between 400 and 700 ng/dl midway between injections. (2|⊕⊕○○)

In men 40 yr of age or older who have a baseline PSA greater than 0.6 ng/ml, we recommend digital examination of the prostate and PSA measurement before initiating treatment, at 3 to 6 months, and then in accordance with evidence-based guidelines for prostate cancer screening, depending on the age and race of the patient. (1|⊕○○○)

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 (29), increase in fat mass (45), and a

loss of muscle mass and strength (45). 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 (46–53). Testosterone therapy increases hair growth in several androgen-sensitive areas. Testosterone therapy of healthy, hypogonadal men also increases fat-free mass (47, 48, 54–57) and muscle strength (47, 54) and decreases fat mass (47, 48, 57). Although testosterone therapy of healthy, hypogonadal men increases bone mineral density depending on compliance (58–60), the effects of testosterone on fracture risk are unknown.

Testosterone therapy improves the positive and reduces the negative aspects of mood (60, 61). Uncontrolled studies report improvements in energy and sense of well-being after testosterone therapy (62). In a small open-label trial, testosterone therapy has been reported to improve some quality-of-life measures such as sexual function, well-being, and mood in men with opioid-induced androgen deficiency (22). The effects of testosterone on cognitive function are poorly understood; some studies report small effects on visuospatial cognition and verbal memory and fluency (63, 64).

Data on the impact of testosterone replacement on insulin sensitivity have yielded conflicting results. Some studies have demonstrated favorable effects in men with obesity (65, 66) or type 2 diabetes (67), and in healthy older men (68). In contrast, other studies have shown no changes in insulin sensitivity after androgen administration to healthy young (69) and older men (70).

Testosterone therapy may be associated with increased risk of serious adverse effects in men with some disorders (Table 4). Metastatic prostate cancer and breast cancer are

TABLE 4. Conditions in which testosterone administration is associated with a high risk of adverse outcome and for which we recommend against using testosterone

Very high risk of serious adverse outcomes
Metastatic prostate cancer
Breast cancer
Moderate to high risk of adverse outcomes
Unevaluated prostate nodule or induration
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 >50%
Severe lower urinary tract symptoms associated with benign prostatic hypertrophy as indicated by AUA/IPSS >19
Uncontrolled or poorly controlled congestive heart failure

hormone-dependent cancers that may be stimulated to grow during testosterone treatment (71); testosterone should not be administered to men with these cancers. Although some clinicians have suggested that patients with organ-confined prostate cancer who have undergone radical prostatectomy and 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 (72–74), but the lack of data from randomized trials precludes a general recommendation.

A prostate nodule or induration or a PSA greater than 4.0 ng/ml may indicate a previously unrecognized prostate cancer. In addition to PSA and digital rectal examination results, the assessment of prostate cancer risk should include consideration of additional risk factors, such as age, family history (greater risk in men having a first-degree relative with prostate cancer), race (greater risk in African-Americans), prior biopsy history, comorbidities, and PSA velocity and density (75, 76). We suggest estimating prostate cancer risk using the prostate cancer risk calculator (http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp), which takes into consideration age, ethnicity, PSA, findings of digital rectal examination, family history, the use of a 5-α reductase inhibitor, and prior biopsy history. Men in the placebo arm of the Prostate Cancer Prevention Trial were observed to have increased risk of an occult prostate cancer even if their PSA was less than 4.0 ng/ml, and the risk increased as the PSA increased above 0.5 ng/ml (75). The prostate cancer risk calculator provides a means for evaluating prostate cancer risk in men who are considering testosterone treatment (76), but it can only be used for men 55 to 95 yr of age (76). In men deemed to be at high risk for prostate cancer, such as African-Americans and men with first-degree relatives with prostate cancer, a PSA level greater than 3 ng/ml should prompt a urological consultation before consideration of testosterone therapy. Furthermore, in men with hematocrit above 50%, untreated obstructive sleep apnea, severe lower urinary tract symptoms, or severe congestive heart failure, testosterone may worsen these conditions (77). Testosterone therapy may suppress spermatogenesis and is not appropriate in men with hypogonadotropic hypogonadism who desire fertility.

