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Review article

Male hypogonadism in the primary care clinic

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Hypogonadism is common in clinical practice but is freqently unrecognized and underdiagnosed. The common causes of male hypogonadism vary with the age of presentation. The overall prevalence of male hypogonadism based upon low serum total testosterone levels is high and increases with age from <5% for men in their twenties and thirties to 12%, 19%, 28%, and 49% for men in their fifties, sixties, seventies, and eighties, respectively [1] . A common cause of hypogonadism in boys and young men is Klinefelter's syndrome, a congenital abnormality occurring in approximately 1:500 men [2] [3] that results in a primary testicular disorder associated with small, undeveloped testes and elevated serum gonadotropins. In older men, hypogonadism is often caused by pituitary dysfunction and gonadotropin deficiency due to hyperprolactinemia, corticosteroid excess, hemochromatosis, or pituitary tumors. As men age, serum testosterone levels tend to decline, and some older men develop a clinical syndrome consistent with hypogonadism, a common syndrome of aging called "**andropause**."

There are many pitfalls in making the diagnosis of male hypogonadism. First, male hypogonadism is sometimes difficult to recognize because the signs and symptoms are often nonspecific and overlap with other common syndromes such as depression or are dismissed as the result of normal aging. Second, the biochemical diagnosis of male hypogonadism is not straightforward because it might not be clear which testosterone assay to select from the many that are available. Finally, even after the diagnosis of male hypogonadism is made, the patient and clinician must weigh the potential benefits and risks of androgen replacement therapy. However, new diagnostic tools and therapies are making decisions easier.

Definition of male hypogonadism

The testes have two functions: production of sex steroid hormones and sperm. Male hypogonadism results from dysfunction of the hypothalamic-pituitary-testis axis and is characterized by decreased secretion of testosterone or spermatogenesis.

Normal male serum levels of testosterone and dihydrotestosterone (DHT) are important in the maintenance of male secondary sexual characteristics, bone and muscle mass, strength, erythropoiesis, cognition, sexual function, and overall well-being. Decreased androgen levels and decreased tissue androgen effect are associated with osteoporosis, weakness, redistribution of body fat, hypoproliferative anemia, decreased libido and sexual function, depression, malaise, and abnormalities in cognition. The syndrome of male hypogonadism is defined by a combination of abnormal serum testosterone levels and the presence of insufficient androgen end-organ tissue effect.

Physiology and pathophysiology

The Leydig cells of the testis produce testosterone, and the Sertoli cells synthesize factors that are essential for normal spermatogenesis. Testicular function is controlled primarily by luteinizing hormone (LH) and follicle stimulating hormone (FSH), gonadotropins produced by the anterior pituitary. LH stimulates the Leydig cells to produce testosterone, and FSH promotes spermatogenesis and secretion of inhibin B through binding to Sertoli cells. Anterior pituitary secretion of LH and FSH depends upon pulsatile hypothalamic secretion of gonadotropin releasing hormone (GnRH). Both testosterone and its metabolites inhibit anterior pituitary secretion of LH and FSH and hypothalamic secretion of GnRH by negative feedback. Inhibin B, a peptide produced by Sertoli cells, inhibits FSH secretion in another classic negative feedback loop (Fig. 1).

Fig. 1. The normal gonadal axis.

Male hypogonadism is categorized into primary and secondary hypogonadism, depending upon the location of dysfunction in the hypothalamic-pituitary-testis axis (Table 1). Primary hypogonadism results from primary testicular dysfunction, secondary hypogonadism results from abnormal anterior pituitary function and inadequate gonadotropin stimulation of the testes, and tertiary hypogonadism results from abnormal hypothalamic secretion of GnRH. Clinically, tertiary hypogonadism is often classified as secondary hypogonadism because GnRH levels cannot be measured in the peripheral blood. Older men with **andropause**, a syndrome associated with an age-related decline in serum testosterone levels below the level of normal in young healthy men, often have a laboratory profile similar to young men with secondary hypogonadism.

Table 1. Male hypogonadism: classification and hormone levels

[a] Serum GnRH levels cannot be measured in peripheral blood.
[b] Inappropriately normal.
[c] Clinically, pituitary and hypothalamic causes of hypogonadism are grouped together and classified as secondary hypogonadism.

Abbreviations: Nl, normal; ⇑, above normal limit; ↓, below normal limit.

