



testosterone deficiency

Persistent depression? Low libido?

Androgen decline may be to blame

Low serum testosterone can often be corrected without using hormones, such as by changing or supplementing a medication.

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When a patient exhibits depressed mood, low energy, anxiety, insomnia, and low libido, do you consider major depression related to testosterone deficiency? Psychiatrists who don't look for hypogonadism may miss a reversible cause of depression, especially in patients whose affective symptoms don't respond to antidepressants.

Evidence is revealing how below-normal androgen levels may affect behavior and psychopathology in both men and women. This article describes:

- possible causes and effects of hypogonadism
- how to recognize and treat depression related to testosterone deficiency
- which lab tests provide the most clinically useful measures of testosterone
- potential benefits and adverse effects of testosterone replacement therapy.

LOW TESTOSTERONE AND DEPRESSION

Testosterone deficiency is particularly common in men with treatment-resistant depression. In one study, hypogonadism (total AM testosterone con-



Table 1

Signs and symptoms of testosterone deficiency

Behavioral

Decreased assertiveness/increased submissiveness
Decreased stress tolerance
Irritability
Depression or lowered mood
Anxiety

Dermatologic

Loss of body and pubic hair (scalp hair is preserved)
Diminished beard growth
Thinning and drying of skin (decreased sebum production)

Metabolic

Mild anemia
Diminished bone mineralization
Obesity or increased body fat (men)
Headaches
Reduced muscle volume and strength
Reduced general vigor and hardiness
Asthenia
Frailty (elderly)

Sexual

Decreased ejaculate volume
Erectile dysfunction or decreased penile tumescence
Decreased sexuality (decreased libido, arousal, responsiveness)

centrations ≤ 350 ng/dL) was detected in 24 (43%) of 56 middle-aged men with treatment-resistant depression.¹

Symptoms. Although most depressed patients are not hypogonadal, testosterone deficiency can cause depressed mood, low self-confidence, timidity, fearfulness, irritability, low libido, and impaired sexual function in men¹⁻⁶ and most likely in women.⁷

Conversely, robust androgen secretion usually promotes good mood, self-confidence, boldness, dominant behavior, and strong libido. Men's normally higher testosterone levels may relate to this sex's lower frequency of depression and generally more violent aggression, compared with women.

Increased male aggression is associated with elevated gonadal steroid levels—from overelaboration of endogenous hormone or, more commonly, use of exogenous anabolic steroids.⁸ Less well-appreciated is that testosterone deficiency in men is frequently associated with irritability,⁹ particularly in response to stress. Correcting testosterone deficiency can improve control of hostile feelings and lead to higher self-esteem and less impulsivity.²

In general, correcting hypogonadism improves mood in men,^{10,11} including those with refractory depression.^{1,12}

Depression in women. Evidence is conflicting and limited on a possible link between testosterone deficiency and depression in women. Psychological well-being in postmenopausal women given exogenous estrogens appears to improve when low-dose testosterone is added. In a recent placebo-controlled trial, testosterone cream, 10 mg/d—sufficient to bring total testosterone to the upper normal range—significantly improved mood in premenopausal women with low libido.¹³

DIAGNOSING HYPOGONADISM

Hypogonadism is usually diagnosed by clinical and biochemical findings. Testosterone deficiency's common signs and symptoms are shown in *Table 1*. Treated diabetes and obesity are significantly related to testosterone deficiency, as are—to a lesser extent—headaches, age > 60 , not smoking, treated asthma, low dominance rating, and sleeping < 5 hr/night.¹⁴

Laboratory evaluation. Measuring total serum testosterone concentrations in blood withdrawn before 9 AM is a useful initial screen for testosterone deficiency. Circulating testosterone concentrations show diurnal variation in both sexes, with higher levels in early morning—typically 7 to 8 AM—and lowest levels in the evening—typically 7 to 8 PM. Morning concentrations of serum

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Box

Sex hormones' effect on body and brain

In men, 90 to 95% of circulating sex hormones originate in the testes; transformation from adrenal-derived DHEA accounts for only about 5 to 10%. In ovulatory women, the ovaries and adrenals (via conversion from DHEA) contribute approximately equally to circulating androgens and estrogens.

Relative concentrations of sex hormones in circulation, CSF, and tissues depend on the concentrations and function of steroidogenic enzymes, whose sexual divergences largely account for differences between men's and women's androgen and estrogen levels.

The brain controls sex hormone synthesis and release and is also an important target organ for sex hormone action. Gonadotropin-releasing hormone (GnRH) released from the hypothalamus is the primary brain regulator of gonadal function, via the so-called hypothalamic-pituitary-gonadal (HPG) axis. Pulsatile GnRH stimulates the anterior pituitary to release luteinizing hormone (LH) and follicular-stimulating hormone (FSH). LH and FSH in turn regulate spermatogenesis, ovulation, and synthesis and release of estrogens and androgens.

