

Multidisciplinary Insights Into the Assessment, Diagnosis, and Management of Hypogonadism

Proceedings From a Roundtable Discussion

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Dear Colleague:

Recognizing the importance of awareness and education regarding hypogonadism—a highly prevalent and often undertreated condition in the United States—experts from the fields of endocrinology, primary care, and urology participated in a roundtable discussion focusing on the recognition and treatment of hypogonadism in men. On April 26, 2008, the distinguished faculty convened in Boston to compile a comprehensive overview of hypogonadism.

One of the greatest challenges in treating hypogonadism in men is learning how to assess and diagnose this condition. Clinical guidelines are unclear, laboratory assays are uncertain, and the symptoms resulting from low testosterone levels are vague and nonspecific. A diagnosis of hypogonadism is often missed because of underlying comorbid conditions, some of which may be exacerbated by low testosterone levels.

The goal of the expert roundtable discussion was to educate clinicians about the following: the complex characteristics of hypogonadism and how it can manifest as a constellation of nonspecific signs and symptoms; the importance of identifying hypogonadism when a man presents with the symptoms of erectile dysfunction, depression, or loss of energy; laboratory testing of testosterone as a tool to assess and diagnose hypogonadism and to manage signs and symptoms; realistic treatment goals based on clinical presentation and laboratory parameters; the options available to treat hypogonadism; and when it is appropriate to refer to specialists.

This publication contains the proceedings from the multidisciplinary panel discussion, a review of the current data on hypogonadism, and recommendations that may be incorporated into your clinical practice. For additional educational activities on hypogonadism, including a downloadable *Esource* slide library, please visit <http://www.TestosteroneUpdate.org>.

Sincerely,

Glenn R. Cunningham, MD
Co-Chairperson

Ridwan Shabsigh, MD
Co-Chairperson

INTENDED AUDIENCE

This activity was developed for endocrinologists, urologists, primary care clinicians, and other health care professionals who treat patients with hypogonadism.

STATEMENT OF NEED

Hypogonadism is a clinical condition in which low levels of serum testosterone are associated with myriad signs and symptoms, including diminished libido and sense of vitality, and erectile dysfunction. It is a highly prevalent condition that affects 4 to 5 million men in the United States, yet it is often unrecognized, underdiagnosed, and undertreated. Reasons for this deficiency include a lack of awareness among clinicians, time constraints in everyday practice, and a lack of established ranges for laboratory parameters.

Diagnosis of hypogonadism can be challenging. It is important for clinicians to recognize that hypogonadism is a condition comprising many signs and symptoms and is not solely dependent on a decreased level of testosterone. Patient history, general health, lifestyle, and testosterone levels should be considered in the diagnosis for hypogonadism. Diagnosing hypogonadism is complicated by several issues, including constellation of signs and symptoms, lack of concrete testosterone thresholds, and wide variability in assays and laboratory measurements. Comorbid conditions, such as type 2 diabetes, obesity, metabolic syndrome, and cardiovascular disease, can affect or be affected by testosterone levels.

Other obstacles clinicians must overcome include therapy selection, monitoring, and adherence. Goals for treatment are to restore serum testosterone levels to normal and to alleviate signs and symptoms associated with low testosterone. This paper will address these clinical challenges and provide insight into various multidisciplinary approaches to the assessment, diagnosis, and management of patients with hypogonadism.

LEARNING OBJECTIVES

At the completion of the activity, participants should be better able to:

- Discuss the complex characteristics of hypogonadism and describe how it can manifest as a cluster of nonspecific signs and symptoms
- Identify hypogonadism when a man presents with comorbid conditions, such as erectile dysfunction, depression, or loss of energy
- Determine treatment goals for patients based on clinical presentation and laboratory parameters
- Review the options available to treat hypogonadism and provide clinical recommendations on how to initiate and monitor testosterone therapy, including baseline assessment, medical history, and laboratory value analysis
- Utilize a multidisciplinary approach to treating hypogonadism and associated conditions by making appropriate referrals to specialists when necessary

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The estimated time to complete this activity is 1.5 hours.

This activity was originally released September 30, 2008, and is eligible for credit through September 30, 2009.

This piece is based on presentations from faculty members and was written by a medical writer. Faculty have final editorial control for the piece.

OVERVIEW

Hypogonadism is defined as a clinical condition in which low levels of serum testosterone are associated with signs and symptoms, including diminished libido and sense of vitality, erectile dysfunction (ED), reduced muscle mass and bone density, mild depression, and anemia.¹ Hypogonadism is prevalent, affecting 4 to 5 million men in the United States, and is underrecognized, underdiagnosed, and undertreated despite available effective therapies.

Most men with hypogonadism, whether symptomatic or asymptomatic, present first to their primary care clinicians. Because of a lack of awareness, coupled with the time constraints of a primary care practice, hypogonadism often goes undiagnosed. To understand their role in the management of hypogonadism and offer patients the best course of action, it is important for primary care clinicians to become more aware of the prevalence and potential morbidity of the condition, its symptoms, methods of diagnosis, and available treatments.

“

If primary care clinicians were more aware of the prevalence of hypogonadism and the associated comorbidities, they would be much more active in screening for low testosterone’

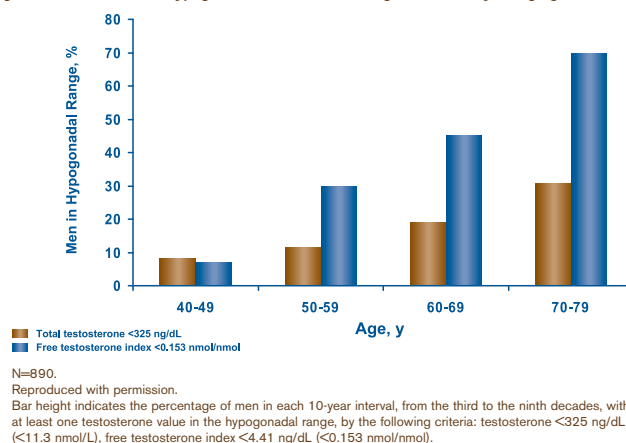
Martin M. Miner, MD ”

Even though many investigations into the potential presence of hypogonadism are initiated by patient complaints, the majority of the male population (91%) does not know at least one of the symptoms of low testosterone.² Research shows that 33% reported having experienced at least 2 hypogonadal symptoms within the last year, an alarming 97% of whom reported that their physician had never broached the subject of low testosterone as possibly related to their symptoms.² The impetus is clear for clinicians to be aware of the population at risk and the presenting signs and symptoms of hypogonadism.

