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What screening tests should you use to evaluate a man with low testosterone?

Evidence-based answer

Obtain a repeat morning testosterone level, as well as levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin to help understand the cause of low testosterone when there is a lack of adequate empiric evidence to guide evaluation, advise the experts. When low or normal FSH and LH levels accompany low testosterone, evaluation of the pituitary gland is recommended.

Chromosomal studies are indicated in prepubertal males with low testosterone and elevated FSH and LH levels to assess for Klinefelter syndrome. Perform a semen analysis if fertility is an issue. Bone densitometry is indicated in men with chronic hypogonadism to identify increased risk of hip fracture (strength of all recommendations: **C**, consensus guidelines and disease-oriented evidence).

Clinical commentary

Diagnosis is often straightforward, but treatment ... not so much

The causes of low testosterone are diverse and vary across the life span (**TABLE**).^{1,2} Although screening tests are integral to the evaluation, a successful diagnostic approach must begin with a detailed history and physical exam. Clinical clues coupled with judiciously selected tests typically lead to a straightforward diagnosis.

The decision whether or not to

treat a patient diagnosed with partial androgen deficiency of aging is often less clear, especially when clinical symptoms are minimal or absent. The benefits of testosterone replacement therapy are significant, but so are the potential risks. Shared decision making with the patient is key to this dilemma.

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FAST TRACK

Experts recommend a repeat morning testosterone level, plus testing levels of FSH, LH, and prolactin to evaluate the cause of low testosterone

Evidence summary

Our search retrieved no randomized controlled clinical trials evaluating the screening tests required to work-up a male with low testosterone. We therefore examined 2 consensus guidelines, 9 review articles, and disease-oriented evidence. The recommendations discussed here are based primarily on consensus

guidelines and disease-oriented evidence.

Hypogonadism increases with age

Hypogonadism is a common endocrinologic disorder in men. Advancing age, increased life expectancy, and a rising prevalence of obesity and type 2 diabetes may increase the occurrence of hypogonadism.³ Many cases result from partial

TABLE

Causes of hypogonadism

CLASS	LOCATION	CAUSES
Primary (low testosterone, elevated FSH)	Testes	<p>Congenital Biosynthesis and chromosomal disorders (rare) Klinefelter syndrome (most common, 1:500-1000 males)</p> <p>Acquired Chemotherapeutic agents Autoimmune disorders Aging Drugs Toxins (eg, alcohol) Infection Trauma Radiation Idiopathic causes</p>
Secondary (low testosterone, normal or low FSH)	Pituitary gland	<p>Congenital Kallmann syndrome (1:10,000 male births) Idiopathic causes Abnormal structural hormone defects</p> <p>Acquired Chronic disease Drugs (eg, chronic opioids) Infection (eg, HIV) Trauma Tumors Idiopathic causes</p>
Age-related (low testosterone, normal or elevated FSH)	Testes/hypothalamus	Aging (common; 1%-2% per year after 65 years of age, 30%-70% at 60-80 years of age)

FSH, follicle-stimulating hormone; HIV, human immunodeficiency virus.
Sources: Darby E et al¹ and Badar F et al.²

androgen deficiency in the aging male, because testosterone levels decline an estimated 1% to 2% per year in adult men.^{1,3} A focused, cost-effective work-up will become ever more critical because an estimated 19% of men will be 65 years or older by 2050.⁴

**Serum testosterone:
The first-choice test**

Serum testosterone measurements are considered the initial test of choice because they're reliable, inexpensive, and widely available. Testosterone levels vary from hour to hour and diurnally, so a repeat morning measurement is recommended to confirm subnormal levels.^{3,5}

In some cases—including patients with obesity, type 2 diabetes, or hypothyroidism—the total testosterone level can

be misleading; tests for free testosterone and sex hormone-binding globulin levels should be ordered. These tests can also help evaluate men with low-normal total testosterone levels (200-400 ng/dL).^{6,7}

Is the patient pre- or postpubertal?

Assessment of low testosterone should distinguish between pre- and postpubertal males. In prepubertal males, chromosomal analysis is indicated because hypothalamic-pituitary-gonadal axis defects are common—especially Klinefelter syndrome (1 in 500 males).^{6,8} Men with very low testosterone levels (<150 ng/dL) or signs and symptoms suggesting pituitary pathology warrant pituitary imaging and measurement of thyroxine, cortisol, and prolactin levels.⁶ Both pre- and postpubertal males

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Prepubertal males with low testosterone and elevated FSH and LH should undergo chromosomal studies to assess for Klinefelter syndrome

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Consider checking for osteoporosis in men with chronic hypogonadism

with low testosterone should have FSH, LH, and prolactin levels tested to differentiate primary from secondary hypogonadism.^{6,9}

Be alert for hemochromatosis and low bone density

Order biopsy or ultrasound examination of testicular masses and iron studies if hemochromatosis is suspected. Hemochromatosis is the most common single gene disorder of Caucasian Americans (1 in 250-300 are homozygous; 1 in 10 are heterozygous) and is associated with hypogonadotropic hypogonadism.^{5,10} In a series of 3 studies, 30% (26 of 89) of men with hemochromatosis had hypogonadism.¹¹ The prevalence of hemochromatosis in males with hypogonadism hasn't been reported.

Because chronic hypogonadism leads to low bone density and increased risk of fracture, baseline bone densitometry may be prudent.¹² A chart review study of nursing home residents found that 66% of men with hip fractures and 20% of men with vertebral fractures had low testosterone.¹³ Notably, 50% of men in their 80s have testosterone levels in the hypogonadal range (<300 ng/dL), compared with 12% of men <50 years.^{1,14}

Recommendations

Scant guidance is available concerning what screening tests to order for a male with low testosterone. The United States Preventive Services Task Force and Canadian Task Force on Preventive Health Care make no recommendations; the Cochrane collaboration has no reviews on the topic. The American Association of Clinical Endocrinologists' (AACE) guidelines are based on expert opinion.³

The AACE consensus guideline used peer review for validation and didn't specify the method used to assess the quality and strength of the evidence used to write the statement. The AACE guideline recommends a history and physical exam, obtaining repeat morning testosterone levels, prolactin, FSH, LH, bone densitometry,

and a semen analysis if fertility is an issue.

In acquired hypogonadism, pituitary imaging is recommended along with thyroid, adrenal, and growth hormone axis testing. Prepubertal males should undergo chromosome analysis, and men with a suspected mass should have a testicular ultrasound examination. ■

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