Table 1. Male hypogonadism: classification and hormone levels

Category	Location of dysfunction	Hormone levels			
		Testosterone	LH	FSH	GnRH[a]
Primary hypogonadism	Testicles	↓ or low Nl	⇑	⇑	⇑
Secondary hypogonadism	Anterior pituitary	↓ or low Nl	↓ or Nl[b]	↓ or Nl[b]	⇑
Tertiary hypogonadism[c]	Hypothalamus	↓	↓	↓	↓
Isolated defect in spermatogenesis	Testicles	Nl	Nl	Nl or ⇑	Nl
Andropause	Testicles and hypothalamus	↓ or low Nl	Nl to ⇑	Nl to ⇑	↓ and aberrant secretion

Diagnosis of hypogonadism

Routine laboratory screening for hypogonadism is not recommended. Diagnosis of the syndrome of hypogonadism requires both the presence of clinical signs or symptoms plus confirmation by appropriate laboratory testing with serum testosterone and gonadotropin levels.

Clinical manifestations of hypogonadism

The clinical manifestations of hypogonadism differ depending upon whether the onset of decreased androgen effect occurs before or after puberty (Table 1 , Box 1). Men with prebubertal hypogonalism might report delayed puberty, infertility, and diminished libido. Physical manifestations include decreased body hair and facial terminal hair, high-pitched voice, small testes and shorter penile length, a small prostate, and gynecomastia. Additionally, prepubertally delayed closure of the epiphyses of the long bones results in unusually long limbs and eunuchoidal proportions. Because prepubertally hypogonadal men have never experienced the manifestations of normal pubertal development, these men might only become aware that they had symptoms of hypogonadism (eg, low libido) after they receive appropriate androgen replacement therapy.

Box 1 Manifestations of hypogonadism acquired prepubertally

Scant body hair and terminal facial hair
High pitched voice
Female pattern of distribution of pubic hair
Small testes: volume <6 cm^3; maximal length <2.5 cm
Small penis: length <5 cm
Little or no scrotal rugae or hyperpigmentation
Small prostate
Eunuchoidal proportions

The history and physical examination findings are subtler in men who present with postpubertal hypogonadism: decreased libido, weakness and decreased muscle mass, fatigue, decreased body and facial hair growth, and decreased sense of well-being (Box 2). Physical manifestations

may include soft but normal-sized testes, slow growing facial hair, or osteopenia. Postpubertal hypogonadism is easy to recognize in men with a syndrome of severe androgen depletion with very low libido, osteoporosis, weakness, and hypoproliferative anemia. However, signs and symptoms of postpubertal hypogonadism are often attributed to normal aging or depression.

Box 2 Manifestations of hypogonadism acquired postpubertally

Decreased libido
Facial terminal hair present but slow growth
Body hair present but decreased
Normal male voice pitch
Testes > 10 cm^3; sometimes soft
Normal penile length
Normal scrotal rugae and hyperpigmentation
Normal adult prostate size
Decreased bone and muscle mass
Normal skeletal proportions
Fatigue or decreased energy and physical function
Hypoproliferative anemia
Increased visceral adiposity

Measurement of serum testosterone

The best method for measurement of serum testosterone is controversial. Ideally, clinicians would like to determine a patient's serum bioactive testosterone level or the amount of testosterone in the serum available to produce an end-organ androgen effect. Unfortunately, serum bioactive testosterone levels are not easily determined. Most circulating testosterone is protein-bound. Approximately 40% of serum testosterone is avidly bound to sex hormone–binding globulin (SHBG) and is not bioactive. Another 58% of serum testosterone, weakly bound to albumin, is thought to be bioavailable because the testosterone rapidly dissociates from albumin into the body tissues [4] [5] [6] [7] [8] . Approximately 2% of “free” or unbound is bioactive. Thus, bioavailable testosterone levels are the sum of testosterone bound to albumin and free testosterone levels. Some laboratories report calculated free testosterone levels based on a complex formula that uses the total testosterone, SHBG, and albumin levels and affinity constants [9] .

Total testosterone levels determined by radioimmunoassay are generally universally available, reliable, and relatively inexpensive. Because of these features plus the many studies using total testosterone measurements in the diagnosis and treatment of hypogonadism, the authors advocate the use of total serum testosterone by radioimmunoassay as a first-line laboratory study in the evaluation of suspected male hypogonadism.

Free testosterone can be measured by a number of methods. The gold standard method, equilibrium dialysis, produces reliable results but is time-consuming and too complicated for routine clinical laboratory use [10] . Free testosterone can also be measured using direct analogue immunoassay kits, but these assays are unreliable and should not be used because they are often inaccurate in the setting of low testosterone levels and high or low SHBG levels [6] [11] [12] . Bioavailable testosterone, also known as non–SHBG-bound testosterone, can be measured using a 50% ammonium sulfate precipitation procedure [8] or can be calculated using measured total testosterone and SHBG levels. The 50% ammonium sulfate precipitation procedure is reliable but not well suited for routine clinical laboratory use [9] . Therefore, until measurement of bioavailable testosterone or calculated free testosterone levels becomes widely available and

validated in a broad spectrum of patients, the authors advocate the use of serum total testosterone measurements as the initial assay.