Prevalence

The Baltimore Longitudinal Study of Aging (N=890) was one of the first studies to demonstrate that age had significant, independent, longitudinal effects on both testosterone level and free testosterone index (testosterone divided by sex hormone-binding globulin [SHBG]).³ Data-adjusted testosterone and free testosterone index values were used to calculate the percentages of men in each decade who were hypogonadal, defined as having at least one visit in that age decade at which testosterone was <325 ng/dL or the free testosterone index was <4.41 ng/dL. In men aged 40 to 79 years, the percentage of men with hypogonadism (as defined by total testosterone or free testosterone index) increased progressively after age 50 (Figure 1).

Figure 1. Prevalence of Hypogonadism: Baltimore Longitudinal Study of Aging³



The Massachusetts Male Aging Study, a 10-year prospective observational survey, compared cross-sectional data with longitudinal data and found that additional diseases are more likely to develop as men age.⁴ This explains why longitudinal data reveal much higher percentages of men who are testosterone deficient than do cross-sectional studies that may exclude men with these conditions.

Araujo and colleagues illustrated that the age trend in the proportion of men with low free testosterone increased at a faster rate than the proportion of men with low total testosterone because of a sharp rise in the proportion of men with elevated SHBG.⁵ Prevalence of symptomatic testosterone deficiency was significantly greater in the 70- to 79-year-old group compared with all other groups (pairwise comparisons, $P < .05$). Extrapolating, the authors estimated that, by 2025, more than 6 million American men between the ages of 30 and 79 years will suffer from symptomatic testosterone deficiency, an increase of 38% from year-2000 estimates.

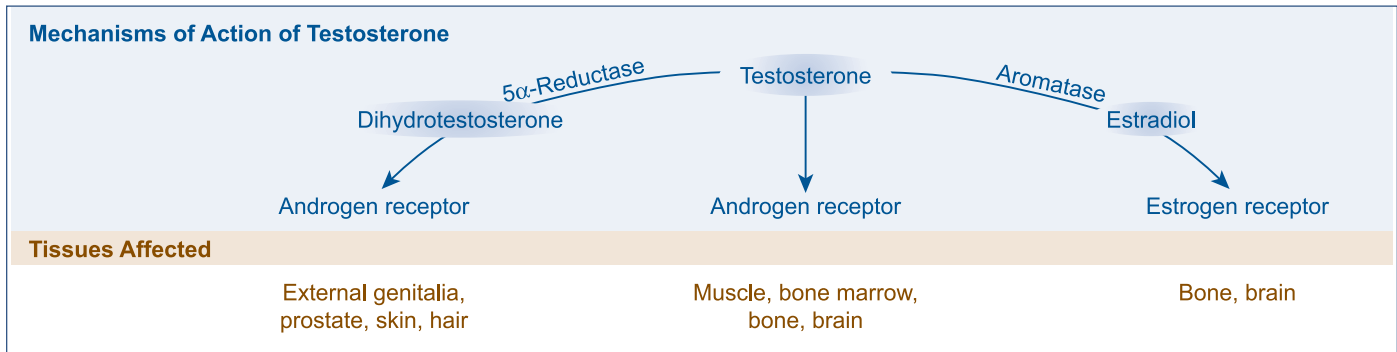
The Hypogonadism in Males (HIM) Study (N=2165) examined the prevalence of hypogonadism (defined as total testosterone <300 ng/dL) in men aged 45 years or older who presented to the offices of primary care clinicians.⁶ The crude prevalence of hypogonadism was found to be 38.7%. As men age, the risk of hypogonadism increased by 17% for each decade. According to Ridwan Shabsigh, MD, Director of the Division of Urology at Maimonides Medical Center in Brooklyn, New York, 66% of individuals in this study with low testosterone were symptomatic.

Sex steroids and hormones

Katherine Margo, MD, Associate Residency Director at the University of Pennsylvania School of Medicine stated in the *Journal of Family Medicine*, “I do not think medical schools are teaching very much about testosterone deficiency now.”⁷

A general knowledge of sex steroids and hormones and how they function in the body is important for all practitioners who will see and treat the majority of men with hypogonadism (Figure 2). Many organs are affected by a man’s androgen status (Figure 3).⁸

Figure 2. Mechanism of Action of Testosterone and Its Effects on Many Different Body Tissues, Systems, and Clinical Outcomes⁸



Adapted with permission.

Figure 3. Testosterone and Its Metabolites Have Physiologic Effects on Many Organs⁸

- | | |
|---|---|
| <ul style="list-style-type: none"> • CNS (↑libido, energy, well-being, spatial cognition) • Hypothalamus/pituitary (↓GnRH, LH, FSH; ↑GH) • Larynx (lowers voice) • Breast (E₂ ↑size) • Liver (↓SHBG, HDL) • Kidney (↑erythropoietin) • Genitals (suppression of spermatogenesis, erections) | <ul style="list-style-type: none"> • Prostate (↑size, secretions) • Skin (↑facial/body hair, sebum production) • Bone (↑BMD) • Muscle (↑lean mass, strength) • Adipose tissue (↑lipolysis, ↓abdominal fat) • Blood (↑hematocrit) • Immune system (↑auto-antibody production) |
|---|---|

BMD, bone mineral density; CNS, central nervous system; E₂, estradiol; FSH, follicle-stimulating hormone; GH, growth hormone; GnRH, gonadotropin-releasing hormone; HDL, high-density lipoprotein; LH, luteinizing hormone; SHBG, sex hormone-binding globulin.

$$\text{Free testosterone index} = \frac{\text{Testosterone}}{\text{SHBG}}$$

The major androgens in the circulation are testosterone, dihydrotestosterone (DHT), androstenedione, and dehydroepiandrosterone and its sulfate, with testosterone being the most important biologically.¹⁰ Testosterone is metabolized into DHT and estradiol through 5α-reductase and aromatase, respectively.

Fear prevailing about the use of hormones and their potential negative effects is driven in part by data regarding the risks of hormone supplementation in women. Martin M. Miner, MD, Clinical Associate Professor of Family Medicine at the Warren Alpert School of Medicine of Brown University in Providence, Rhode Island, has stated that it is important for clinicians to be aware, and to educate their patients, that the

goal of hormone therapy is to reestablish normal physiologic levels of serum testosterone.