The brain also regulates adrenal sex hormone synthesis and release but by the hypothalamic-pituitary-adrenal (HPA) axis, via pituitary adrenocorticotropic hormone (ACTH). Unlike cortisol, which is also regulated by ACTH, negative feedback suppression of ACTH by DHEA, if it occurs at all, is not significant.

Testosterone begins to decline with age in men after the third decade and in women after menopause. Approximately 90% of men in their 80s have biochemical hypogonadism (testosterone or free testosterone <2.5th percentile for young men), as do 35% of men in their 60s.¹⁵ Age-related increases in sex hormone-binding globulin (SHBG) compound the effects of diminishing total testosterone synthesis. Thus, free testosterone decreases with aging proportionately faster than total testosterone.

and salivary testosterone decline an average 50% to 60% from zenith to nadir.

Total testosterone includes protein-bound and unbound testosterone and is a good measure of testosterone synthesis (*Box*).¹⁵ Normal circulating total testosterone levels are:

- 325 to 1,000 ng/dL in men
- 25 to 90 ng/dL in women (approximately 10% of male levels).

Testosterone assays are usually insensitive in the lower concentration ranges. This makes establishing testosterone deficiency difficult in women.

When total testosterone level is equivocal or low, repeat total testosterone levels once or twice and measure free testosterone, which is the biologically active form. More than 95% of circulating testosterone is bound to plasma proteins, including SHBG and albumin. Also measure free testosterone during the initial screen when you suspect testosterone deficiency.

In cycling women, sex hormone concentrations spike during ovulation and are low when the follicular phase begins. Although longitudinal evaluation is more accurate, the more practical cross-sectional screen (AM blood) in the late follicular or late luteal phase is usually adequate.

Evaluating women taking oral contraceptives is biochemically straightforward, as exogenous estrogen suppresses ovarian sex hormone production and induces steady testosterone concentrations.

Postmenopausal women can be screened for sex hormone concentrations on virtually any morning, although perimenopausal women (within 5 years of last menstrual period) are, like premenopausal women, best studied longitudinally. DHEA and DHEA-S concentrations are perhaps more important to measure in women than in men because these sex steroids are responsible for a comparatively much larger component of circulating testosterone in women.

Follow-up tests. If testosterone deficiency is established, measure circulating pituitary hormones LH, FSH, and prolactin to determine if hypogo-

nadism is primary (gonadal) or secondary to another abnormality (of the brain or pituitary):

- Elevated LH and/or FSH levels are seen in primary hypogonadism, as the pituitary attempts to compensate for poorly functioning or sluggish gonads by increasing their stimulation.

- Diminished or inappropriately normal LH levels during testosterone deficiency (when high levels should be seen) are consistent with central or secondary hypogonadism.

- A combination of primary and secondary hypogonadism is common with advanced age.

Measure serum prolactin concentrations when evaluating hypogonadism because hyperprolactinemia is a common cause.

If the patient is testosterone-deficient, also assess other endocrine systems. If one fails or becomes inflamed, other glands or hormone systems often show insufficiency or inflammation as well, perhaps because of a common pathologic process. Circulating testosterone levels may be normal or elevated in testosterone insensitivity or hyposensitivity syndromes.

CORRECTING DEFICIENCY

Testosterone deficiency can often be corrected without using androgens, such as by changing or supplementing a medication.

Hyperprolactinemia is a common cause of central hypogonadism and testosterone deficiency in psychiatric patients, often as an adverse effect of psychotropics (particularly antipsychotics). Hyperprolactinemia suppresses GnRH and, in turn, LH and gonadal synthesis of testosterone. Hyperprolactinemia depresses libido and causes infertility in both sexes and amenorrhea in women.

Medication changes can usually correct psychotropic-induced hyperprolactinemia. Elevated prolactin levels from other causes (such as a pituitary prolactinoma) usually respond to dopamine agonists such as bromocriptine or cabergoline.

Zinc deficiency can lower testosterone levels. Zinc is highly enriched in the testes and prostate, where it accumulates via a zinc uptake system. The cerebral cortex is also zinc-enriched.