In some clinical situations, it is appropriate to determine the serum-free testosterone level by equilibrium dialysis, bioavailable testosterone, or calculated free testosterone level despite the higher cost and time. Clinical situations that cause elevated or decreased levels of SHBG might result in misleadingly normal or low total testosterone measurements. Obesity, type II diabetes, and hypothyroidism are associated with low SHBG levels and might result in low total serum testosterone levels but normal free-serum testosterone levels by equilibrium dialysis. In older men, elevated SHBG might result in falsely normal serum total testosterone levels but low free-serum testosterone levels by equilibrium dialysis [13] .

The timing of phlebotomy is important in the interpretation of testosterone levels. Total testosterone levels in healthy young men vary with a circadian rhythm. Testosterone levels reach a peak at approximately 8 AM and decline to a nadir at approximately 8 PM [14] . It is best to obtain the blood sample before 10 AM because the normal range for total testosterone levels is based upon peak morning measurements of young normal men. The circadian rhythm of male testosterone secretion is markedly attenuated in older men. The timing of the blood sample, therefore, might not be as crucial in older men [14] .

Measurement of serum gonadotropins (LH and FSH)

Measurement of serum gonadotropins is necessary to determine whether the patient has primary hypogonadism, secondary hypogonadism, or **andropause**. Making a diagnosis of primary versus secondary hypogonadism determines the subsequent evaluation and treatment considerations for the hypogonadal patient. We recommend measuring both LH and FSH when evaluating male patients for hypogonadism. LH levels are a good marker of normal testicular secretion of sex steroid hormones because LH secretion is regulated primarily by circulating levels of testosterone and its metabolites (dihydrotestosterone and estradiol). Unfortunately, LH levels fluctuate considerably (sometimes out of the normal range) throughout the day because of its pulsatile secretion and short half-life. FSH levels tend to be more constant because of less variable secretion and a long serum half-life, but FSH is not a uniformly reliable marker of testicular testosterone secretion.

Evaluation of the cause of male hypogonadism

When a patient presents with signs and symptoms of hypogonadism, the clinician should draw a serum sample before 10 AM for serum total testosterone, LH, and FSH. A low or low-normal serum total testosterone and elevated LH and FSH levels confirm a diagnosis of primary hypogonadism (Box 3). No further work-up is necessary, and androgen replacement therapy should be initiated. If evidence of prepubertal hypogonadism is evident (eg, small testes, eunuchoidal proportions), the clinician might consider ordering a karyotype analysis to evaluate for Klinefelter's syndrome (XXY).

Box 3 Common causes of primary hypogonadism

Prepubertal onset (small testes)
- Klinefelter's syndrome (XXY males)

Postpubertal onset (normal testes)
- Mumps orchitis (does not usually cause hypogonadism if prepubertal)
- Autoimmune orchitis
- Trauma
- Testicular irradiation or surgery

A low serum testosterone level and low or inappropriately normal LH and FSH levels suggest secondary hypogonadism. Acute illness can suppress the hypothalamic-pituitary-testis axis and result in a misleading diagnosis of secondary hypogonadism; therefore, drawing serum testosterone levels during acute illness should be avoided. In patients with conditions associated with low SHBG levels and low-normal serum total testosterone level (200 ng/dL to 350 ng/dL and low to normal gonadotropin levels (suggestive of possible secondary hypogonadism), a bioavailable testosterone (free plus weakly bound) or calculated free testosterone level should be determined. Risk factors associated with low serum total testosterone levels due to low serum SHBG include the following: age >60, diabetes mellitus, Cushing's syndrome, sleeplessness (≤5 hours a night), acute severe stress, and obesity (BMI > 30) [15] [16] .