Comorbid conditions

Because primary care physicians see men with a variety of health issues, it is important to be aware of other medical conditions and how they can affect or be affected by testosterone levels (Table 1).¹⁰ Several medications can cause levels of testosterone to decrease, including gonadotropin-releasing hormone agonists and antagonists, estrogens and progestins, glucocorticoids, ketoconazole, aldactone, thiazide diuretics, opiates, anabolic steroids, amiodarone, and psychotropic agents.¹⁰ Aldactone, cimetidine, flutamide, and androgen antagonists also impair testosterone activity at the receptor.¹¹

Table 1. Conditions and Medications That Can Cause Hypogonadism¹⁰

Acute Critical Illness	Chronic Systemic Diseases	Drugs
Surgical trauma Myocardial infarction	Type 2 diabetes Chronic obstructive pulmonary disease Chronic liver disease Chronic renal failure Endocrine diseases • Primary testicular lesions • Cushing syndrome • Prolactinoma and other tumors Sickle cell disease	GnRH analogs Antiandrogens Alkylating agents Systemic glucocorticoids Opiates Cannabinoids Neuroleptic drugs

GnRH, gonadotropin-releasing hormone.

Expert snapshot

Comorbidities common with hypogonadism

Metabolic syndrome

Type 2 diabetes

Obesity

Sleep apnea

Chronic obstructive pulmonary disease

Anemia

Cardiovascular disease

Sarcopenia

Depression

Rheumatoid arthritis

Osteoporosis, frailty

Memory loss

The objectives of the HIM study were to identify men with hypogonadism and comorbidities in patients presenting to primary care physicians' offices. Results revealed that several common medical conditions are significantly associated with low levels of testosterone: hypertension, hyperlipidemia, diabetes, and obesity ($P < .001$ for all). Asthma/chronic obstructive pulmonary disease was also correlated with hypogonadism ($P = .013$).⁶

A cross-sectional study by Rhoden and colleagues (N=746) in a urology center evaluated the relationship between type 2 diabetes and serum free and total testosterone levels.¹² Subnormal total testosterone levels were more strongly associated with elevated body mass index (BMI) and waist:hip ratio than with diabetes, indicating that total testosterone levels are more influenced by obesity and central adiposity.¹² Although the physiologic reason has not been established, it has been shown that as BMI increases, there is a parallel decrease in SHBG and total and free testosterone levels.¹³

A study of more than 350 men by Kapoor and colleagues took this association a step further, evaluating both biochemical measures of testosterone and symptoms of hypogonadism as they relate to the presence of type 2 diabetes.¹⁴ Results showed that symptomatic hypogonadism is highly prevalent in men with type 2 diabetes, with ED being the most common symptom of hypogonadism in men with diabetes (>70%). This highlights the importance of measuring testosterone in men presenting with ED and type 2 diabetes, a condition frequently seen by primary care clinicians.

It has been established that metabolic syndrome is associated with subsequent development of type 2 diabetes and cardiovascular disease. Similar to the association between low testosterone levels and the prevalence of type 2 diabetes, low testosterone levels are also associated with higher prevalence of metabolic syndrome.^{15,16} Muller and colleagues showed that lower levels of testosterone and SHBG in aging men are independently associated with lower insulin sensitivity and an increased risk of metabolic syndrome.¹⁵

Makhsida and colleagues conducted a review from 1988 to 2004 of the associations between hypogonadism, testosterone, and metabolic syndrome and concluded that not only is hypogonadism a component of metabolic syndrome, but testosterone therapy may "have the tremendous potential to slow

or halt the progression from metabolic syndrome to overt diabetes or cardiovascular disease via beneficial effects on insulin regulation, lipid profile, and blood pressure."¹⁷

Another condition seen often in primary care is depression. The Rancho Bernardo Study (N=856; men aged 50-89 y) showed an association between bioavailable testosterone and mild depression as measured by Beck Depression Index scores.¹⁸ The authors concluded that testosterone therapy may improve depressed mood in older men with low levels of bioavailable testosterone, although the overall data on the effect of testosterone on mood are mixed.

Studies report that low levels of testosterone are associated with increased mortality. In a retrospective study (N=858),¹⁹ male veterans aged 40 years and older who had testosterone levels measured were followed for 8 years. After adjusting for age, morbidity, and other clinical covariates, low testosterone levels (<250 ng/dL) were associated with increased mortality ($P < .001$).

Similarly, The Rancho Bernardo Study (N=794), a prospective study that followed men with low testosterone (<241 ng/dL) for up to 20 years, demonstrated that low testosterone in older men was associated with increased mortality, particularly from cardiovascular disease and respiratory diseases, independent of multiple risk factors and preexisting comorbid conditions.²⁰

The associations between testosterone and coronary artery disease, diabetes, metabolic syndrome, obesity, and BMI are clearly significant. Because primary care physicians are on the frontline to recognize, diagnose, and then treat hypogonadism, it is important for them to be aware of the nuances and challenges associated with this condition. A variety of effective treatment options are available, and a multidisciplinary approach may be warranted for the complicated patient.

Key messages

Hypogonadism:

- Is associated with aging
- Is common, underdiagnosed, and undertreated, despite observable symptoms
- Is associated with chronic medical conditions that may negatively affect overall health
- May impact mortality

ASSESSMENT AND DIAGNOSIS

Clinicians face a variety of diagnostic challenges with regard to hypogonadism, including recognizing a constellation of signs and symptoms and not solely looking at decreased testosterone levels. Signs and symptoms are often vague, particularly in middle-aged and older men in whom age-related conditions can overlay symptoms of testosterone deficiency, making it difficult to identify.²¹⁻²³ Loss of libido and ED are 2 hallmark symptoms of hypogonadism. Lethargy is commonly seen in these men. Mood and behavioral symptoms, specifically depression, irritability, and loss of motivation, may also occur with low testosterone levels.¹¹ Testosterone deficiency has a deleterious effect on bone mass and is a risk factor for osteoporosis. Furthermore, reduced muscle mass and muscle strength is associated with low testosterone levels. Regression of secondary sexual characteristics, such as reduced ancillary and pubic hair, is another sign of hypogonadism in men. Small testes (<4.0 x <2 cm) and gynecomastia suggest possible hypogonadism.

