JAMA | Review

Adult Male Hypogonadism
A Review

Bradley D. Anawalt, MD; Kim M. O'Connor, MD; Mathis Grossmann, MD, PhD

IMPORTANCE Male hypogonadism is a clinical syndrome of signs and symptoms of testosterone deficiency and consistently low morning serum testosterone concentrations. The prevalence of hypogonadism due to hypothalamus, pituitary, or testes pathology is less than 1%, and the prevalence due to obesity (body mass index ≥30) is from 2% to 8%.

OBSERVATIONS The most common signs and symptoms of hypogonadism are decreased libido, decreased spontaneous erections, and small testes. Primary hypogonadism is characterized by deficient testicular production of testosterone despite elevated luteinizing hormone (LH) concentrations. The most common cause of primary hypogonadism is Klinefelter syndrome (≥2 X chromosomes and 1 Y chromosome), which affects 2 in 1000 men and is frequently undiagnosed. Secondary hypogonadism is caused by hypothalamic or pituitary dysfunction and is characterized by low testosterone concentrations and low or inappropriately normal LH and follicle-stimulating hormone (FSH) concentrations. The most common permanent causes of secondary hypogonadism are head and neck radiation and severe head trauma. The most common potentially reversible causes of secondary hypogonadism are obesity, severe illness, and medication use (opioids, corticosteroids, checkpoint inhibitors, and medications that cause hyperprolactinemia). Testing for hypogonadism is reserved for men with signs and symptoms of androgen deficiency. Hypogonadism is confirmed if an individual's serum testosterone concentration is less than 264 to 300 ng/dL in at least 2 fasting samples collected between 7 and 10 AM and measured with an accurate and external quality-controlled assay. Assessment of calculated free testosterone concentration derived using total testosterone and sex hormone–binding globulin (SHBG) concentrations is necessary for men with obesity, diabetes, and other conditions that cause low serum SHBG concentrations. Patients diagnosed with hypogonadism should have serum FSH and LH concentrations measured to distinguish primary from secondary hypogonadism. For men with obesity-induced hypogonadism, the recommended first-line management is weight loss. In men with obesity, weight loss of at least 5% typically increases serum total testosterone concentration significantly, and weight loss is associated with improved physical function, libido, and erectile function. Men with permanent hypogonadism, or those unable to discontinue medications that cause hypogonadism, may be treated with testosterone. The testosterone formulation (injection, gel, or pill) and dosage should be individualized with monitoring of serum testosterone concentration, hematocrit percentage, and possibly prostate-specific antigen concentration.

CONCLUSIONS AND RELEVANCE Primary hypogonadism affects less than 1% of men, whereas secondary hypogonadism due to obesity (body mass index ≥30) occurs in 2% to 8%. First-line treatment for obesity-induced hypogonadism is weight loss. Testosterone therapy should be initiated for men with permanent hypogonadism or those who are unable to discontinue medications that cause hypogonadism.

Author Affiliations: Department of Medicine, School of Medicine, University of Washington, Seattle (Anawalt, O'Connor); Department of Medicine (Austin Health), University of Melbourne, Melbourne, Victoria, Australia (Grossmann); Department of Endocrinology, Austin Health, Heidelberg, Victoria, Australia (Grossmann).

Corresponding Author: Bradley D. Anawalt, MD, Department of Medicine, University of Washington School of Medicine, 1959 NE Pacific St, Box 356420, Seattle, WA 98195 (banawalt@medicine.washington.edu).

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Male hypogonadism is a syndrome of signs and symptoms of androgen deficiency and consistently low, fasting, early morning serum testosterone concentrations.[1-7] Male hypogonadism is categorized as primary (due to testicular dysfunction) or secondary (due to hypothalamic or pituitary dysfunction), and is either permanent or reversible, depending on the etiology. The most common etiology of permanent primary hypogonadism is Klinefelter syndrome, occurring in approximately 2 males per 1000; other etiologies include testicular trauma, infection, or chemotherapy.[8]

Permanent secondary hypogonadism may be caused by damage to the pituitary or hypothalamus from tumors, radiation therapy, severe head trauma, or iron overload. Permanent primary and secondary hypogonadism are both rare, occurring in less than 1% of males.[8] Obesity is the most common potentially reversible cause of secondary hypogonadism, occurring in 2% to 8% of men.[8-13] Glucocorticoids, opioids, checkpoint inhibitors, and medications that cause hyperprolactinemia are also causes of secondary hypogonadism that are potentially reversible with treatment of the underlying cause.[1-8]

This review will discuss the pathophysiology, epidemiology, clinical presentation, diagnosis, and treatment of male hypogonadism but will not discuss male fertility (**Box 1**).

Box 1. Frequently Asked Questions About Adult Male Hypogonadism

Which men should be tested for hypogonadism?
Men with decreased libido, small testes, decreased spontaneous early morning erections, and/or unexplained anemia should be tested for hypogonadism. Men with nonspecific symptoms such as low energy, decreased concentration ("brain fog"), or depressed mood do not require testing for hypogonadism. Age-based screening for male hypogonadism is not recommended.

Which tests should be performed to diagnose hypogonadism?
Men with signs and symptoms of hypogonadism and low serum testosterone in 2 or more fasting blood samples drawn between 7 and 10 AM should undergo measurement of serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations. Karyotyping for Klinefelter syndrome should be considered for men with elevated serum LH and FSH concentrations (ie, primary hypogonadism). Men with low or inappropriately normal serum LH and FSH concentrations (ie, secondary hypogonadism) should be evaluated for androgen or opioid use or abuse, history of severe head trauma, Cushing syndrome, iron overload, and use of medications that increase serum prolactin concentration. Men with secondary hypogonadism should have serum prolactin concentration measured, and those with very low serum testosterone concentrations (<150 ng/dL), low serum LH and FSH concentrations, hyperprolactinemia, or severe or new-onset headaches or visual changes should undergo sellar magnetic resonance imaging to evaluate for a pituitary or sellar mass.

Which men should be treated with testosterone?
Testosterone therapy should be initiated for men with primary hypogonadism and no history of prostate or breast cancer. Men with secondary hypogonadism due to drugs (eg, opioids, corticosteroids, androgens, checkpoint inhibitors, or medications that induce hyperprolactinemia) typically regain eugonadism with discontinuation of the causative medication. Men with secondary hypogonadism due to large pituitary tumors, iron overload syndrome, head and neck radiation, or severe head trauma typically have irreversible hypogonadism and should be treated with testosterone if they have no history of prostate or breast cancer. Because weight loss is associated with increased serum testosterone concentration and improved quality of life, physical function, libido, and erectile function, men with obesity-induced hypogonadism should attempt weight loss before consideration of testosterone therapy.