When the diagnosis of secondary hypogonadism has been confirmed, common causes of secondary hypogonadism should be investigated (Box 4). Common causes of secondary hypogonadism include hyperprolactinemia, hemochromatosis, pituitary tumor (macroadenoma >1 cm), medications (Box 5), morbid obesity, cirrhosis, uremia, and Cushing's syndrome. Acquired idiopathic hypogonadotropic hypogonadism is considered a diagnosis of exclusion. All men with secondary hypogonadism should be evaluated for hemochromatosis and hyperprolactinemia. The recommended screening test for hemochromatosis is a serum transferrin saturation (serum iron concentration divided by total iron-binding capacity, multiplied by 100) [17] . Serum ferritin levels are not adequate for hemochromatosis screening [17] [18] [19] . An iron saturation of 45% excludes hemochromatosis as a cause of male hypogonadism. Prolactin levels may be determined at any time of the day because they do not vary significantly throughout the day. Men with abnormal prolactin levels may be referred to an endocrinologist for further evaluation, including pituitary imaging to look for a pituitary tumor [20] . Routine laboratory screening for Cushing's syndrome is not necessary if a careful history and physical examination do not suggest hypercortisolism. If history and physical exam suggest hypercortisolism based on easy bruisability, decreased skin thickness, violaceous striae, proximal muscle weakness or osteoporosis, an overnight low dose dexamethasone suppression test or 24-hour urinary free cortisol should be performed.

Box 4 Common causes of secondary hypogonadism

- Prepubertal onset (small testes)
  - Kallmann's syndrome
  - Idiopathic hypogonadotropic hypogonadism
  - Pituitary tumor (craniopharyngioma)
  - Uremia
  - Severe systemic illness
  - Cranial irradiation
  - Hyperprolactinemia
- Postpubertal onset (normal testes)
  - Acquired idiopathic hypogonadotropic hypogonadism
  - Pituitary macroadenomas
  - Uremia
  - Severe systemic illness
  - Cranial irradiation
  - Hyperprolactinemia
  - Hemochromatosis
  - Cushing's syndrome
  - Cirrhosis
  - Morbid obesity

Box 5 Drugs commonly associated with male hypogonadism

- Primary hypogonadism
  - Decreased Leydig cell production of testosterone
    - Corticosteroids
    - Ethanol
    - Ketoconazole (high dosages)
  - Decreased conversion of testosterone to dihydrotestosterone
    - Finasteride (rarely cause decreased libido and erectile dysfunction)
  - Androgen receptor blockade
    - Spironolactone
    - Flutamide
    - Cimetidine
- Secondary hypogonadism
  - Decreased pituitary secretion of gonadotropins
    - Corticosteroids
    - Ethanol
    - GnRH analogues (eg, Lupron)
    - Estrogens (eg, megestrol acetate)
    - Progestins
    - Medications that raise prolactin levels (psychotropic drugs, metoclopramide, opiates)

All younger men (<60) with unexplained secondary hypogonadism or men > 60 with secondary hypogonadism and very low serum levels of testosterone (<200 ng/dL) require pituitary imaging to exclude a large, compressive, pituitary macroadenoma. An MRI of the pituitary region is superior to CT in detecting smaller lesions, but a CT with contrast is less expensive and is adequate for detecting macroadenomas. In men > 60, the incidence of hypogonadal testosterone levels based on total testosterone is 19% and increases to 34% when free testosterone levels are used [1] . Most of these older men with low serum testosterone levels have normal serum gonadotropins consistent with secondary hypogonadism. The prevalence of pituitary macroadenomas is very low, and it is not cost effective to perform pituitary imaging for all

men > 60 and labs consistent with secondary hypogonadism. Therefore, in the absence of signs and symptoms of pituitary mass effect or hypopituitarism, it is not cost effective to evaluate all men > 60 for pituitary lesions. Pituitary imaging is recommended in older men with secondary hypogonadism and one of the following: very low serum total testosterone levels (<200 ng/dL), symptoms of a pituitary tumor (headache or visual changes), or central hypothyroidism (low serum T4 and low or normal TSH).

In summary, the diagnosis of hypogonadism should be confirmed by serum testosterone levels on two occasions with at least one serum sample obtained in the early morning. Primary hypogonadism with elevated gonadotropins does not require further evaluation, but secondary hypogonadism requires a thorough evaluation for a definitive diagnosis (Fig. 2).

Fig. 2. Evaluation and treatment of male hypogonadism in the primary care clinic.

Treatment recommendations

Men with hypogonadism related to specific primary or secondary hypogonadism such as Klinefelter's syndrome or pituitary macroadenoma clearly benefit from androgen replacement therapy. Adequate androgen replacement therapy increases bone mineral density, lean body mass and strength, and hematocrit [21] [22] [23] [24] [25] [26] [27] [28] [29] . In addition, appropriate androgen replacement therapy results in improved self-reported energy level, mood, and sexual function [21] [29] [30] .

The balance between the benefits and risks of androgen therapy is more controversial in older men with **andropause** or men with chronic illness. At least some older men with **andropause** or with chronic illness associated with low circulating testosterone levels will benefit from androgen replacement therapy.