Zinc's recommended daily allowance (RDA) is 15 mg for men and 12 mg for women. Mild zinc deficiency is common, affecting, for example, about 30% of healthy older men in Detroit¹⁶ and many depressed patients.¹⁷

Remarkably, dietary zinc restriction (to one-third of the RDA) in healthy young men reduces serum testosterone levels by 75% after 5 to 6 months. Conversely, giving a zinc supplement, 30 mg/d, to marginally zinc-deficient older men nearly doubled their serum testosterone concentrations after 6 months.¹⁸

Because serum zinc concentrations do not reliably reflect zinc status, the most expedient clinical approach is to supplement with the RDA—found in widely available multivitamins. Zinc is generally considered low-risk for toxicity, although high doses should be avoided. Much is unknown about zinc's role in the CNS, where it apparently can be neuroprotective or neurotoxic.

Androgen suppressants. Cholesterol-lowering agents—whether they inhibit cholesterol biosynthesis or absorption—can sometimes lower serum androgen levels. Included are antihyperlipidemic pharmaceuticals and plant sterols that compete with cholesterol for gut absorption. Plant sterols such as beta-sitosterol are marketed as cholesterol-lowering food supplements.

Volatile and fatty oils of the saw palmetto berry (*Serenoa repens* or *Sabal serrulata*)—a frequently used over-the-counter phytotherapy for benign prostatic hypertrophy—have antiandrogen properties. They inhibit 5-alpha reductase types I and II, reducing testosterone's conversion to dihydrotestosterone.¹⁹ Flaxseed oil (linseed oil), another over-the-counter herbal supplement, also may alter testosterone levels.

Cholesterol-lowering agents and saw palmetto can lower serum androgen levels

continued



Table 2

Recommended testosterone-replacement preparations

Preparation	Usual dosage (men)
Transdermal patch (2.5 or 5 mg each)	1 to 2 patch(es) applied daily
Gel	5 to 10 mg/d (in 5 to 10 grams of gel, applied once daily)
Oral methyltestosterone	10 to 200 mg/d
Testosterone enanthate IM injection	50 to 400 mg every 2 weeks
Buccal testosterone adhesive	60 to 90 mg/d
Sex hormone precursor	Usual dosage for testosterone replacement (women)
Oral DHEA	25 to 50 mg once daily

DHEA: dehydroepiandrosterone

Exogenous glucocorticoids suppress DHEA release by negative feedback suppression of adrenocorticotrophic hormone (ACTH) at the anterior pituitary. To protect against sex hormone deficiency, give DHEA in replacement doses whenever more than a few glucocorticoid doses are given. This applies particularly to postmenopausal women, in whom DHEA is the major source of circulating androgens.

TESTOSTERONE REPLACEMENT

Preliminary data suggest that correcting testosterone deficiency in depressed men can have an antidepressant effect, especially in men who respond inadequately to standard antidepressants. Moreover, like antidepressants, testosterone replacement therapy can induce hypomania or mania in some individuals.

Depression and/or anxiety associated with sustained, irreversible serum testosterone deficiency—usually with other signs of testosterone deficiency (*Table 1*)—is the major psychiatric indication for testosterone replacement. Borderline biochemical testosterone deficiency and psychiatric symptoms in a “treatment-resistant” patient—especially one at risk for suicide—may justify an empirical testosterone replacement

trial. Do not continue such a trial indefinitely without compelling reasons, however, because gonadal function recovery can be delayed for months after even a 12-week testosterone trial.²⁰

Recommended agents for testosterone replacement are shown in *Table 2*. In men, testosterone preparations are normally used to increase testosterone levels. In women, I prescribe DHEA (discussed below). In young men and women with secondary hypogonadism, pulsatile use of gonadotropins may be necessary to induce spermatogenesis or ovulation—interventions outside the scope of psychiatric practice.

Contraindications to androgen replacement include hyperandrogenism, prostate cancer, antisocial personality, current mania, pedophilia, hypersexuality, and any psychiatric syndrome characterized by violent or predatory behavior. Pregnant patients (or women without a reliable birth control method) should not receive testosterone. Use caution when replacing androgens in patients with benign prostatic hypertrophy, hypomania, or a history of mania or hypomania.

An antidepressant response to adequate exogenous testosterone (enough to raise free testosterone levels to mid-normal range) is generally seen within 4 weeks. If psychological

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improvement is not observed, testosterone replacement may still prove beneficial if reversing hypogonadism improves the efficacy of subsequent antidepressants.

Dosage forms for men. Transdermal testosterone patches are normally applied to clean, dry skin on the upper arms, abdomen, thigh, or back and rotated among sites to avoid dermal irritation. When the non-scrotal patch is applied at night, testosterone concentrations mimic the circadian pattern seen in young men without causing supraphysiologic transients.²¹

Testosterone gel is applied every morning—also in a rotating manner—to clean, dry, intact skin and allowed to dry. Absorption is rapid, with measurable testosterone increases within 30 minutes. Approximately 10% of the testosterone is absorbed, delivering 5 to 10 mg/d into the circulation after 5 to 10 grams of gel (containing 50 to 100 mg of testosterone) is applied. Steady-state concentrations are achieved within 2 to 3 days, so dosages can be adjusted quickly.