Methods

We searched PubMed for English-language articles published from 1990 until January 1, 2026, using the following key words: androgen deficiency, testosterone deficiency, hypogonadism, primary hypogonadism, secondary hypogonadism, male hypogonadism, Klinefelter syndrome, free testosterone, iron overload syndrome, hemochromatosis, and testosterone replacement. We supplemented these searches with Google Scholar searches and by assessment of references cited in the reviewed articles. The searches were limited to men.

We focused on meta-analyses, systematic reviews, international or national society practice guidelines, and randomized clinical trials, but included observational studies if higher-quality evidence was not available. Because the first large, placebo-controlled trials of testosterone treatments of men with hypogonadism were published between 2016 and 2025, we excluded meta-analyses, systematic reviews, and practice guidelines published before 2016. We included 117 articles: 56 clinical trials (including 26 placebo-controlled trials), 17 meta-analyses or systematic reviews, 13 clinical guidelines, 17 cross-sectional or longitudinal observational studies, 1 pharmacology study, 8 narrative reviews, 2 editorials, and 3 website links.

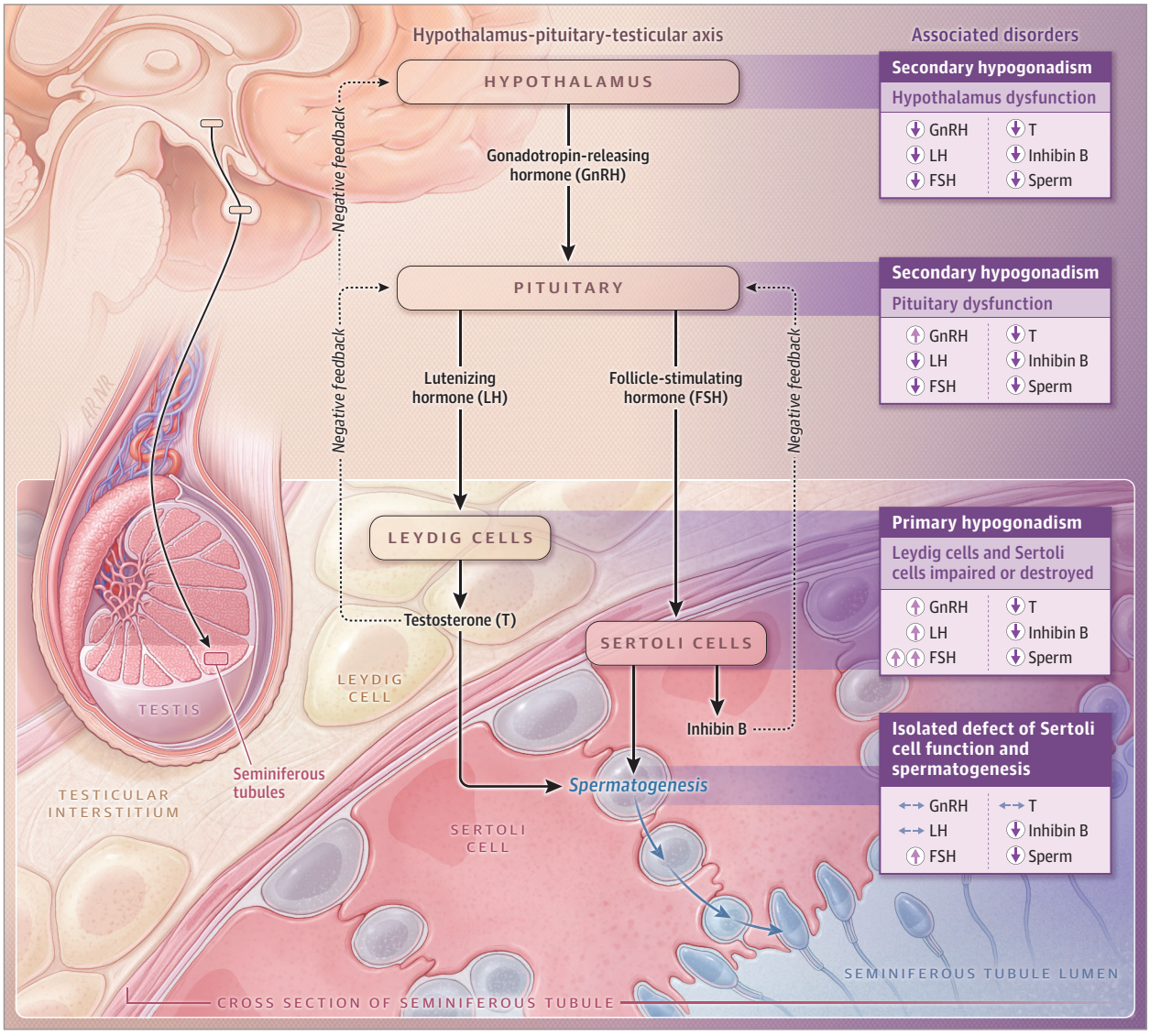
Physiology and Pathophysiology

Testosterone production is regulated by the hypothalamic-pituitary-testicular axis in a bidirectional hormone feedback loop (**Figure 1**). Testicular Leydig cells produce and secrete testosterone and estradiol when stimulated by luteinizing hormone (LH). After 35 years of age, men have progressive loss of hypothalamic production of gonadotropin-releasing hormone[13] that reduces stimulation of pituitary secretion of LH.[13] This effect increases the likelihood that men older than 50 years may develop hypogonadism due to medications that suppress hypothalamic gonadotropin-releasing hormone secretion (eg, opioids, corticosteroids, androgens, and drugs that increase serum prolactin concentration).

Aging is also associated with decreased Leydig cell function that results in decreased testosterone secretion in response to LH stimulation.[13] However, these age-associated changes that decrease testosterone secretion are partially offset by an age-associated decreased metabolism of testosterone. Obesity is the major cause of population-level declines in testosterone concentrations and hypogonadism associated with aging.[8,13]

Testosterone induces virilization, male reproductive development, muscle and skeletal mass and strength, and male sexual behavior and function. Testosterone stimulates erythropoiesis through

Figure 1. Illustration of the Hypothalamus-Pituitary-Testicular Axis and Associated Disorders Affecting Levels of Serum Gonadotropins, Testosterone, and Sperm



increased iron transportation to the bone marrow (mediated by hepcidin), erythropoietin secretion, and direct bone marrow stimulation.[14,15]

Follicle-stimulating hormone (FSH) stimulates the Sertoli cells to make inhibin B and nurture spermatogenesis. Both FSH and high intratesticular testosterone concentrations are necessary for normal spermatogenesis. In primary hypogonadism, concentrations of LH and FSH are both elevated, with higher concentrations of FSH than LH (Figure 1). Primary hypogonadism represents decreased function of both testes because a single healthy testis can maintain normal testosterone and sperm. In secondary hypogonadism, concentrations of LH and FSH are low or inappropriately normal.