Andropause

Serum testosterone levels decline with aging [1] [13] [31] . It is uncertain whether this decline represents a pathophysiological abnormality that should be treated or simply a normal age-related process. The signs and symptoms associated with aging (weakness, sarcopenia, osteoporosis, depressed mood, cognitive dysfunction) are similar to the signs and symptoms associated with unequivocal hypogonadism in younger men (eg, primary hypogonadism due to Klinefelter's syndrome or secondary hypogonadism due to a pituitary tumor). A number of recent studies have correlated signs and symptoms such as age-related osteopenia and sarcopenia [32] [33] [34] with decreased serum testosterone levels in older men. The term “**andropause**” has been used to describe the syndrome of age-related androgen deficiency, but its diagnosis and treatment are controversial. The controversy is difficult to resolve because there are no large, long-term studies of the safety and benefits of exogenous testosterone supplementation in older men.

There have been three longer term (1- to 3-year follow-up, respectively) randomized controlled trials [35] [36] [37] [38] , demonstrating positive effects of testosterone replacement therapy on body composition and bone mineral density in older men with low to low-normal serum testosterone levels. Age-related decreases of libido and sexual performance have also been postulated to be

related to androgen decline in aging. Libido improves significantly with androgen replacement in healthy, young, hypogonadal men and [21] [28] [29] older, hypogonadal men [39] [40] . However, little evidence exists to support the hypothesis that older men with low-normal serum testosterone levels will uniformly experience improved sexual function after receiving supplemental androgen therapy.

Although small, short-term studies indicate a possible improvement in age-related sarcopenia and bone mineral density from androgen replacement therapy, no long-term data exist regarding safety or clinically relevant outcomes such as the ability to live independently, the prevention of fracture, or the impact on frailty in older men. Overall, studies suggest that older men with very low serum total testosterone levels (<200 ng/dL) are most likely to benefit from androgen replacement therapy. Older men with significant symptoms of androgen deficiency and testosterone levels between 200 ng/dL and 350 ng/dL might benefit from androgen replacement therapy. In this group, however, the risks must be considered carefully. A 6- to 12-month treatment trial should achieve much of the anabolic effects of androgen replacement therapy and could be attempted safely in most patients. Patients should be carefully reassessed for benefit and side effects during and after the trial to determine whether to continue androgen replacement therapy. Unlike men with **andropause** where the benefit of therapy is controversial, older men with primary hypogonadism or secondary hypogonadism due to confirmed hypothalamopituitary disease should be considered for androgen replacement therapy regardless of age.

Therapeutic options

Androgen replacement therapy relieves the symptoms of male hypogonadism and prevents the long-term sequelae of decreased androgen effect (eg, osteoporosis). The treatment goal is to provide physiological levels of testosterone while minimizing the side effects, expense, and difficulty with administration. The most commonly used testosterone preparations are the esterified testosterones (testosterone enanthate and cypionate) formulated in an oil vehicle for intramuscular injection, transdermal testosterone patch systems, and a new transdermal testosterone gel (Table 2).

Table 2. Commercial formulations of testosterone therapy

Data from [44] [49] [50] .

	Dosage	Treatment serum testosterone	Adverse drug effects	Cost per month ($)
Testoderm scrotal patch (Alza)	5 mg patch on shaved scrotal skin daily	Low- to mid-normal range	Poor adherence to scrotal skin	□95
Androderm patch (Watson)	5-mg patch on torso, arms, or legs daily	Low- to mid-normal range	□35–70% develop skin rash	□110
Testoderm TTS patch (Alza)	4- or 6-mg patch on torso, arms, or buttocks daily	Low- to mid-normal range	□10% develop skin rash	□100
Androgel (Unimed)	5–10 g on upper arm or abdomen daily	Mid- to upper-normal range	Possible transfer to female partners	□150
Testosterone cypionate or enanthate	100–250 mg IM every 7–14 days	Mid- to slightly supraphysiologic range	Pain with injections	2–4 +/−office visit

Intramuscular testosterone esters

Testosterone esters form deposits and are gradually released into the bloodstream. The two most commonly used testosterone esters, testosterone enanthate and cypionate, have similar pharmacokinetics and are administered as a single intramuscular injection of 100 to 200 mg every 7 to 14 days. The mean serum testosterone concentration increases to slightly higher than the upper limit of normal 24 to 48 hours after intramuscular injection of testosterone enanthate or cypionate and gradually decreases to a nadir in the mid- to low-normal range before the subsequent injection [41] [42] . Serum gonadotropins are generally suppressed to the normal range or lower after 6 to 8 weeks of therapy with replacement dosages of intramuscular testosterone [41] and cannot be used clinically as markers of adequate androgen replacement therapy (unlike TSH levels for monitoring thyroid replacement therapy). Some experts [2] recommend checking the serum testosterone level on the day that is mid-interval between intramuscular doses to determine if the serum testosterone level is in the mid-normal range. Often, improvement or reversal of the patient's symptomatology is a reasonable guide for adjusting the dosage and frequency of intramuscular testosterone therapy and measuring serum testosterone levels is unnecessary.