Some patients regard 10 grams of gel as too messy to apply comfortably. Testosterone gel residuals can be washed from the skin with soap and water. Prolonged coated-skin contact with another person, such as a sex partner, can increase testosterone concentrations in the untreated individual.

Oral testosterone is absorbed poorly (often requiring high dosages) and cleared rapidly (half-life: 10 to 100 minutes). Only 10-mg capsules of methyltestosterone preparations are readily available—a dose too small for most men and too large for women. Many pharmacists can formulate other dosages for individual patients. Twice-daily doses are often used. Gum irritation and altered taste can occur when using buccal mucoadhesive testosterone.

Oil-based testosterone injections (such as IM testosterone enanthate) are absorbed slowly and cannot reproduce normal circadian testosterone rhythms and concentrations. In some cases, however, the long-acting effects of IM testosterone are beneficial.

DHEA acutely increases testosterone and estrogens in both men and women after a single physiologic

Table 3

Potential adverse effects of testosterone replacement therapy

General

- Acne and oily skin
- Increased hematocrit
- Hepatic toxicity
- Worsening of glucose intolerance
- Sodium retention

Behavioral/psychiatric

- Aggressiveness
- Explosiveness
- Hypomania or mania
- Hypersexuality
- Violence

Metabolic (men)

- Gynecomastia
- Gonadal suppression
- Worsening of prostate cancer

Metabolic (women)

- Hirsutism
- Clitoromegaly
- Gonadal suppression
- Voice lowering

dose. During maintenance DHEA replacement, however, clinically significant increases in both sex hormones are seen only in women. DHEA is preferred to increase testosterone levels in women, as it is converted to appropriate proportions of androgens and estrogens by endogenous steroidogenic enzymes.

DHEA, which occurs in yams, is available over-the-counter as a “food supplement” or “nutritional supplement.” However, many of these preparations, which are not regulated by the FDA, are unreliable because of poor quality control.²²

Aromatase inhibitors were developed as antibreast-cancer agents but also may treat testosterone deficiency. Testosterone administration increases circulating estrogens because testosterone is metabolized by the



enzyme aromatase to estradiol. Aromatase inhibitors may prevent excessive estradiol levels—and associated adverse effects, such as gynecomastia—that are sometimes seen during testosterone replacement therapy in men. Available aromatase inhibitors include anastrozole, exemestane, and letrozole.

POTENTIAL ADVERSE EFFECTS

Short-term testosterone replacement is generally low-risk. Acne is the most common adverse effect (Table 3).

The incidence of adverse events increases as testosterone concentrations are elevated above the normal range. For example, about 5% of men experience a manic or hypomanic arousal within 2 to 6 weeks of induced supraphysiologic testosterone levels.⁸

Gonadal suppression. Exogenous testosterone (or high-dose DHEA) suppresses endogenous gonadal function in men and premenopausal women. When a sustained course of exogenous androgens is discontinued, gonadal suppression usually does not reverse completely for several months or longer.

Prostatic hypertrophy, commonly considered to be testosterone driven, may be a risk of testosterone replacement therapy. Emergent urinary retention during testosterone replacement therapy has been reported, so use caution when giving testosterone to men with prostatic hypertrophy.

Barring evidence to the contrary, testosterone

therapy is contraindicated in patients with prostate cancer. Baseline and post-treatment prostate-specific antigen measures are recommended.

Other risks in men. Men occasionally develop gynecomastia during testosterone replacement, perhaps because of testosterone aromatization to estradiol. Beyond increased hematocrit levels and associated problems, testosterone’s cardiovascular risks are unclear. Testosterone deficiency also has been linked to increased atherosclerosis risk in older men.²³

Risks in women. Overtreating women with testosterone (DHEA) can promote hirsutism (including facial hair), loss of hair on scalp, voice lowering, clitoromegaly, breast regression, and muscle hypertrophy.

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Testosterone deficiency is a common but often unrecognized cause of depression. Assess testosterone levels in patients with recurrent or severe mood and anxiety disorders. Testosterone replacement can have decisive antidepressant and anxiolytic effects in some hypogonadal patients.

BottomLine

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Related resources

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DRUG BRAND NAMES

Methyltestosterone (oral) • Android, Methitest, Testred, Virilon
 Testosterone (buccal) • Striant
 Testosterone (gel) • AndroGel, Testim
 Testosterone (transdermal) • Androderm, Testoderm
 Testosterone enanthate (IM injection) • Delatestryl

DISCLOSURE

Dr. Geraciotti reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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