Permanent causes of secondary hypogonadism are typically associated with low serum concentrations of LH and FSH. In contrast, reversible causes of secondary hypogonadism may be associated with low or inappropriately normal serum concentrations of LH and FSH due to secretion of LH, FSH, or both, with low bioactivity.[16,17] Both serum concentrations of FSH and LH should be measured because FSH has a long serum half-life and relatively stable blood concentrations, whereas serum concentration of LH is pulsatile, peaking every 90 to 120 minutes. Thus, a high serum concentration of LH could be due to sampling a peak serum concentration of LH. Isolated elevation of serum FSH concentration occurs in men with dysfunctional spermatogenesis but preserved normal production of testosterone and normal serum testosterone concentration (Figure 1).

Approximately 2% of circulating testosterone is unbound by proteins (or free). The remaining testosterone is bound by proteins, primarily sex hormone–binding globulin (SHBG) and albumin.[18,19] Because SHBG is a large protein that binds testosterone avidly, it prevents testosterone from diffusing into target tissues. In contrast, albumin binds testosterone more loosely, which allows albumin-bound testosterone to dissociate and become biologically avail-

Table 1. Typology and Causes of Hypogonadism

Type of hypogonadism	Causes	Serum concentrations		Treatment of hypogonadism
		FSH and LH	Testosterone and SHBG	
Permanent primary	Common Klinefelter syndrome Childhood chemotherapy Rare Congenital abnormalities of testicular hormonal synthesis Adult mumps orchitis Testicular trauma	• Increased FSH • Increased LH • FSH concentration is >LH concentration	• Decreased total testosterone • Decreased free testosterone • Normal or normal to high SHBG	• Testosterone • Infertility is unresponsive to gonadotropin therapy
Reversible primary	Rare Medications that interfere with testosterone synthesis such as high-dosage ketoconazole	• Increased FSH • Increased LH • FSH concentration is >LH concentration	• Decreased total testosterone • Decreased free testosterone • Normal or normal to high SHBG	• Stop culprit medication • Gonadal function including fertility reverts to baseline
Permanent secondary	Common Cranial radiation Severe head trauma Uncommon Large sellar tumors (>1 cm) such as pituitary macroadenoma[a] Iron overload syndromes Checkpoint inhibitors[b] Rare Congenital hypogonadotropic hypogonadism[c]	• Decreased or normal FSH and LH	• Decreased total testosterone • Decreased free testosterone • Normal SHBG	• Testosterone therapy • Fertility may be restored with gonadotropin therapy
Reversible secondary	Common Obesity Acute or chronic systemic illness Corticosteroids Opioids Androgens Hyperprolactinemia due to medications or small prolactinoma	• Decreased or normal FSH and LH	• Decreased total testosterone • Decreased free testosterone • Normal to slightly decreased SHBG	• Treat underlying cause • Gonadal function including fertility reverts to baseline
Pseudohypogonadism	Common Obesity Insulin resistance Type 2 diabetes	• Normal FSH and LH	• Decreased to very decreased SHBG	• No treatment (eugonadal)

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone–binding globulin.

[a] A small percentage of patients recover to eugonadism after surgical removal.

[b] Many men, but not all, who develop checkpoint inhibitor–induced secondary hypogonadism will recover to eugonadism after use of the checkpoint inhibitor is discontinued.

[c] A small percentage of patients spontaneously revert to eugonadism.

able, particularly in organs that have longer blood transit times (such as the brain and liver).

Obesity-induced hyperinsulinemia and increased hepatic fat decrease production of SHBG in the liver. Serum total testosterone concentration may decline below the reference range because of low SHBG concentrations, but serum free testosterone concentration typically remains within the reference range, which confirms eugonadism. Obesity also can lower testosterone production independently of its effects on SHBG and can cause symptomatic hypogonadism with concordantly low serum total and free testosterone concentrations. Mechanisms include obesity-induced inflammation, leptin resistance, and increased adipose tissue aromatization of testosterone to estradiol, which feeds back to the pituitary to decrease LH and FSH secretion, resulting in laboratory testing consistent with secondary hypogonadism.[13]

Primary Hypogonadism

Permanent primary hypogonadism with elevated concentrations of LH and FSH is most commonly caused by Klinefelter syndrome, a genetic condition in men with 2 or more X chromosomes and 1 Y chromosome that occurs in 2:1000 males (**Table 1**), characterized by progressive fibrosis and destruction of Leydig cells.[8] Klinefelter syndrome, which is typically characterized by absent or delayed puberty, small testes, and infertility, is the most common male chromosomal abnormality; however, at least 50% of men with Klinefelter syndrome are undiagnosed.[8]

Alkylating chemotherapy is another common cause of permanent primary hypogonadism.[8] A congenital defect in Leydig cell production of testosterone, testicular trauma, and severe postpuber-

tal mumps orchitis are rare causes of permanent primary hypogonadism. Reversible primary hypogonadism is also rare and can be caused by medications (such as high doses of ketoconazole) that interfere with testosterone synthesis (Table 1).

Secondary Hypogonadism

The most common cause of hypogonadism is reversible secondary hypogonadism due to obesity, which occurs in 2% to 8% of men.[8] The prevalence of obesity-induced hypogonadism rises with increasing body mass index (BMI; calculated as weight in kilograms divided by height in meters squared). In the cross-sectional European Male Aging Study (n = 3369 men; mean age, 59.7 years [SEM, 0.3 years]; mean BMI, 27.8 [SEM, 0.1]), the prevalence of hypogonadism (defined as low total and low calculated free testosterone plus a triad of decreased frequency of sexual thoughts, decreased spontaneous morning erections, and decreased erectile function) was 0.4% in men with a BMI of less than 25, 1.6% in men with a BMI of 25 to less than 30, and 5.2% in men with a BMI of 30 or greater.[11] A study of 5078 Chinese men (mean age, 55.7 years [SD, 9.4 years]; mean BMI, 24.3 [SD, 3.3]) reported a prevalence of 7.8% of hypogonadism based on a low calculated concentration of free testosterone and sexual symptoms.[12] Both studies excluded men with causes of hypogonadism other than obesity.

In addition to obesity, causes of reversible secondary hypogonadism include hyperprolactinemia (endogenous or induced by medication use), corticosteroids, opioids, and withdrawal from androgens. When the causative medication is stopped, medication-induced secondary hypogonadism of less than 1 year in duration typically resolves, with normalization of serum testosterone concentration within weeks to several months. Iron overload from frequent blood transfusions (eg, >20 units of red blood cells in ≤2 years) or hemochromatosis may decrease pituitary secretion of LH by gonadotrope cells and cause secondary hypogonadism,[20,21] which is reversible if treated before permanent gonadotrope cell damage occurs. Testosterone concentrations should not be tested during acute illness or flare-ups of chronic severe systemic disease that can cause a biochemical profile similar to secondary hypogonadism (eugonadal sick syndrome) that reverses after recovery from illness (Table 1).[2]

Permanent causes of secondary hypogonadism with low serum concentrations of LH and FSH include head and neck radiation, large pituitary sellar tumors, severe head trauma, brain surgery, checkpoint inhibitor therapy, and congenital hypogonadotropic hypogonadism (Table 1). Recovery from secondary hypogonadism occurs in a small percentage of patients with pituitary macroadenoma (>1 cm) after surgical removal of the adenoma and can occur spontaneously for many men with checkpoint inhibitor–induced secondary hypogonadism after cessation of the checkpoint inhibitor.