Open-label studies in young, hypogonadal men have found a low frequency of adverse events with replacement doses of testosterone. 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. A systematic review of testosterone therapy in men with low or low normal

TABLE 5. Potential adverse effects of testosterone replacement

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
Uncommon adverse events for which there is weak evidence
    of association with testosterone administration
    Gynecomastia
    Male pattern balding (familial)
    Growth of breast cancer
    Induction or worsening of obstructive sleep apnea
Formulation-specific adverse effects
    Intramuscular injections of testosterone enanthate,
       cypionate, or undecanoate
      Fluctuation in mood or libido
      Pain at injection site
      Excessive erythrocytosis (especially in older patients)
      Coughing episodes immediately after the im injection[a]
    Transdermal patches
      Frequent skin reactions at application site
    Transdermal gel
      Potential risk for testosterone 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
    Buccal testosterone tablets
      Alterations in taste
      Irritation of gums
    Pellet implants
      Infection, expulsion of pellet
    Oral tablets
      Effects on liver and cholesterol (methyltestosterone)[b]

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

[b] Liver toxicity has been reported mostly with oral 17-α alkylated androgens. The frequency of skin reactions is higher with the testosterone patch than with the transdermal gels.

testosterone levels included 37 randomized controlled testosterone trials in hypogonadal men, healthy older men, men with sexual dysfunction, HIV-infected men with weight loss, and in men with a variety of other conditions (2). This meta-analysis of low-quality evidence, mostly because of large loss to follow-up and inconsistent results across studies, found that testosterone therapy was associated with greater increases in hemoglobin, hematocrit, and PSA, and a greater decrease in high-density lipoprotein cholesterol level than placebo (2). These effects were most marked in studies enrolling older patients with low testosterone levels using im testosterone preparations. Overall mortality, cardiovascular event rates, prostate cancer, lower urinary tract symptom scores, and systolic and diastolic blood pressure did not differ among testosterone- and placebo-treated men (2).

2.1.2 Placebo-controlled, randomized trials

A systematic review found no randomized, placebo-controlled trials of the effect of testosterone therapy on depression, cognition, fragility fractures, quality of life, or cardiovascular outcomes in young, hypogonadal men (3). In trials that reported the effect of testosterone on libido (3, 4, 46, 78–80) and erectile function (81–87) in hypogonadal men, testosterone therapy was associated with greater improvements in libido [difference between testosterone and placebo groups, 1.2; 95% confidence interval (CI), 0.3, 2.2] but no significant improvements in self-reported erectile function (0.8; 95% CI, −0.05, 1.6) compared with placebo (4). In a systematic review of testosterone trials that were published before October 2004 and that enrolled men with low testosterone levels (4), testosterone therapy was associated with a moderate nonsignificant and inconsistent effect on satisfaction with erectile function (random effects pooled effect size, 0.80; 95% CI, −0.10, 1.60), a large effect on libido (pooled effect size, 1.31; 95% CI, 0.40, 2.25), and no significant effect on overall sexual satisfaction (4). Trials that enrolled patients with low or low-normal testosterone levels at baseline showed a small effect on satisfaction with erectile function (pooled effect size, 0.34; 95% CI, 0.03, 0.65), moderate nonsignificant effect on libido (pooled effect size, 0.41; 95% CI, −0.01, 0.83), and no significant effect on overall sexual satisfaction. The inconsistency across trials and imprecision of pooled estimates weaken these inferences (4). The trials of the effects of testosterone therapy on erectile response to selective phosphodiesterase 5 inhibitors have been inconclusive (87–93).