In general, the starting dosage of intramuscular testosterone enanthate or cypionate is 150 to 200 mg every 2 weeks. In older men, or men with very low serum levels of testosterone (<200 ng/dL), it is prudent to initiate therapy with lower dosages of intramuscular testosterone such as 50 to 100 mg intramuscular every 2 weeks, then titrate up the dose as tolerated. This slow increase will lessen the sudden mood fluctuations and changes in sexual function and interest that some men find unpleasant. Up to a quarter of older men develop polycythemia when 200 mg intramuscular testosterone enanthate is initiated [39] . Therefore, 150 mg intramuscular testosterone every 2 weeks is often the maximum tolerated dosage in older men. If a patient receiving 150 to 200 mg IM testosterone ester every 2 weeks reports fluctuations in mood, sexual function, or interest that might be related to the high peak levels (at 24 to 48 hours) and trough levels (at 2 weeks), the dosage can be changed to 75 to 100 mg IM every week or a transdermal testosterone preparation can be substituted. Conversely, if a patient receiving 150 to 200 mg IM testosterone ester every 2 weeks reports decreased energy, sense of well-being, or libido a few days before his scheduled injection, the interval may be shortened to 10 days between injections or the dosage may be increased by 25 to 50 mg biweekly.

Intramuscular testosterone therapy is generally safe, well tolerated, inexpensive, and provides robust serum testosterone levels in hypogonadal men [43] . The largest disadvantage to testosterone esters is the need for potentially painful, deep intramuscular injection every 1 to 2 weeks. Most men, however, can be taught to self-administer the intramuscular injections, and even men on coumadin or with a bleeding diathesis may safely use intramuscular injections.

Transdermal testosterone patch systems

Transdermal testosterone patches can provide for physiological testosterone replacement in 85% to 90% of men [44] [45] [46] and, unlike oral and intramuscular testosterone formulations, restore the normal circadian rhythm of testosterone levels in hypogonadal men [47] . Three different testosterone patch systems are available for use in hypogonadal men. Testosterone patches are applied daily, produce peak serum testosterone levels in the early morning, and provide a gradual decline in serum testosterone levels throughout the day [44] . The first transdermal patch was Testoderm, a scrotal patch. This scrotal patch does not adhere very well to skin and can only be placed on shaved scrotal skin. This patch system is not a popular choice for most men.

Two nonscrotal transdermal skin patches, Androderm and Testoderm TTS, have been developed for use on the torso and limbs. Because nonscrotal skin does not absorb testosterone as well as scrotal skin, both Androderm and Testoderm TTS require a vehicle that enhances the absorption of testosterone. Both patches commonly cause a skin irritation and rash. In one study of Androderm, 60% of men developed transient skin irritation from the patch, but only □10% of the men discontinued the patch [47] . The newer nonscrotal patch formulation, Testoderm TTS, produces less skin rash and irritation [48] but tends to fall off during exercise. Because the pharmacokinetics of the scrotal and nonscrotal patch differ, to mimic normal physiology and achieve peak serum testosterone levels in the morning, patients apply scrotal patches in the morning or nonscrotal patches in the early evening.

In comparison to intramuscular testosterone esters, the transdermal patch systems cause little erythrocytosis and gynecomastia [47] . The transdermal patch systems are also more expensive, do not always provide adequate serum testosterone levels for larger hypogonadal men, and the dosages are not easily adjusted. In contradistinction to intramuscular androgen replacement therapy, men using transdermal testosterone replacement systems require monitoring of peak morning serum testosterone levels to verify adequate androgen replacement levels.

Transdermal testosterone gel

Androgel, a 1% testosterone gel, has recently become available for the treatment of male hypogonadism [49] . Testosterone gel applied to the nonscrotal skin once daily rapidly increases serum testosterone levels in hypogonadal men to the mid- to upper-normal range [50] . The transdermal testosterone gel is applied to the skin, quickly dries, and □10% is absorbed into the systemic circulation. The recommended starting dosage of gel is 50 to 100 mg of testosterone gel each morning delivering 5 to 10 mg per day of testosterone. The gel produces less skin irritation than the nonscrotal patch system (□6% of men using testosterone gel versus □66% using the Androderm patch) [29] but carries a risk of transferring the unabsorbed gel to intimate contacts. The risk of transferring the unabsorbed testosterone gel to others can be limited by showering shortly after applying the gel. The dosage of testosterone can easily be titrated with the gel formulation, but morning peak testosterone must be determined to confirm adequate androgen replacement therapy. Additionally, the current price of Androgel is prohibitively expensive for many patients.