Clinical Presentation

Adult men with hypogonadism may present with decreased libido, decreased spontaneous and/or morning erections, new onset of tender breast growth, osteoporosis, unexplained anemia, or infertility. The sensitivity and specificity of symptoms of androgen deficiency have not been established. Three sexual symptoms (decreased libido, spontaneous morning erections, and mild erectile dysfunction) are the most sensitive and specific indicators of testosterone deficiency in the general population.

In the European Male Aging Study (age range, 40-79 years; mean age, 59.7 years [SEM, 0.3]; mean BMI, 27.8 [SEM, 0.1]), only these 3 sexual symptoms (and not a psychological symptom such as low energy or a physical symptom such as inability to walk >1 km without stopping) had a statistically significant syndromic clustering in those with a low serum testosterone concentration.[11] However, in the European Male Aging Study, men with normal serum total testosterone concentrations also had a high percentage of 1 or more of these symptoms: 25% to 40% reported decreased early morning erections, 30% to 40% reported decreased erectile function, and 15% to 30% reported decreased libido and sexual thoughts.[11]

Measurement of Serum Testosterone

Serum total testosterone assays vary significantly in accuracy and precision. In addition, the reference ranges of testosterone assays are set by local laboratories and are not uniform.[2,6,22,23] Many large commercial laboratories use total testosterone assays that have been certified and harmonized to yield similar results to other certified testosterone assays by the US Centers for Disease Control and Prevention's Hormone Standardization Program (HOST).[22] The testosterone reference range is based on early morning blood measurements from healthy young men, and the lower limit of the testosterone assay reference range in HOST-certified assays is 264 to 300 ng/dL.[22-26] In a study of US and European healthy men (100 men aged 19-39 years who were randomly selected from 1185 men enrolled in 4 different cross-sectional studies), a testosterone concentration of 264 ng/dL on a HOST-certified assay corresponded to the 2.5th percentile and 303 ng/dL corresponded to the 5th percentile.[27]

Assessment of Free Testosterone

Although widely available, direct measurement of serum free testosterone with an immunoassay is inaccurate and should not be used.[2,18,19,23,28] The reference standards for measurement of free testosterone use equilibrium dialysis or ultrafiltration—methods that are expensive and available only in specialized laboratories.[18,19,28] When an accurate total testosterone assay is used, calculation of free testosterone by one of several formulae (that incorporate SHBG concentration into the calculation) correlates well with measurement by equilibrium dialysis.[18,19,23,28] Calculated free testosterone should be ordered, with the calculation performed by the laboratory that performs the assay. The reference range of free testosterone is not clearly established, but a lower limit of normal of 50 to 65 pg/mL has been suggested.[29]

Serum total and free testosterone concentrations are typically concordantly low in hypogonadal men with a BMI less than 25.[30,31] However, factors associated with low serum SHBG may result in a low serum total testosterone concentration but a normal serum free testosterone concentration in eugonadal men (pseudohypogonadism) (Table 1).[2,18,19,28] The most common causes of low serum SHBG are obesity, type 2 diabetes, and insulin resistance (**Box 2**).[2,18,19,28,32-34]

Androgens and glucocorticoids can also lower SHBG. Increased SHBG is found with older age, chronic or binge alcohol intake, and hepatitis or other acute and chronic hepatopathy with preserved liver synthetic function.[2,18,28] Untreated thyroid disease also affects concentrations of SHBG (Box 2). International society guidelines recommend assessment of serum free testosterone by equilibrium dialysis or a calculated free testosterone in men with risk factors for an abnormal serum SHBG concentration.[1,2,4-7,35]

Box 2. Causes of Abnormal Sex Hormone–Binding Globulin (SHBG) Concentration in Men

Decreased serum SHBG concentration

Common causes
- Obesity
- Type 2 diabetes
- Insulin resistance
- Hypothyroidism (untreated or partially treated; high concentration of thyroid-stimulating hormone)
- Polymorphisms for *SHBG* gene
- Use of androgens or glucocorticoids

Uncommon causes
- Some progestins
- Cirrhosis with decreased synthetic function

Increased serum SHBG concentration

Common causes
- Aging
- Hyperthyroidism (untreated or partially treated; low concentration of thyroid-stimulating hormone)
- Polymorphisms for *SHBG* gene
- Chronic or binge excessive alcohol intake
- Chronic liver disease with preserved synthetic function

Uncommon causes
- Nephrotic syndrome
- Estrogens
- Untreated or undertreated HIV infection
- Severe energy deficit (reduced caloric intake, excessive exercise, or both)

Assessment and Diagnosis

Evaluation for hypogonadism is indicated for patients with symptoms suggestive of hypogonadism, such as decreased libido or decreased spontaneous morning erections. Screening for hypogonadism is not indicated in asymptomatic men.[2] A history or physical examination indicating undescended testes suggests congenital hypogonadism.[36] Measured by physical examination, an adult testicular volume is of 15 cm^3 or greater is considered normal; a testicular volume of 12 cm^3 or less indicates prepubertal onset of hypogonadism and is a classic finding of Klinefelter syndrome.[8,36-38]

Testicular volumes can be accurately measured by comparison with the Prader orchidometer (a string of ovoids of standardized volumes). Prader orchidometers are inexpensive, widely available, and have a high concordance with ultrasonography (κ = 0.7-0.9); however, the measurements are consistently higher by about 20% compared with ultrasound.[39-42] Testicular volume cannot be accurately assessed with calipers, cloth tape measure, or comparison with objects such as a walnut.

Hypogonadism requires consistently low serum testosterone concentrations. Serum total testosterone should be measured in a fasting (≥6 hours) blood sample drawn between 7 and 10 AM. A low testosterone result must be confirmed with a second fasting early morning sample and an assessment of free testosterone.[1-7,43-45] Even a single normal serum testosterone result strongly suggests that the man is eugonadal.