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

2.1.C Values

The recommendation to offer testosterone therapy to healthy, hypogonadal men with classic 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

TABLE 6. Clinical pharmacology of some testosterone formulations

Formulation	Regimen	Pharmacokinetic profile	DHT and E2	Advantages	Disadvantages
T enanthate or cypionate	150–200 mg im every 2 wk or 75–100 mg/wk	After a single 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
1% testosterone gel	Available in sachets, tubes and pumps 5–10 g T gel containing 50–100 mg T every d	Restores serum T and E2 levels to 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; skin irritation in a small proportion of treated men; moderately high DHT levels
Transdermal testosterone patch	1 or 2 patches, designed to nominally deliver 5–10 mg T over 24 h applied every d on nonpressure areas	Restores serum T, DHT, and E2 levels to the physiological male range	T:DHT and T:E2 levels are in the physiological male range	Ease of application, corrects symptoms of androgen deficiency	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 occurs frequently in many patients
Buccal, bioadhesive, T tablets	30 mg controlled release, bioadhesive tablets 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
T pellets	3–6 pellets implanted sc; dose and regimen vary with formulation	Serum T peaks at 1 month and then is sustained in normal range for 3–6 months, depending on formulation	T:DHT and T:E2 ratios do not change	Corrects symptoms of androgen deficiency	Requires surgical incision for insertions; pellets may extrude spontaneously

(Continued)

TABLE 6. Continued

Formulation	Regimen	Pharmacokinetic profile	DHT and E2	Advantages	Disadvantages
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
Oral T undecanoate[a]	40 to 80 mg orally, twice daily or three 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: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	European regimen 1000 mg im, followed by 1000 mg at 6 wk, and 1000 mg every 10–14 wk	When administered at a dose of 750 to 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); cough reported immediately after injection in a very small number of men
Testosterone-in-adhesive matrix patch	2 × 60 cm² patches delivering approximately 4.8 mg T/d	Restores serum T, DHT and E_2 to the physiological range	T:DHT and T:E_2 are in the physiological range	Lasts 2 d	Some skin irritation

DHT, Dihydrotestosterone; E2, estradiol; T, testosterone.

[a] These formulations are not approved for clinical use in the United States, but are available outside the United States in many countries. Physicians in countries where these formulations are available should follow the approved drug regimens.

TABLE 7. Some recommended regimens[a] for testosterone replacement therapy

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150 to 200 mg administered every 2 wk, or 75–100 mg of testosterone enanthate or cypionate administered im weekly

One or two 5-mg 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

Testosterone pellets (dose and regimen vary with the formulation used)

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[a] Formulations available in other countries but not in the United States include: 1) oral testosterone undecanoate (typically used at a dose of 40 to 80 mg orally two or three times daily with meals); 2) two testosterone matrix patches 30, 45, or 60 cm^2 applied every 2 d; 3); injectable testosterone undecanoate 1000 mg followed by a second 1000-mg injection 6 wk later, and then 1000 mg every 10 to 14 wk. Physicians in countries where these formulations are available should follow the approved drug regimens. See Tables 6 and 8 for additional safety and pharmacokinetics information.

for healthy, young men. In men receiving testosterone enanthate or cypionate, serum testosterone levels vary during the dosing interval; we suggest aiming for testosterone levels between 350 and 750 ng/dl 1 wk after the injection. 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). Outside the United States, oral testosterone undecanoate, a matrix transdermal testosterone patch, and injectable testosterone undecanoate 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.

When the goal of treatment is to replace testosterone, treatment of men whose hypogonadism is of prepubertal onset is similar to that of men with hypogonadism of postpubertal onset, as described above. In contrast, when the goal of treatment is to restore fertility, men with hypogonadism of prepubertal onset are more likely to require replacement of FSH as well as LH, whereas men with postpubertal onset are more likely to require replacement of LH only (94–97).

Monitoring androgen-deficient men receiving testosterone therapy

Androgen-deficient men receiving testosterone therapy who are at least 40 yr of age with a baseline PSA greater than 0.6 ng/ml should be followed using 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 (77, 98). 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 (99). Transient PSA elevations may be due to other prostatic disorders. PSA levels may be increased by prostatitis, benign prostatic hyperplasia, prostate trauma, urinary tract infections, prostate cancer, and assay variability. If prostatitis is suspected, appropriate antibiotic treatment has been reported to decrease PSA by approximately 30% (100, 101). Therefore, we recommend that PSA elevations be confirmed by repeating the test.

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 (102). 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 (98). 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 initiation of testosterone therapy. In men for whom sequential PSA measurements are available for more than 2 yr, Carter (103) has proposed the use of PSA velocity to identify men at higher risk for prostate cancer. For periods of more than 2 yr, PSA velocity greater than 0.4 ng/ml · yr should warrant a urological evaluation and more intensive future surveillance for prostate cancer (103).