Side effects of androgen therapy in hypogonadal men

Androgen replacement therapy is well tolerated, and serious side effects are rare. As discussed previously, erythrocytosis is more common in elderly men [39] but can be avoided or treated by simply reducing the testosterone dosage. Other rare side effects include acne, worsening fluid retention, and induction or worsening of sleep apnea [51] [52] . Gynecomastia and transient breast tenderness occurs in some men at the onset of therapy. Some men with very low levels of testosterone (<200 ng/dL) notice a rapid change in libido or mood if full dosages of intramuscular androgen replacement are immediately initiated. The impact of these effects can be lessened by warning patients and their partners about the possible physical changes that occur with testosterone, and by either slowly increasing the intramuscular dosage of testosterone or using transdermal testosterone therapy.

Testosterone stimulates the growth of normal prostatic tissue and prostate cancer, and androgen deprivation is a mainstay of therapy for advanced prostate cancer [53] [54] . Testosterone has not, however, been shown to cause prostate cancer. Male hypogonadism is associated with decreased prostate volumes, and testosterone therapy restores prostate volumes to those similar to age-matched controls [55] [56] . Although a theoretical risk exists of precipitating symptomatic prostatic enlargement with the initiation of testosterone therapy, studies have not shown

increased incidence of prostatic obstruction with testosterone therapy [36] [55] [56] . Most of the increase of prostate volume occurs in the initial 3 months of therapy [55] .

With androgen replacement therapy, prostate-specific antigen levels tend to rise to the levels of age-matched controls [36] [55] [56] [57] . However, some studies have not shown prostate-specific antigen levels to rise significantly after treatment of hypogonadal men with androgen replacement therapy [21] [35] [39] . It seems unlikely that hypogonadal men treated with testosterone replacement therapy incur any increased risk of prostatic disease above that of age-matched eugonadal men.

Although testosterone therapy does not appear to induce prostate cancer, testosterone replacement therapy might cause an occult prostate cancer to become clinically significant. Many experts disagree as to the appropriate schedule of prostate cancer monitoring or as to whether any monitoring should be completed. The recent 2001 **Andropause** Consensus Conference recommended digital rectal examination, prostate specific antigen (PSA), and American Urologic Association prostate symptom scores at baseline, 3, 6, and 12 months and annually [58] . When PSA levels increase > 1.4 ng/mL between two measurements or > 1.5 ng/mL over 2 years and remain elevated, the consensus panel recommended a referral for urological evaluation. Following these guidelines takes an aggressive approach to screening for prostate cancer. On the other hand, prostate cancer screening is controversial in primary care, and routine PSA screening might cause patients to undergo unnecessary or painful procedures without proven benefit [59] [60] . We recommend that the caregiver and the patient discuss the risks and benefits of routine PSA screening in all men > 50 years who are receiving androgen replacement therapy.

The relationship among androgens, cardiovascular disease, and cardiovascular risk factors is complex. The risk of coronary artery disease (CAD) is lower in premenopausal women than men, suggesting that testosterone might be deleterious to cardiovascular health [61] . The administration of exogenous testosterone to hypogonadal men and eugonadal men is associated with a small, dosage-dependent decrease in high density lipoprotein cholesterol (HDL) [62] [63] [64] . Low serum levels of HDL are linked to increased risk of CAD [61] [65] . However, available literature suggests either a neutral or favorable relationship between serum androgen (testosterone and dehydroepiandrosterone) levels and cardiovascular disease in men [66] . The majority of cross-sectional studies also shows a positive relationship between serum testosterone levels and levels of HDL in men [67] . Exogenous testosterone also tends to suppress levels of atherogenic low density lipoprotein cholesterol and lipoprotein(a) particles, whereas suppression of endogenous testosterone production in young men tends to increase levels of lipoprotein(a) [63] [67] [68] .

In cross-sectional studies [69] [70] [71] and a recent case-control study [72] , lower serum total testosterone levels have been associated with CAD risk factors such as hyperinsulinemia and decreased glucose tolerance. Exogenous testosterone has also been shown to cause coronary vasodilation in men with CAD, and the acute administration of intravenous exogenous testosterone to men with CAD and low serum testosterone levels delays the onset of ischemic changes on electrocardiography during exercise tolerance testing [73] [74] . In a recently presented study, exogenous testosterone improved exercise performance in older men with mildly decreased left ventricular function [75] .