Fasting reduces physiological variation of serum testosterone and typically yields results that are 10% to 20% higher than the nonfasting state, thus reducing overdiagnosis of hypogonadism.[43] Serum testosterone concentration peaks in the early morning and gradually declines until the next morning.[44,45] Testosterone measurement after 10 AM, therefore, may result in an incorrect diagnosis of hypogonadism. Night shift workers should have testosterone measured within a few hours of awakening.[46-48] Testosterone should not be assessed in patients with acute illness.[2]

For men with consistently low fasting morning serum testosterone on at least 2 occasions, serum FSH and LH concentrations should be measured to distinguish primary hypogonadism from secondary hypogonadism (Figures 1 and 2). For men with primary hypogonadism, karyotyping for Klinefelter syndrome should be considered.[37] For men with secondary hypogonadism, additional assessment for the underlying etiology should be performed. Prescription and nonprescription medications must be reviewed for recent use of opioids, nontestosterone androgens, medications that increase prolactin (such as risperidone, haloperidol, metoclopramide), and checkpoint inhibitors.

Biochemical assessment for Cushing syndrome should be performed in patients with purple striae on their torso, easily bruised skin, or proximal muscle weakness. Prolactin and iron saturation and ferritin concentrations should be measured in men younger than 50 years and in those who received more than 20 units of red blood cell transfusions in the past 2 years.[20,21] Brain magnetic resonance imaging with contrast with fine sellar (pituitary) cuts should be obtained to exclude a large sellar tumor for men with secondary hypogonadism who are younger than 50 years or have newly onset or worsened headaches or visual abnormalities, hyperprolactinemia, serum FSH or LH concentrations below the lower limit of normal, or a serum total testosterone concentration of less than 150 ng/dL (Figure 2).[2]

Testosterone Therapy

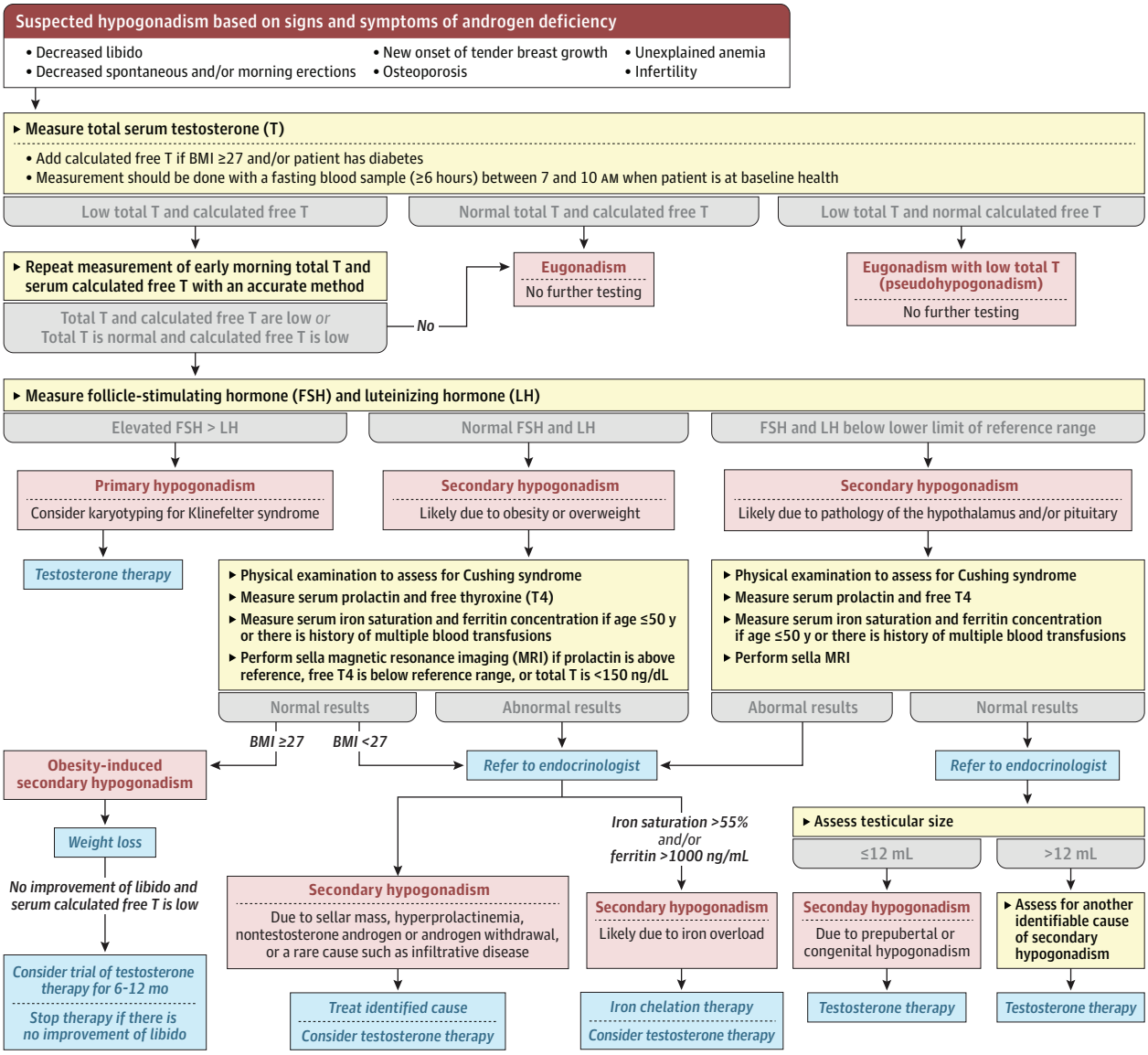
Permanent Primary or Secondary Hypogonadism

Men with permanent primary or secondary hypogonadism should be treated with lifelong testosterone therapy that improves libido and sexual function; sense of well-being; muscle mass and strength; and bone density, strength, and quality.[49-69]

Reversible Secondary Hypogonadism

Men with secondary hypogonadism due to use of opioids, corticosteroids, androgens, and medications that cause hyperprolactinemia should discontinue the causative drug, if possible. To en-

Figure 2. Algorithm for the Evaluation and Management of Male Hypogonadism



Body mass index (BMI) is calculated as weight in kilograms divided by height in meters squared.

hance recovery to eugonadism, it is optimal to stop the causative drug without tapering the dosage. The patient should be advised that recovery of libido, resolution of other symptoms of hypogonadism, and return of baseline hypothalamus-pituitary-testicular axis function and serum testosterone concentration may take weeks to months. Testosterone therapy with a tapering of the dosage will extend the recovery time and should be avoided.