Because the risk of prostate cancer is very low in men younger than age 40, they may not need prostate monitoring. The AUA's Best Practice Statement (2009) (104) recommends obtaining a baseline PSA at age 40 and then determining future screening intervals based on this value. Men at least 40 yr of age who have a baseline PSA value above the median (0.6 ng/ml) and who are receiving testosterone therapy should undergo prostate monitoring by digital rectal examination and PSA measurement 3 to 6 months after initiating therapy and then in accordance with the recommended guidelines, taking into account the age, race, family history, and other risk factors. The combined application of PSA and digital prostate examination improves the prostate cancer detection rate when compared with either test alone (105–108).

Testosterone administration in hypogonadal men is associated with a dose-dependent increase in hemoglobin levels (109–111); the increase in hemoglobin is greater in older men than in young hypogonadal men (110, 111). Baseline hematocrit above 50% is a relative contraindication to testosterone therapy because some of these men will develop a hematocrit above 54% when treated with testosterone. Men with hematocrit level above 50% should undergo further clinical evaluation before consid-

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TABLE 8. Monitoring men receiving testosterone therapy

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1. Evaluate the patient 3 to 6 months after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects.
2. Monitor testosterone level 3 to 6 months after initiation of testosterone therapy:
   Therapy should aim to raise serum testosterone level into the mid-normal range.
   Injectable testosterone enanthate or cypionate: measure serum testosterone level midway between injections. If testosterone is >700 ng/dl (24.5 nmol/liter) or <400 ng/dl (14.1 nmol/liter), adjust dose or frequency.
   Transdermal patches: assess testosterone level 3–12 h after application of the patch; adjust dose to achieve testosterone level in the mid-normal range.
   Buccal testosterone bioadhesive tablet: assess level immediately before or after application of fresh system.
   Transdermal gels: assess testosterone level any time after patient has been on treatment for at least 1 wk; adjust dose to achieve serum testosterone level in the mid-normal range.
   Testosterone pellets: measure testosterone levels at the end of the dosing interval. Adjust the number of pellets and/or the dosing interval to achieve serum testosterone levels in the normal range.
   Oral testosterone undecanoate[a]: monitor serum testosterone level 3 to 5 h after ingestion.
   Injectable testosterone undecanoate: measure serum testosterone level just prior to each subsequent injection and adjust the dosing interval to maintain serum testosterone in mid-normal range.
3. Check hematocrit at baseline, at 3 to 6 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.
4. 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.
5. In men 40 yr of age or older with baseline PSA greater than 0.6 ng/ml, perform digital rectal examination and check PSA level before initiating treatment, at 3 to 6 months, and then in accordance with guidelines for prostate cancer screening depending on the age and race of the patient.
6. Obtain urological consultation if there is:
   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/IPSS of >19.
7. 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, cypionate, and undecanoate): ask about fluctuations in mood or libido, and rarely cough after injections.
   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.
   Testosterone pellets: look for signs of infection, fibrosis, or pellet extrusion.

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[a] Not approved for clinical use in the United States.

eration of testosterone therapy. Men receiving testosterone therapy should have hematocrit measured at baseline and 3 to 6 months after initiation of testosterone therapy.

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 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, overall sexual activity, and attentiveness to erotic stimuli (4, 46–53, 59, 78–83). 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 (53, 84).

Libido

Among randomized trials that enrolled patients with total testosterone levels below 300 ng/dl (10.4 nmol/liter), two parallel trials (48, 82) and three crossover trials (49, 79, 83) reported effects on libido; the longest trial followed participants for 6 months (4, 79). The results of these trials were inconsistent but revealed a large improve-

ment in libido (1.3 SD units; 95% CI, 0.4, 2.2) (4). (Quality of evidence: ⊕⊕○○)