Older patients	=	Poor concentration, height loss
	vs	
Younger patients	=	Decreased energy, erectile dysfunction

Factors influencing the signs and symptoms of hypogonadism include age of onset, severity and duration, comorbid illnesses, variations in androgen sensitivity, and effects of previous testosterone therapy.¹⁰

The Endocrine Society created guidelines for diagnosing testosterone deficiency in men, emphasizing that a low level of testosterone is a major component of a diagnosis but only part of the syndrome²²:

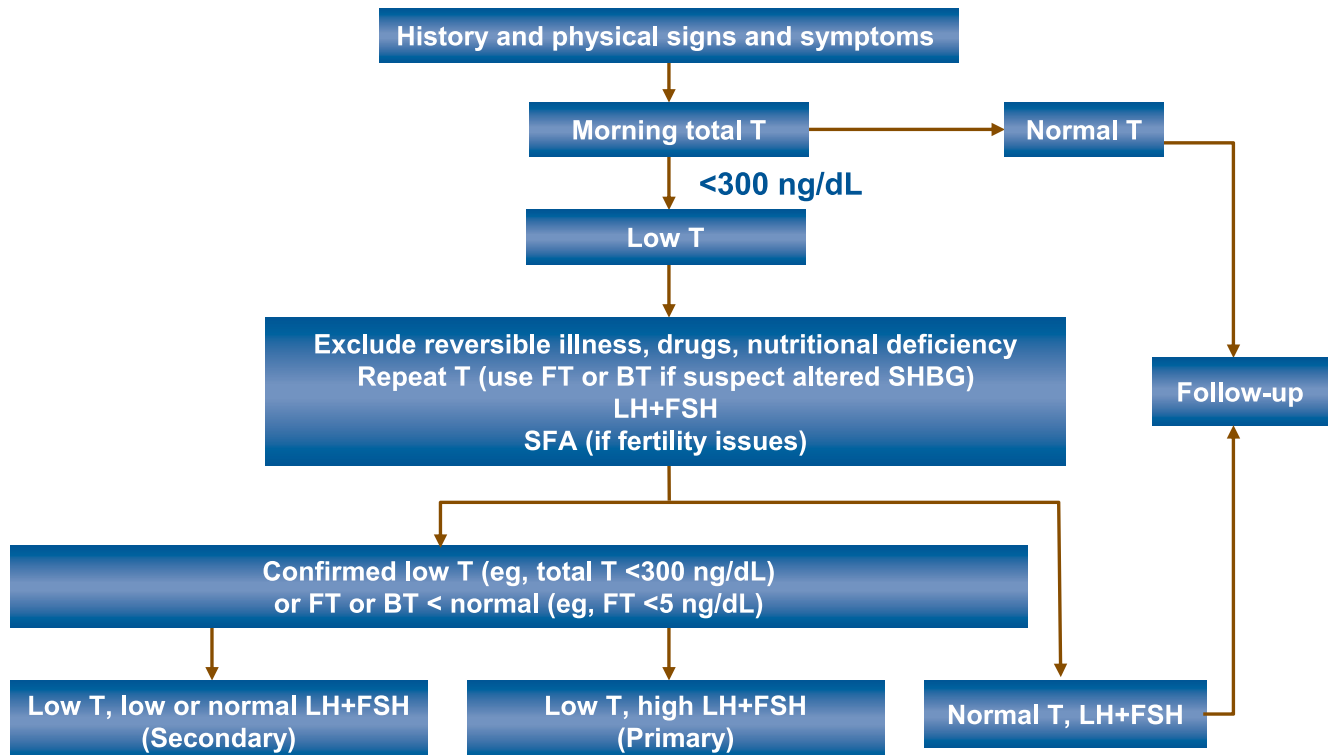
- Diagnose hypogonadism in men with consistent signs and symptoms as well as low serum testosterone levels
- Measure morning total testosterone by a reliable assay as the initial diagnostic test
- Confirm low levels of total testosterone with repeat measurement and/or a free or bioavailable testosterone level
- Do not diagnosis testosterone deficiency during an acute or subacute illness

Theoretically then, the algorithm for diagnosing hypogonadism should be straightforward: Evaluate a man's general health and lifestyle and measure his testosterone levels (Figure 4).²² If a man has low levels of testosterone, a luteinizing hormone (LH)

Expert snapshot
 Conditions seen most often in hypogonadal men at presentation:

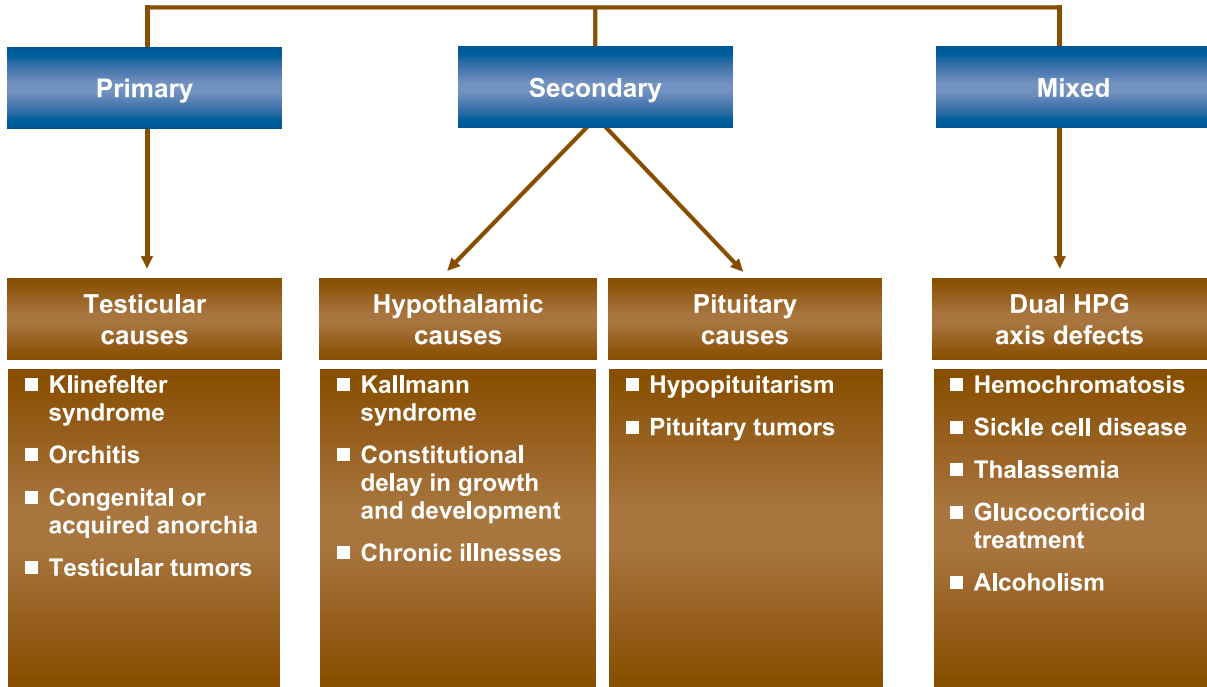
- Lethargy
- Obesity
- ED

Figure 4. Diagnostic Evaluation of Adult Men With Suspected Hypogonadism²²



BT, bioavailable testosterone; FSH, follicle-stimulating hormone; FT, free testosterone; LH, luteinizing hormone; SFA, seminal fluid analysis; SHBG, sex hormone-binding globulin; T, testosterone. Reproduced with permission.