First-line therapy for men with obesity-associated hypogonadism is weight loss. For men with obesity, weight loss of at least 5% to 10% is associated improved quality of life, physical function, and libido; for those with concomitant type 2 diabetes, weight loss also reduces all-cause mortality.[70-75] In addition, weight loss of at least 5% to 10% is associated with increased testosterone concentrations (that may rise into the normal range) and improved erectile function. A 2024 meta-analysis[76] of 19 studies of low-calorie diets (n = 735 men) and 44 studies of bariatric surgery (n = 1039 men) with a median follow-up of 6 months demonstrated that mean serum testosterone increased by 72 ng/dL (95% CI, 54.7-89.3 ng/dL) after following a low calorie diet and by 207 ng/dL (95% CI, 172.8-241.9 ng/dL) after bariatric surgery; mean serum free testosterone also increased proportionately to weight loss. Results were similar when restricted to 14 randomized clinical trials of low-calorie diets or bariatric surgery.[76]

A 2022 meta-analysis[77] of 4 randomized clinical trials including 599 men with BMIs greater than 25 demonstrated improvement in the International Index of Erectile Function (IIEF) scores by 1.65 (95% CI, 0.96-2.33; minimal clinically significant change, 2.0) with weight loss after 1 year of lifestyle changes. A 2023 meta-analysis[78] of 14 studies including 580 men undergoing bariatric surgery demonstrated that serum testosterone concentration increased by 156 ng/dL (95% CI, 72-166 ng/dL; $P < .001$ vs baseline) and IIEF scores improved by 1.19 (95% CI, 0.72-1.66; $P < .001$

Table 2. Outcome Results for Patients Participating in the Testosterone Trials and the Substudies of the Testosterone Trials

Trial	Patients	Description	Baseline or outcome results
Testosterone Trials[a]	Included 790 participants aged ≥65 y with a mean serum total testosterone concentration of ≤275 ng/dL who had signs and symptoms of testosterone deficiency	Randomized to daily application of T gel or placebo gel for 1 y; dosage was adjusted to the serum total testosterone concentration within the reference range	Baseline serum total testosterone concentration: mean, 233 ng/dL
			Treatment goal: mean serum total testosterone concentration of approximately 500 ng/dL
Substudies of the Testosterone Trials[b]			
Sexual Function Trial	Included 459 men with self-reported low libido and low sexual desire based on validated PDQ-4 and DISF-M-II	Primary outcome: overall sexual activity increased moderately based on summation of 12 domains of the PDQ-4[c,d]	Effect size, 0.45 (95% CI, 0.30 to 0.60), $P < .001$
			Ten of 12 domains of activity had significant increases (significance range, $P < .001$ to $P = .26$)
			Flirting by others and spontaneous erections during the day tended to increase (lower limit of 95% CI was 0; $P > .05$)
		Important secondary outcomes: improved sexual desire and moderate effect	Effect size, 0.44 (95% CI, 0.32 to 0.56), $P < .001$
			Improved erectile dysfunction with a small to moderate effect size of 0.32 (95% CI, 0.20 to 0.44)
Physical Function Trial	Included 390 men with self-reported difficulty with walking or climbing stairs and gait speed <1.2 m/s (assessed with the 6-min walk test)	Primary outcome: physical function, gait speed, and mobility (measured by PROMIS PF10 questionnaire with several questions about self-assessed difficulty with walking)	No improvement in men with a baseline gait speed <1.2 m/s treated with testosterone vs placebo (change in distance with 6-min walk test: 3.5 m [95% CI, −2.6 to 9.7], $P = .24$)
		Important secondary outcomes: improved gait speed and mobility in the men with baseline gait speed >1.2 m/s vs placebo	Change in gait speed and distance assessed with 6-min walk test: 14.2 m (95% CI, 6.5 to 21.9), $P < .001$; represents an approximately 3% increase in speed over baseline
Vitality Trial	Included 474 men with low vitality based on a low FACIT Fatigue Scale score	Primary outcome: vitality (defined as an increase in FACIT Fatigue Scale score ≥4) in testosterone vs placebo group	There was no improvement of vitality with testosterone treatment
		Important secondary outcomes: vitality, mood, and depressive symptoms[e]	There were small improvements (effect size <0.2) in vitality, mood, and depressive symptoms (assessed with several validated questionnaires)
Cognitive Function Trial	Included 493 men with associated memory impairment	Cognitive function using a wide range of cognitive tests	No effect on cognitive function using a wide range of cognitive tests

Abbreviations: DISF-M-II, Derogatis Interview for Sexual Functioning in Men II; FACIT, Functional Assessment of Chronic Illness Therapy; PDQ-4, Personality Diagnostic Questionnaire version 4; PROMIS PF10, Patient-Reported Outcomes Measurement Information System Physical Function version 10.

[a] To enroll in these trials overall, participants had to qualify for either the Sexual Function Trial, the Physical Function Trial, or the Vitality Trial. They could participate in multiple substudies of the Testosterone Trials.

[b] There were 3 additional substudies for markers of health outcomes, but not health outcomes, as their primary outcomes (these studies assessed anemia, cardiovascular health, and bone health).

[c] The findings (except no benefit for erectile dysfunction) were confirmed in the Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) study.[25,26]

[d] The 12 domains were sexual daydreams, anticipation of sex, sexual interaction with partner (many participants did not have partners), flirting by participant, orgasm, flirting by others, ejaculation, sexual intercourse, masturbation, spontaneous erection at night, spontaneous erection during the day, sexual arousal erection.

[e] Findings were confirmed in the TRAVERSE study.[25,26]

vs baseline). No large, placebo-controlled trials have been published examining the effects of potent weight loss drugs (eg, glucagon-like peptide-1 receptor agonists) on serum testosterone concentration and androgen-related outcomes in men with obesity-associated hypogonadism.[78,79]

For men aged 45 years or older with hypogonadism, the Testosterone Trials and the Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) study,[24-26] suggest that testosterone therapy might be indicated in men with obesity-induced hypogonadism and low libido or unexplained anemia.[80] The Testosterone Trials,[24] a 1-year, placebo-controlled trial of testosterone therapy, included 790 men (mean age, 72.1 years [SD, 5.7 years]; mean BMI, 31.0 [SD, 3.5] in the testosterone group; the data for the placebo group were slightly but not significantly different and the combined data were not provided) with a serum total testosterone concentration less than 275 ng/dL and one of the following symptoms: low libido, self-reported difficulty walking or inability to walk 400 m in 6 minutes, and self-reported low vitality plus at least mild fatigue.