Among trials that enrolled men with total testosterone levels greater than 300 ng/dl (10.4 nmol/liter), a meta-analysis reported four trials that evaluated effects on libido (4). Not included in the meta-analysis is a recent placebo-controlled study of men at least 55 yr of age with total testosterone levels less than 430 ng/dl (<15 nmol/liter); in this trial, testosterone treatment improved sexual desire (80). However, in the meta-analysis, the pooled effect of testosterone on libido was not significant (0.4 SD units; 95% CI, −0.01, 0.8) (76). Lack of precision around this estimate weakens this inference. (Quality of evidence: ⊕⊕○○)

Erectile dysfunction

A meta-analysis by Jain *et al.* (85) evaluated the effects of testosterone therapy in men with ED. Among 16 published studies (85), 57% of subjects experienced an improvement in erectile function. In a later systematic review of randomized placebo-controlled trials that enrolled patients with total testosterone less than 300 ng/dl (10.4 nmol/liter) (4), two parallel trials and two crossover trials reported effects on erectile function. The results were inconsistent across trials, and the pooled estimate was not significant (0.8 SD units; 95% CI, −0.1, 1.6) (4). (Quality of evidence: ⊕○○○)

Among trials that enrolled men with total testosterone greater than 300 ng/dl (10.4 nmol/liter), several parallel trials enrolled men with ED in whom sildenafil had failed (87–93), and three crossover trials enrolled men with either low libido or ED (112, 113). These trials reported inconsistent and nonsignificant effects on erectile function (0.3 SD units; 95% CI, −0.03, 0.65) (4). The inconsistency across trials and the imprecision of the pooled estimate weaken our inferences. (Quality of evidence: ⊕○○○)

Other sexual outcomes

Several studies have evaluated the effects of testosterone treatment in men who failed to respond to a phosphodiesterase 5 inhibitor (87–93). Some of these studies were not placebo controlled, and the degree of testosterone deficiency varied among trials (87–93, 112, 113). Several trials reported on the impact of testosterone therapy on other sexual outcomes, namely, orgasmic and ejaculatory function, intercourse, and overall satisfaction (4). Generally, the effect of testosterone was positive, but small sample sizes, inconsistent findings, and incomplete reporting yielded imprecise estimates. (Quality of evidence: ⊕○○○)

2.2.C Values

Our recommendation to offer testosterone therapy to men with low libido 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. A decision to treat older men depends on the physician's and the patient's assessment of risks and benefits and costs. 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 (see *Sections 1.1 and 2.1*). Men with sexual dysfunction should be evaluated for the underlying causes, including low testosterone levels.

2.3 Older men with low serum testosterone concentration

2.3.A Recommendation

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

We suggest that clinicians consider offering testosterone therapy on an individualized basis to older men with 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|⊕○○○)

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 the lower limit of normal for healthy young men [280–300 ng/dl (9.7–10.4 nmol/liter)]; others favored a level less than 200 ng/dl (6.9 nmol/liter). The panelists who favored treating men who had values less than 300 ng/dl were more influenced by the observation that men who have values below that level often have symptoms that might be attributable to low testosterone. The panelists who favored not treating unless the serum testosterone was as low as 200 ng/dl were more influenced by the lack of testosterone treatment effects in randomized clinical trials when subjects had pretreatment values of 300 ng/dl but suggestions of beneficial effects when the pretreatment values were closer to 200 ng/dl. The lack of definitive studies precludes an unequivocal recommendation and emphasizes the need for additional research.

2.3.B Evidence

Several cross-sectional and longitudinal studies demonstrate that serum total and free testosterone concentrations in men fall with increasing age (7–9, 84, 103, 104, 114, 115). Although the fall is gradual, by the eighth decade, according to one study, 30% of men had total testosterone values in the hypogonadal range, and 50% had low free testosterone values (8). The rate of age-related decline in serum testosterone levels varies in different individuals and is affected by chronic disease, adiposity, and medications (7, 9, 114–117).

Testosterone trials in older men

In randomized, placebo-controlled trials of 3 months to 3 yr in older men with low-normal to low testosterone concentrations, testosterone administration was associated with varying degrees of elevation in testosterone levels (68, 119–131). 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, variable dosing regimens, 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 (68, 119–131).