Figure 5. Classification of Hypogonadism^{22,24}



HPG, hypothalamic-pituitary-gonadal.

concentration should be obtained to determine whether the low level is the result of a defect at the testicular level or at the hypothalamic-pituitary-gonadal axis (Figure 5).^{22,24} In practice, however, diagnosis is not that simple.

There is no established threshold for testosterone that defines hypogonadism; there is no “magic number.”²⁵ Further, measurements vary depending on circadian and circannual rhythms, episodic secretion, variations in assays, and variations in SHBG concentrations.²²

Expert snapshot

Question: What range of testosterone levels prompts further investigation?

Answer: 200 to 400 ng/dL

According to the Endocrine Society, a man should be screened for hypogonadism if he presents with any of the following conditions²²:

- Sellar mass, radiation to the sellar region, or other diseases of the sellar region
- Medications that affect testosterone production or metabolism
- Weight loss associated with human immunodeficiency syndrome
- End-stage renal disease or maintenance hemodialysis
- Moderate to severe chronic obstructive lung disease
- Osteoporosis or low-trauma fracture (particularly in younger men)
- Type 2 diabetes or metabolic syndrome

Physical examination and history

A detailed physical examination and comprehensive history is important in the diagnosis of hypogonadism.²⁴ Specifics that should be elicited and documented in this process are outlined in Table 2.

Table 2. Evaluating Adult Men With Suspected Hypogonadism

- Comprehensive history^{22,24}
- Gynecomastia^{22,24}
- Secondary sexual characteristics (decreased body hair, decreased beard growth)^{22,24}
- Testicular examination, noting size and consistency^{22,24}
 - Approximate ranges for normal adult testes²⁴
 - Volume 20-30 mL
 - Length 4.5-6.5 cm
 - Width 2.8-3.3 cm
- Prostate assessment, noting palpability²⁴
- Body mass index²²

Tools

Several tools are available to screen for testosterone deficiency in men, but each one lacks sensitivity or specificity. Therefore, it might be preferable to use probing questions.

Expert snapshot

Because time constraints are always an issue, office questionnaires for medical history and reasons for visit should include 1 or 2 questions to trigger further investigation by the physician into causes of low testosterone.

Diagnostic tests

Accurate measurement of testosterone levels is essential to diagnose hypogonadism; however, this too is fraught with challenges. The methods to measure total testosterone include immunoassays, immunometric assays, and, most recently, mass spectrometry.²⁶ Recognizing the difficulties in measuring testosterone, the Endocrine Society established a task force to review the issues.

Wang and colleagues demonstrated a wide variation in testosterone measurements, both between laboratories and between assays.²⁷ Values as low as 160 ng/dL and as high as 508 ng/dL were reported on the same sample. This illustrates how variability complicates making an accurate diagnosis.

To address this issue, the Centers for Disease Control and Boston University are collaborating to standardize testosterone assays across laboratories. Their goal is to develop recommendations for defining androgen deficiency, potentially using a risk-type profile similar to that of the Framingham Heart Disease study, rather than discrete cutoff values.^{28,29}

Another issue with diagnosing testosterone deficiency is the lack of reliable reference ranges, the statistical distribution of hormone concentrations in a healthy population. Such reference ranges are typically generated from small samples, not population-based samples. However, vigorously established reference ranges are not available for most hormones, not just testosterone.

Total testosterone	Sum of protein-bound and free testosterone in circulation ²²
Bioavailable testosterone	Free testosterone plus testosterone loosely bound to albumin ²²
Free testosterone	The 0.5%-3.0% of testosterone not bound to albumin or SHBG ²²

Total testosterone is the most widely available and least expensive assay.²³ Free testosterone is that not bound to SHBG or albumin and amounts to only 0.5% to 3.0% of total testosterone.²² Although this is a more accurate assessment of hypogonadism, the direct or analog free testosterone assay is inaccurate. Equilibrium dialysis is a much more dependable measure, but very few laboratories are capable of performing this complicated assay.

Calculating the free testosterone index, total testosterone divided by SHBG, also is unreliable for individual patients.^{23,24} Bioavailable testosterone (ie, not bound to SHBG) may be the most reliable test, indicating how much testosterone is available to target tissues, but this test is expensive and not widely available.²³ Calculations of free testosterone or bioavailable testosterone using the mass action equation provide useful and reliable estimates.

The free and bioavailable testosterone calculator is available from the International Society for the Study of the Aging Male's Web site at <http://issam.ch/freetesto.htm>³⁰

When should clinicians measure free testosterone levels? Free testosterone should be measured for men with conditions that will markedly alter their SHBG levels, such as obesity, chronic inflammatory disease (eg, HIV), hyperthyroidism, or liver disease and for older men who have higher SHBG with borderline free testosterone (200-350 ng/dL).²²

In men found to be testosterone deficient, measurement of LH and follicle-stimulating hormone (FSH) levels can help determine whether the defect is at the testicular level (ie, primary) or at the hypothalamic-pituitary site (ie, secondary).²² Table 3 illustrates the laboratory and other studies that can be used to further evaluate for hypogonadism.²⁴ Additional workups for men with hypogonadism include measuring serum levels of prolactin, ferritin, iron-binding capacity, prostate-specific antigen (PSA) and digital rectal examination (DRE),¹ dual-energy x-ray absorptiometry (DEXA) scan to determine bone mineral density (BMD), and brain magnetic resonance imaging. Karyotyping should be conducted for men with undiagnosed primary testicular disease to rule out Klinefelter syndrome.²²

In summary, there are many challenges to diagnosing hypogonadism. However, if clinicians are aware of the limitations and abreast of

current data, they can more accurately diagnose and appropriately treat their male patients who have testosterone deficiency.