The overall results of the Testosterone Trials and nested substudies of the trial[24,80-84] showed that testosterone therapy resulted in increased libido and increased sexual activity that was defined broadly (**Table 2**); modest improvement of erectile function; modest benefits for selected tests of vitality, mood, and well-being; resolution of anemia for men with anemia that had no identifiable cause; and greater likelihood to report increased energy than those who were randomized to placebo. There were no benefits for cognitive function.[85] Although the benefit of testosterone therapy exceeded the minimally clinically significant effect in IIEF score (2.64 [95% CI, 1.68-3.61]), the reported benefit with 4 different oral, type 5 phosphodiesterase inhibitors is greater (mean difference in IIEF score compared with placebo: 5.92 to 8.07; the 95% CI excluded 0 for all pairwise comparisons).[81,86]

The placebo-controlled TRAVERSE study of testosterone therapy for up to 4 years (mean follow-up, 3.75 years) including 5204 men (mean age, 63.3 years [SD, 7.9 years]; mean BMI, 35.0 [SD, 5.7]) was designed to determine the cardiovascular safety of testosterone therapy for men with cardiovascular disease or those at high

risk of cardiovascular disease, serum testosterone concentration less than 300 ng/dL, and a sign or symptom (some of which were nonspecific) of hypogonadism (Table 2).[25,26] The primary outcome was the composite of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke). Testosterone did not increase major adverse cardiovascular events compared with placebo, although twice as many testosterone-treated men had pulmonary emboli (24 vs 12; formal statistics were not reported).[25]

In the prespecified substudies of sexual function, bone fracture, and anemia, testosterone increased libido and sexual activities (broadly defined), but did not improve erectile function (Table 2).[80,87] Anemia resolved in about 50% of the men with unexplained anemia who received testosterone, and an increase of 1 g/dL in hemoglobin was associated with increased energy.[88] Although testosterone therapy was shown to increase bone density and strength for men with obesity-induced hypogonadism in the Testosterone Trials, testosterone did not decrease the number of major osteoporotic fractures (hip, spine, or wrist) in the TRAVERSE study.[89-92] The TRAVERSE study did not measure bone density, but the Testosterone Trials did.[89] For men with obesity-induced secondary hypogonadism, weight loss remains the first-line therapy before testosterone therapy is initiated.

Treatment

Considerations Before Initiating Testosterone Therapy

Because all formulations of testosterone therapy increase hematocrit by 5% to 15% relative to baseline, it is recommended to assess the pretreatment hematocrit before initiation of testosterone therapy. Men with baseline high to normal or high percentages of hematocrit should be evaluated for sleep apnea, and evaluation for polycythemia vera may be considered if sleep apnea has been excluded.

A 2022 meta-analysis[93] (29 studies; 3393 men) demonstrated that hematocrit increased by 3% (95% CI, 1.8%-4.3%) with use of transdermal testosterone gel, by 4% (95% CI, 2.9%-5.1%) with oral testosterone undecanoate, by 4.3% (95% CI, 0.7%-8.0%) with short-acting intramuscular testosterone enanthate or cypionate, and by 1.6% (95% CI, 0.3%-3.0%) with long-acting intramuscular testosterone undecanoate. However, in the Testosterone for Diabetes trial (including >1000 men), which was published after the 2022 meta-analysis,[93] intramuscular testosterone undecanoate caused significant erythrocytosis (hematocrit >54%) in 22% of the participants; however, only 1% of the participants withdrew from the study due to persistent erythrocytosis.[94]

Men aged 50 years or older at average risk of prostate cancer should be offered prostate-specific antigen (PSA) testing prior to initiation of testosterone therapy, after being informed about the benefits and potential harms of PSA-based screening and the uncertainty of the long-term risk of testosterone therapy on prostate cancer.[95-97] Many experts recommend PSA-based screening before initiation of testosterone therapy for all men aged 55 to 70 years and men aged 45 to 55 years who have higher risk of prostate cancer. A risk calculator (such as the online Prostate Cancer Prevention Trial calculator) is helpful to define the risk of prostate cancer.[98]

Absolute and Relative Contraindications for Testosterone Therapy

Contraindications to testosterone therapy include untreated prostate cancer; a history of invasive, aggressive, or metastatic prostate cancer; an unevaluated prostate nodule; and breast cancer.[2] Relative contraindications for testosterone therapy include severe lower urinary tract symptoms (eg, International Prostate Symptom Score >19), recent major adverse cardiovascular events (eg, myocardial infarction within the past 6 months), and high pretreatment risk of thromboembolic disease (eg, untreated heart failure).[2]

Although clinical and epidemiological studies have not shown increased risk of prostate cancer with testosterone therapy, these studies excluded men at high risk, did not include systematic surveillance with prostate biopsies, or were of short duration (<5 years).[24,80,97,99-102] In addition, the Testosterone Trials and the TRAVERSE study excluded men with high pretreatment serum PSA concentrations (>3.0 ng/mL for the TRAVERSE study) or severe lower urinary tract symptoms.[24-26,80,98,100]

In the TRAVERSE study, there was no significant difference in incident prostate cancer or high-grade prostate cancer; 5 of 2569 men (0.19%) treated with testosterone were diagnosed with high-grade prostate cancer (Gleason score 4 + 3 or higher) vs 3 of 2602 men (0.12%) treated with placebo.[100] There was also no significant difference in lower urinary tract symptoms and incident acute urinary retention between the testosterone and placebo groups in the TRAVERSE study. The Testosterone Trials, the TRAVERSE study, and recent meta-analyses have shown no increased rate of major adverse cardiovascular events, including venous thrombosis.[24,25,80,101-105] Based on these studies, the US Food and Drug Administration (FDA) recently removed a black box warning about possible increased risk of major adverse cardiovascular events associated with exogenous testosterone, although a warning for a possible increase of 2 to 4 mm Hg in systolic blood pressure has been added.[106-109]

Testosterone Therapy Goals

The goal of testosterone therapy is to improve signs and symptoms of hypogonadism by restoring and maintaining serum testosterone concentration within the reference range when measured at the appropriate time for the testosterone formulation (formulation-specific times for testosterone measurement appear in **Table 3**).[110,111]

Testosterone Formulation Options

The selection of the route and formulation of testosterone therapy is based on patient preference, cost, insurance coverage, product availability, and adverse effects (Table 3). The most commonly prescribed FDA-approved testosterone formulations in the US and worldwide are intramuscular injections and transdermal gels.[68] Short-acting intramuscular testosterone cypionate and enanthate are the least expensive treatment options and may be injected at intervals between 7 and 14 days.[112]

Longer-acting intramuscular testosterone undecanoate may be injected at intervals of 10 and 14 weeks. In the US, a 750-mg formulation of testosterone undecanoate is administered as a loading dose at weeks 0 and 4 and then every 10 weeks. Outside the US, there is a 1000-mg formulation that is administered at 0 and 6 weeks and then every 10 and 14 weeks but its use has not been approved by the FDA. There are a variety of patented and