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 and were published before March 2005 yielded inconsistent and imprecise results (118, 120, 122, 132); these trials 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) (132). 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, 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 (125). The body weight change did not differ significantly between groups (−0.6 kg; 95% CI, −2.0, 0.8) (125).

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) (125). Changes in lower-extremity muscle strength and measures of physical function were reported in only a few studies and were inconsistent. Some studies reported no changes in performance-based measures of physical function (68, 119, 121), whereas one study reported improvement in a composite measure of physical function (121). Most of the studies included men who had no functional limitations and used measures of physical function that had a low ceiling.

Sexual function

Two placebo-controlled trials yielded imprecise results regarding the effect of testosterone on overall sexual satisfaction (0.2 SD units; 95% CI, −0.02, 0.57) (4).

Quality of life

Four placebo-controlled randomized trials reported on testosterone's effect on quality of life (119, 129, 133, 134). The results were inconsistent across trials and imprecise. However, testosterone therapy was associated with significantly greater improvement in the physical function domain score than was placebo (0.5 SD units; 95% CI, 0.03, 0.9) (125).

Depression

The effects of testosterone therapy on depression have been inconsistent across trials. A recent systematic review of randomized trials reported significantly greater improvements in depression scores in testosterone-treated men than in placebo-treated men (135). However, several randomized trials have found no significant effects of testosterone therapy on depression in older men with low or low-normal testosterone levels (127, 133). The inconsistent and imprecise results limit the inferential strength.

Cognition

Three placebo-controlled, randomized trials (130, 133, 136), one of which studied patients with Alzheimer's dementia and low testosterone levels (136), 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 (77), 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 higher in the testosterone group than in the placebo group, although differences between groups were not statistically significant (77). Testosterone-treated men were nearly four

times more likely than placebo-treated men to experience hematocrit above 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 was placebo (77).

A meta-analysis by Haddad *et al.* (3) of studies found through October 2004 enrolling older men with low testosterone levels yielded insignificant changes in major lipid fractions [total cholesterol standardized mean difference (SMD), −0.22 (−0.71 to 0.27); low-density lipoprotein cholesterol SMD, 0.06 (−0.30 to 0.42); high-density lipoprotein cholesterol SMD, 0.04 (−0.39 to 0.40); and triglycerides SMD, −0.27 (−0.61 to 0.08)].

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

Physicians should recognize considerable disagreement among experts on this issue because of the lack of evidence base to reach consensus recommendations (35, 36, 125). Nonspecific age-related symptoms and low T levels often coexist in older men without a clear causal link. Neither the safety nor the efficacy of T therapy in older men with low testosterone level has been demonstrated. Should clinicians and their patients choose testosterone therapy, 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)].

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. (2|⊕⊕○○)

2.4.1.B Evidence

There is a high prevalence of low testosterone levels in HIV-infected men (37, 38, 137): 20–25% of HIV-infected men on highly active antiretroviral therapy have low testosterone levels (137). Low testosterone levels are associated with weight loss, progression to AIDS (138), wasting (139), depression, and loss of muscle mass and exercise capacity (139).

Body weight and LBM

In a systematic review of randomized, placebo-controlled trials of testosterone therapy in HIV-infected patients with weight loss that reported body composition (125), 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 was placebo. Difference in LBM between placebo and testosterone groups was greater in trials that used testosterone esters (+3.34 kg) (140).

Muscle strength

In three of four trials that measured muscle strength (141–145), testosterone administration was associated with improvements in maximal voluntary strength.

Other outcomes

In a systematic review of placebo-controlled trials, we found four reporting on depression in patients with HIV infection (62, 146–148). 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. 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 (see *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 testosterone therapy to men receiving high doses of glucocorticoids who have low testosterone levels to promote preservation of LBM and bone mineral density. (2|⊕⊕○○)

2.4.2.B Evidence

Testosterone levels are lower in glucocorticoid-treated men than in age-matched controls (39). There is a high prevalence of low testosterone levels in glucocorticoid-treated men due to glucocorticoid-induced suppression of all components of the hypothalamic-pituitary-testicular 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 (149).

In two placebo-controlled trials (150, 151), 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 was 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. However, these inferences are weakened by the small size of these studies, their short duration, 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 and 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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