Key messages

- Measure testosterone levels in men with signs and symptoms of hypogonadism
- Measure total testosterone levels by a reliable assay, preferably in the morning, and confirm low values with repeat measurement
- Use the normative ranges specific to the assay
- Use ancillary clinical and laboratory data to corroborate the diagnosis

Table 3. Further Evaluation of Hypogonadism Based on American Association of Clinical Endocrinologists Guidelines²⁴

Laboratory Studies	Other Studies
Testosterone	Bone densitometry
Gonadotropins	Pituitary imaging
Luteinizing hormone	Genetic studies
Follicle-stimulating hormone	Testicular biopsy, scrotal exploration

CLINICAL CONSIDERATIONS AND MANAGEMENT OF HYPOGONADISM

Candidates for testosterone therapy and indications

Although controversy surrounds the concept of male andropause or late-onset hypogonadism, there is growing evidence that age-related decreases in testosterone and associated symptomatology may respond to treatment with testosterone therapy.²⁴ Testosterone therapy is also used as a second-line therapy in hypogonadal patients with ED and only when there is deficiency.^{23,31} There is also debate over the potential risks of testosterone therapy to prostate health. General guidelines exist; however, it is important that therapy be individualized to each patient's unique medical profile and current condition.^{32,33}

Goals and benefits of testosterone therapy

The goals of testosterone therapy for hypogonadism are to restore serum testosterone levels to normal and minimize the signs and symptoms. The Institute of Medicine recommends that the goal of therapy should be to restore testosterone levels to those seen in young adult males aged 20 to 40 years (ie, 21.8 nmol/L [627 ng/dL]).³⁴ Supraphysiologic levels should be avoided and are not necessary to maintain the physiologic circadian rhythm of testosterone levels.³¹

Treatment of low testosterone with testosterone therapy may provide patients with significant improvements in other areas. Benefits of testosterone therapy include improvements in bone density, muscle mass, body composition, mood, erythropoiesis, energy, and sexual desire and performance.^{1,22,35}

A long-term (12 months) study of 371 hypogonadal men reported that testosterone therapy resulted in a significant increase in lean body mass and significant decrease in fat mass from baseline ($P < .001$ for both); there was no significant change in total body mass.³⁵ Sexual function, as measured by sexual desire, performance, motivation, satisfaction with duration of erection, percentage of full erection, and ability to have spontaneous erections, showed significant improvement from baseline at all time points of the extension study ($P < .001$). Improvements in mood were also observed and were maintained over the course of the study. There was also a significant ($P < .001$) change in BMD of the lumbar spine as measured by DEXA scan.

Another area of interest is the potential beneficial effect of testosterone on metabolic syndrome and its components. Kapoor and colleagues looked at the effect of testosterone on insulin resistance and glycemic control in 24 hypogonadal men with type 2 diabetes who were older than age 30 years.³⁶ Testosterone improved fasting insulin sensitivity (-1.73, $P = .02$) as measured by the homeostasis model assessment index, which is the ratio of insulin levels to fasting glucose control. Glycosylated hemoglobin and fasting blood glucose were reduced (-0.37 and -1.58 mmol/L, respectively; $P = .03$ for both). Visceral adiposity as measured by waist circumference was reduced (-1.63 cm, $P = .03$), as was waist:hip ratio (-0.30, $P = .01$). There was also a decrease in total cholesterol (-0.4 mmol/L, $P = .03$), but there was no effect on blood pressure. Taken together, the improvements in insulin resistance and glycemic control represent a potential overall reduction in associated cardiovascular risk. However, other studies have failed to observe a beneficial effect on diabetes control.

Risks

As with any pharmacotherapy, there are some potential risks associated with treatment. Table 4 lists potential adverse events associated with testosterone therapy.^{1,22}

With regard to sleep apnea, the true association with testosterone therapy is not clear. Many hypogonadal men are at an increased risk for sleep apnea as a result of obesity.^{13,37} Also, clinicians should be aware that the studies correlating sleep apnea to testosterone treatment used supraphysiologic levels and do not necessarily indicate that testosterone treatment with physiologic levels will cause sleep apnea.

A meta-analysis of randomized, placebo-controlled trials by Calof and colleagues revealed that testosterone therapy in older men was associated with a significantly higher risk of hematocrit $> 50\%$, confirming the need to carefully monitor hematocrit in this population.³⁸

Testosterone therapy: risk to the prostate

There is a long-standing belief held by the medical community that low testosterone levels are protective against prostate cancer and that, conversely, normal or elevated testosterone levels may cause cancers to grow. This simplistic belief is mostly historical and contrary to a growing body of evidence. However, this concept is perhaps the single greatest barrier to initiating testosterone therapy.

Initially, prostate cancer is androgen-dependent: The cancer regresses when testosterone levels are lowered to castrate levels, and allowing testosterone to return to normal levels may cause prostate cancer to recur.³⁹ However, the testosterone-prostate relationship is not as simple as an on/off switch or a 1:1 ratio. When testosterone levels rise above the near-castration range, there is little detectable effect: PSA does not change, nor does prostate volume. This important, key distinction suggests a saturation curve, whereby at near-castration range, testosterone levels are important, and profound effect is seen on prostate cancer growth. However, there has been no evidence of such effect beyond these ranges.⁴⁰

Paradoxically, low testosterone levels have been associated with higher Gleason scores and more advanced stage at presentation.⁴¹ A paradox also exists in the percentage of age-matched men with prostate cancer in the general population compared with those in testosterone therapy trials. About 15% of men with a PSA

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Testosterone does not cause prostate cancer but may cause a cancer to become clinically apparent

Glenn R. Cunningham, MD

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Table 4. Adverse Events Associated With Testosterone Therapy^{1,22}

Evidence of Association With Testosterone Therapy	Weak Evidence of Association With Testosterone Therapy
Erythrocytosis (wide range of risk)	Gynecomastia
Acne and oily skin (infrequent)	Male pattern baldness (familial)
Detection of subclinical prostate cancer	Worsening of symptoms of benign prostatic hyperplasia
Reduced sperm production and fertility	Growth of breast cancer
Testicular atrophy or infertility (common, especially in younger men; usually reversible with cessation of treatment)	Induction of or worsening of obstructive sleep apnea (infrequent)

Adapted with permission.

≤4.0 ng/mL have biopsy-detectable prostate cancer. Prostate cancer has been diagnosed in testosterone therapy trials in men aged approximately 65 years and older.^{1,42,43} If raising testosterone levels into the normal range caused an increase in the risk of prostate cancer, then a higher percentage of prostate cancer would be expected in trials in which men were receiving testosterone. The same is true for the age-related incidence of prostate cancer, which begins when men are in their 40s, not their 20s, the time for peak serum levels of testosterone. In fact, the prevalence of prostate cancer increases inversely as testosterone levels decline with age. However, these studies have not been powered to detect an increase in clinical prostate cancer.