Table 3. Testosterone Formulations for Treatment of Male Hypogonadism

Formulations and typical dosages	Interval for serum testosterone measurement and goal nadir	Dosage adjustment based on low or high serum testosterone	Advantages	Disadvantages
Testosterone injections				
• Testosterone enanthate • Testosterone cypionate • Dosage: 75-100 mg/wk or 150-200 mg every 2 wk	• Measure at midinterval between injections 3-6 mo after initiation or at 3-6 mo after any change in dosage • Goal nadir: 350-750 ng/dL at midinterval	• If not at midinterval goal, dosage should be changed by 10%-25%	• Least expensive • No contact transference to women or children • Can make greater adjustments to dosage	• Some injection site pain • More likely to cause erythrocytosis than transdermal formulations
• Testosterone undecanoate[a] • Dosage: 750 mg at 0 wk and 4 wk and then every 10 wk	• Measure at nadir just before injection 6 mo after initiation and 6 mo after any change in dosage • Goal nadir: 300-450 ng/dL	• If not at goal, interval between injections should be changed by 1-2 wk	• Less frequent injections • No contact transference to women or children	• More expensive than injectable testosterone cypionate or enanthate • Requires clinic visit for injection • Small risk of nonfatal pulmonary oil microembolism (causing cough and dyspnea) (approximately 1:1000) • Dosage adjustment more limited • More likely to cause erythrocytosis than transdermal formulations
• Testosterone pellets • Dosage: 6-10 pellets implanted subcutaneously every 3-4 mo	• Measure just before pellet insertion at 3-4 mo after initiation and 3-4 mo after any change in dosage • Goal nadir: 300-400 ng/dL	• If not at goal, the number of pellets should be adjusted	• Convenient for some men • No contact transference to women or children	• More expensive than injectable testosterone cypionate or enanthate • Requires procedure • Risk of extrusion, rupture, bleeding, and infection • More likely to cause erythrocytosis than transdermal formulations • Dosage adjustment very limited • Not easily removed
Transdermal formulations				
• Testosterone gels • Dosage: varies by product, but usually applied daily • Application sites vary by product	• Measure 2-6 h after gel application 4-6 wk after initiation or change in dosage • Goal nadir: 300-800 ng/dL	• If not at goal 2-6 h after applications, the gel dosage should be changed • Gel pumps offer more flexibility in changing the dosage	• No injections • Lower serum testosterone peaks • Lower rate of erythrocytosis vs injection and pellets	• More expensive than injectable testosterone cypionate or enanthate • Skin irritation common • Contact transference to women and children if skin-to-skin contact at unwashed application site • Cannot bathe, wash application site, or swim for at least 4 h after application
• Testosterone patches • Not available in the US				• Not available in the US
Oral formulations				
• Testosterone undecanoate capsules • Dosage: varies by product, but all are ingested twice/d with or just after meals	• Varies by product	• Varies by product	• Oral • No contact or transference to women or children	• More expensive than injectable testosterone cypionate or enanthate • Dosage adjustment more limited • Possible slightly greater increase of blood pressure vs other formulations (3-5 mm Hg vs 2-4 mm Hg) • Widely variable serum testosterone concentrations • Requires ingestion twice/d with or just after a meal in the morning and evening
Rarely used formulations				
• Transbuccal tablet • Not available in the US				• Not available in the US
• Nasal gel • Dosage: 3 times/d via pump delivery system	• Dosage is not generally adjusted based on testosterone measurements because serum concentrations vary too widely		• No injections • No contact transference to women or children	• Must be applied 3 times/d • Nasal irritation • No blowing of nose or sniffing for 1 h after application • Dosage adjustment imprecise • Application requires more instruction

[a] A 1000-mg intramuscular formulation is available outside the US. It is administered at week 0, week 6, and then every 10 to 12 weeks.

generic testosterone gels available in the US and outside the US with dosage and application sites that are specific to the formulations.

Testosterone esters (eg, testosterone cypionate or enanthate) may also be administered subcutaneously. Administration with a standard syringe and needle results in larger variation of serum testosterone than with a proprietary injection system or intramuscular injections.[113,114] Other FDA-approved testosterone formulations include oral capsules, intranasal gels, buccal tablets, and injectable pellets (Table 3). Compounded testosterone formulations are not approved by the FDA and should be avoided due to lack of external quality control. In one study, only 30% to 50% of compounded testosterone batches from 10 different Canadian pharmacies contained amounts within 20% of the stated dose; one formulation contained almost no testosterone.[115]

Monitoring

The hematocrit percentage and the morning testosterone concentration should be measured 3 months after initiation of testosterone therapy or after a dose modification (timing of testosterone measurement appears in Table 3). For men taking stable dosages of testosterone, routine monitoring consists of annual measurement of serum total testosterone concentration and hematocrit percentage. There is no consensus about PSA-based screening during long-term exogenous testosterone therapy, so this testing should be based on shared decision-making between patients and clinicians.[2,6,95-97]

Men should be advised that testosterone therapy typically increases serum PSA concentration by 0.2 to 0.5 mg/dL. However, in the Testosterone Trials,[100] serum PSA concentration increased by greater than 1.7 mg/dL in approximately 2.5% of testosterone-treated participants and by 3.4 mg/dL in approximately 5%. Men with serum PSA concentrations that exceed 4 mg/dL (or age-adjusted PSA thresholds) should be evaluated by a urologist.

Practical Considerations

Female and prepubertal children who have prolonged skin-to-skin contact with a man who has applied topical testosterone (gel or cream) may develop virilization. Women can experience hirsutism, acne, and increased libido, and children may develop enlarged genitalia and premature pubic hair. Due to the risk of virilization with topical testosterone, hypogonadal men with infants may prefer testosterone injections.

Men who use topical testosterone should wash their hands after applying the gel or cream and should wear clothing over the application site. Another option is to keep the testosterone application site covered for 4 hours and then wash it. However, washing the gel site within 4 hours of application reduces serum testosterone concentration in the treated man. For many men, applying the testosterone gel after bathing in the morning is most practical. Swimming may be done 4 hours after application of topical testosterone.

Erythrocytosis due to testosterone therapy is treated by reducing the dosage. For erythrocytosis with intramuscular testosterone therapy, the dose may be reduced or the interval between injections can be extended. Switching from intramuscular to transdermal testosterone, which is less likely to cause erythrocytosis, may be helpful.

If testosterone therapy is initiated in men with persistent obesity-induced hypogonadism after weight loss measures, this therapy should be discontinued after 6 months (without tapering the dosage) if libido has not increased or hematocrit has not increased by 1 g/dL for men with baseline unexplained anemia. These men should be informed that after testosterone treatment discontinuation, their libido might be lower for up to 2 to 3 months while their hypothalamus-pituitary-testicular axis function and serum testosterone concentration return to baseline.

Long-term studies are needed to determine the effect of exogenous testosterone on prostatic disease, cardiovascular outcomes, and prevention of diabetes.[80,97,116,117]

Limitations

This review has several limitations. First, the quality of the evidence was not formally analyzed. Second, some relevant articles may have been missed. Third, long-term prospective studies of testosterone therapy for men with permanent hypogonadism and placebo-controlled trials of testosterone therapy for men with hypogonadism due to opioid use or corticosteroid use are lacking.

Conclusions

Primary hypogonadism affects less than 1% of men, whereas secondary hypogonadism due to obesity (BMI ≥30) occurs in 2% to 8%. First-line treatment for obesity-induced hypogonadism is weight loss. Testosterone therapy should be initiated for men with permanent hypogonadism or those who are unable to discontinue medications that cause hypogonadism.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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