Thus, based upon limited, short-term data in mostly young men, it appears that testosterone replacement therapy does not have hazardous cardiovascular effects and might be beneficial in hypogonadal men. Before androgen replacement therapy can be considered safe for long-term use in older men, the long-term effect of testosterone replacement therapy on lipids, insulin levels and glucose tolerance, and other CAD risk factors should be carefully studied.

Clinical approach

Male hypogonadism is commonly seen in clinical practice, can easily be diagnosed and treated by the primary care provider, and if left untreated causes considerable morbidity. Symptoms and signs such as gynecomastia, decreased libido, fatigue, depressed mood, weakness, or an atraumatic fracture should trigger the provider to consider the diagnosis of hypogonadism. In older men, the symptoms of hypogonadism might be confused as normal manifestations of aging, and a diagnosis of hypogonadism can be easily overlooked. When symptoms or physical exam suggest hypogonadism, early morning total serum testosterone, LH, and FSH levels should be determined. The total serum testosterone level is currently the most validated, inexpensive, easily obtainable, and reliable measurement of serum testosterone. In patients with untreated hypothyroidism, morbid obesity, diabetes, and aging, if the serum total testosterone is low-normal or normal in the setting of signs and symptoms of hypogonadism, the level of serum bioavailable testosterone (free plus weakly bound), calculated free or free testosterone by equilibrium dialysis should be determined. The commonly used free testosterone assay by the analogue method should be abandoned.

It is essential in the evaluation of male hypogonadism to measure serum gonadotropins and distinguish between primary and secondary hypogonadism. Further investigation into the cause of the hypogonadal syndrome is determined by this important diagnostic distinction. Primary hypogonadism is treated with androgen replacement therapy without further laboratory investigation except possible karyotype analysis to make a definitive diagnosis of Klinefelter's syndrome. Once a diagnosis of secondary hypogonadism has been made, hemochromatosis, hyperprolactinemia, secondary hypothyroidism, Cushing's syndrome, and a large pituitary tumor must be considered and excluded. Older men (>60 years) with low to low-normal serum total testosterone levels (200 to 350 ng/dL), normal serum prolactin levels, normal T4 and TSH levels, and no headache or visual changes do not require an imaging study of the pituitary.

The benefits of androgen replacement therapy outweigh the risks for most young, hypogonadal men. Increased bone density, lean body mass, strength, hematocrit, and improved mood occur with androgen replacement in hypogonadal men. Men with very low serum levels of total testosterone (<200 ng/dL) and men with serum levels of testosterone <350 ng/dL and primary hypogonadism most clearly benefit from androgen replacement therapy. Younger men (<60 years) with secondary hypogonadism and serum testosterone levels between 200 ng/dL and 350 ng/dL should be treated with androgen replacement therapy if they have clinical manifestations of hypogonadism that improve with a trial of androgen replacement therapy.

The long-term risks versus benefits of androgen replacement therapy in older men with low-normal serum testosterone levels still have not been determined. When a clinician decides to recommend androgen replacement therapy in older men, it is imperative that the patient be informed that the long-term benefits and risks to therapy are uncertain. A discussion should be conducted before the initiation of androgen replacement therapy and a joint decision made regarding prostate cancer screening and PSA monitoring. If a patient and physician elect to begin a trial of androgen replacement therapy, 6 months is generally an adequate trial to determine the outcome of most androgen effects. In contradistinction, the trophic effects on bone will take 24 to 36 months to reach maximal effect, and a decision should not be made before that time about the effects of androgen replacement therapy on bone mineral density.

The choice of androgen replacement is based on cost, convenience, the amount of androgen clinically necessary, and ultimately the patient's preference. Intramuscular testosterone esters (enanthate and cypionate) are the least expensive therapy, but they require biweekly intramuscular injections and do not reproduce the normal male circadian hormone pattern. Transdermal patches and gel require a less invasive route of administration, making them an attractive alternative for many men, but they are much more costly than intramuscular testosterone therapy. Transdermal patch systems either require scrotal shaving or have a relatively high risk of skin irritation and can be difficult to titrate to an adequate androgen effect in some men. Transdermal gel is very expensive and can be transferred to sexual partners but

provides robust serum testosterone levels and causes little skin irritation. We recommend using intramuscular testosterone esters or testosterone gel as the first-line androgen replacement therapies for most hypogonadal men.

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