A study by Marks and colleagues of 40 men aged 44 to 78 years concluded that testosterone therapy increased serum testosterone

and DHT levels without affecting prostate tissue and expressions of several androgen dependent genes, suggesting that the risks to the prostate from testosterone therapy “may not be as great as once believed, especially if the results of the pretreatment biopsy are negative.”⁴⁴ Yet, monitoring for signs of prostate cancer is mandatory during testosterone therapy¹(Table 5).

An important landmark study by the Endogenous Hormones and Prostate Cancer Collaborative Group was published this year. This study compared 18 prospective longitudinal studies that analyzed whether differences in circulating levels of sex hormones were related to prostate cancer risk. This collaborative analysis definitively found no association between serum concentrations of sex hormones, including testosterone, and the risk of developing prostate cancer.⁴⁵

Table 5. Monitoring Prostate Health During Testosterone Therapy

Parameter	Frequency	Comment
DRE ^{1,22}	Baseline; at 3, 6, and 12 mo; yearly thereafter	Biopsy if abnormal baseline and if abnormal during treatment
Voiding, IPSS score ^{1,22}	Baseline; prostate-related symptom assessment every 6 to 12 mo	
PSA level	Baseline; at 3 and 6 mo; yearly thereafter ^{1,22}	Biopsy if PSA >4.0 ng/mL ¹ Biopsy if PSA increases 1.0 ng/mL or greater within any 12-mo period ¹ Repeat PSA measurement for PSA increase of 0.7 to 0.9 ng/mL in 1 y ¹

DRE, digital rectal examination; IPSS, International Prostate Symptom Scale; PSA, prostate-specific antigen.

Expert snapshot

Testosterone and the prostate

Practitioners should counsel their patients with the following 4 points in mind:

1. Testosterone therapy is absolutely contraindicated in men with metastatic prostate cancer
2. There is no evidence that testosterone therapy causes prostate cancer in men
3. There is no evidence that someone who is hypogonadal and made eugonadal has a higher risk for prostate cancer
4. Every patient receiving testosterone therapy should be monitored for prostate-related health changes, especially men older than 50 years and men at high risk (ie, family history of prostate cancer); monitoring should begin at age 40 years for African Americans and for men who have a first-degree relative with prostate cancer

Key messages

- Hypogonadal, symptomatic men should be treated with testosterone therapy
- Testosterone therapy can alleviate the symptoms associated with low testosterone levels
- The goal is a testosterone level of at least 300 to 600 ng/dL
- Treatment should be individualized for each patient
- The potential risks to prostate health from testosterone therapy are not be great as once believed

TREATMENT OPTIONS AND MONITORING RECOMMENDATIONS

Treatment options

Several types of testosterone treatment are on the market today and in development, including topical, transdermal, transbuccal, intramuscular injection, and subcutaneous implants, each with specific dosing recommendations, potential adverse effects, and general pros and cons (Table 6).²² The ideal formulation is safe, effective at providing physiologic levels of testosterone, convenient, and cost-effective.

A novel, long-acting intramuscular injectable formulation, testosterone undecanoate, is being evaluated in the United States. It has been approved and launched in more than 80 countries in Europe and Asia in a dosage of 1000 mg in castor oil administered up to every 12 weeks.⁴⁶ This dosing regimen requires only 4 injections per year, eliminating adherence issues and thereby improving patient outcomes.

Table 6. Testosterone Therapy and Formulation-Specific Adverse Events²²

Formulation	Adverse Effect
Injectable Testosterone cypionate/enanthate Testosterone undecanoate ^a	Mood fluctuations or changes in libido Pain at injection site Erythrocytosis Low incidence of pain at injection site
Implants Testosterone pellets	Potential infections or expulsion
Topical Topical gel Patch system	Skin-to-skin transference Skin irritation
Buccal Buccal system	Alterations in taste and irritation of gums and oral mucosa

^aIn development in the United States.

“ A key benefit of injectable testosterone is that monitoring is easier because patients have to return to the office
 Ajay Nehra, MD ”

testosterone varies (Table 7).²² As accurate measurement is an important component of monitoring patients for efficacy and safety, it is important for primary care clinicians to be aware of these differences.

When monitoring the effects of testosterone therapy, it is necessary to measure testosterone but equally important to assess the efficacy of treatment with regard to the signs and symptoms of low testosterone. Because testosterone affects various organs and tissues, men receiving testosterone therapy should be evaluated at baseline and at follow-up visits, generally at 3, 6, and 12 months after the initiation of therapy and yearly thereafter.¹

Monitoring recommendations

Because testosterone is delivered via different mechanisms depending on the route of administration, the ideal time to get an accurate measure of

Table 7. Monitoring Testosterone Levels: When to Measure Based on Formulation²²

Formulation	When to Measure Testosterone Level
Injectable Testosterone cypionate or enanthate Testosterone undecanoate	Midway between injections; if >700 ng/dL or <350 ng/dL, adjust dose or frequency Before each injection, adjust dosing interval to maintain testosterone level in mid-normal range
Topical Topical gel Patch system Buccal system	Any time after patient has received treatment for at least 1 wk 3-12 h after application of patch Immediately before application of fresh system

Adapted with permission.

Baseline assessments should include a DRE and blood tests to measure PSA and hemoglobin or hematocrit. Voiding symptoms can be assessed by obtaining a history or using an instrument such as the International Prostatic Symptom Scale. Patients should be questioned regarding symptoms of sleep apnea. If the PSA level is >4.0 ng/mL or the DRE finding is abnormal, a prostate biopsy should be performed.^{1,22}

At follow-up, urinary symptoms and the presence or exacerbation of sleep apnea or gynecomastia should be monitored. Because increased testosterone levels appear to stimulate erythropoiesis, hemoglobin or hematocrit should be monitored during

therapy.^{1,22} The risk of erythrocytosis appears to vary with the type of testosterone formulation.¹

DRE should be repeated at follow-up visits. If the PSA level is >4.0 ng/mL or increases by ≥ 1.0 ng/mL in 1 year, a prostate biopsy should be performed or the patient should be referred to a urologist.^{1,22} For increases in PSA levels of 0.7 to 0.9 ng/mL in 1 year, the PSA measurement should be repeated in 3 to 6 months, and a biopsy should be performed if a further increase is detected.¹

Guidelines have been established by several organizations with regard to monitoring during testosterone treatment. Similar in nature and intent, these guidelines are provided in Table 8.^{1,22,24,31}

Table 8. A. Monitoring During Testosterone Therapy B. International Society of Andrology, International Society for the Study of the Aging Male, and European Association of Urology Recommendations C. American Association of Clinical Endocrinologists Recommendations^{1,22,24,31}

A. Parameter	Test Frequency				Goal/Comments
	Baseline	1-2 Mo	3-6 Mo	Annually	
Symptom assessment	X	X	X	X	Evaluate whether symptoms have responded to treatment or if there are adverse effects
Testosterone level	X	X	X	X	Goal is to restore serum testosterone to mid-normal range
PSA level	X		X	X	
DRE findings	X		X	X	Biopsy if abnormal at baseline and if abnormal during treatment
Breast examination findings	X		X	X	Detect gynecomastia; mammograms only as indicated
Hematocrit level	X		X	X	If hematocrit is $>54\%$, stop therapy until hematocrit decreases to a safe level
Sleep apnea	X		X	X	Ask about fatigue during the day and disordered sleep
Voiding, IPSS score	X		X	X	
DEXA findings	X				Every 2-5 y if testosterone score is <-2.0 at baseline

B. Parameter	Test Frequency
DRE, PSA, hematologic assessments in men aged >45 y	Baseline Quarterly for the first 12 mo Yearly thereafter
Bone density	Every 2 y if abnormal at baseline

C. Parameter	Test Frequency
Side effects	Every 3-4 mo for the first year
Testosterone levels Injectables Gels Patches	Midpoint between injections Timing of measurement not important Measure 4-8 h after application
Prostate examination and prostate-related symptom evaluation	Every 6-12 mo
PSA	Every 12 mo
Hematocrit	Every 6 mo for the first 18 mo and yearly thereafter if stable and normal; decrease or discontinue testosterone therapy if hematocrit increases to $>50\%$
Lipid profile	Baseline, every 6-12 mo, yearly thereafter

DEXA, dual-energy x-ray absorptiometry; DRE, digital rectal examination; IPSS, International Prostate Symptom Scale; PSA, prostate-specific antigen.

Optimizing testosterone therapy in hypogonadism

After clinicians identify hypogonadism and initiate treatment, it is important to counsel patients, along with the monitoring for safety and efficacy discussed previously. Appropriate counseling and education—explaining that testosterone therapy should not be solely equated with sexual function, setting realistic expectations, and discussing the risks, benefits, and perceived fears of therapy—will all help to increase adherence and improve patient outcomes.

“

To optimize the treatment of hypogonadal men who are obese, “...combine androgen with a lifestyle alteration process rather than just treating it as a strictly hormonal situation

Robert S. Tan, MD

”

Expert snapshot

To improve patient adherence:

- Involve the patient in treatment selection
- Individualize the treatment plan
- Set specific and realistic goals
- Provide patient education
- Listen to the patient: be aware of his priorities, goals, time constraints, and expectations
- Conduct regular follow-up and monitoring; include a follow-up phone call from office

Team approach

Although in many cases, primary care physicians can successfully treat men with hypogonadism, there are some instances when a team approach would be more appropriate. Primary care physicians should consider referring to an endocrinologist a patient who exhibits signs or symptoms of a pituitary tumor, including visual field abnormalities, headaches, hyperprolactinemia, or hypopituitarism or who has a testosterone level <150 ng/dL with normal LH and FSH levels (Table 9). A patient should be referred to a urologist if he has a PSA level >4.0 ng/mL, a yearly increase in his PSA level of >0.75 to 1.0 ng/mL, a prostatic abnormality detected by DRE, or an American Urological Association score or International Prostate Symptom Score >19.^{1,22} Other specialists that may become involved in the treatment of patients with low testosterone levels are cardiologists and sleep specialists.

“

We need to literally legitimize the primary care clinician who just screens and then refers if there are any questions or any abnormality

Richard Sadovsky, MD

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Key messages

- Treatment goals should be based on resolution of symptoms and signs of low testosterone
- A variety of delivery systems and formulations of testosterone are available, each with its own advantages and disadvantages
- An ideal formulation of testosterone would safely and effectively reestablish physiologic levels of testosterone while being convenient to administer and cost-effective
- Without documented, verifiable evidence of the risks of testosterone therapy, it is important to screen patients before initiating testosterone therapy and to monitor the prostate during therapy
- Counseling and education, along with realistic goals and continuous follow-up, are essential to optimizing testosterone therapy
- An interdisciplinary team approach may be needed to treat a patient with hypogonadism, and primary care clinicians should feel comfortable referring patients to specialists when appropriate

CONCLUSION

Hypogonadism is underrecognized, underdiagnosed, and undertreated for many reasons. Being aware of these reasons and having a deeper understanding of the condition will help primary care clinicians recognize and treat this disorder.

Diagnosing hypogonadism is complicated by myriad issues, including overlaying symptomatology, lack of concrete testosterone thresholds, and wide variability in assays and laboratory measurements.

Table 9. Reasons for a Patient to Be Referred to a Specialist

Considerations for Referral to Endocrinologist	Considerations for Referral to Urologist
Signs and symptoms of pituitary tumor <ul style="list-style-type: none"> • Visual field abnormalities • Headaches • Hyperprolactinemia or hypopituitarism • Testosterone <150 ng/dL with normal LH and FSH levels²² • Other pituitary abnormalities • Further consideration for unclear etiology 	PSA >4.0 ng/mL Increase in serum or plasma PSA concentration >0.75 to 1.0 ng/mL in any 12-mo treatment period Prostatic abnormality detected by DRE AUA or IPSS symptom score >19

AUA, American Urological Association; DRE, digital rectal examination; FSH, follicle-stimulating hormone; IPSS, International Prostate Symptom Scale; LH, luteinizing hormone; PSA, prostate-specific antigen.

Hypogonadism is associated with comorbid conditions, including depression, ED, increased BMI and waist circumference, type 2 diabetes, metabolic syndrome, coronary artery disease, and other chronic illnesses. All of these are routinely seen by primary care clinicians, which highlights the importance for physicians to be aware of how testosterone levels can be related to and affected by these conditions.

A variety of safe, effective formulations of testosterone are available. As clinicians and patients become more aware of this

condition and how to properly diagnosis and treat it, the number of testosterone prescriptions is expected to rise. The medical community is increasingly treating testosterone deficiency (not aging), as highlighted by Andre T. Guay, MD, Director of the Center for Sexual Function, Lahey Clinic Northshore, and Clinical Assistant Professor of Medicine (Endocrinology) at Harvard Medical School in Boston, Massachusetts. Prostate health should be assessed at baseline and periodically during treatment. Treatment goals should be to resolve signs and symptoms of hypogonadism and improve the patient's quality of life.

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