



Decreased Testosterone (Hypogonadism) - Part I

Evaluation and Treatment Recommendations

DHEA – Part II

Beneficial Supplement with Increasing Proof of Efficacy

Part I - Decreased Testosterone (Hypogonadism)

Clinical Effects of Low Testosterone

Low testosterone and depression

Testosterone deficiency is particularly common in men with treatment-resistant depression. In one study, hypogonadism (total a.m. testosterone concentrations (350 ng/dL or less) 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 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 over-elaboration of endogenous (internal) hormone or, more commonly, use of exogenous (external) anabolic steroids.⁸

Less well-appreciated is that testosterone deficiency in men is frequently associated with irritability,⁹ particularly in response to stress. Fatigue is another symptom men with low testosterone levels complain of. Correcting testosterone deficiency can improve energy levels, yet control 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

Testosterone Improves Women's Sex Lives

A recently published dissertation²⁵ shows that testosterone has both a physiological and a psychological impact on women's sexuality. Several previous studies have shown that hormones like estrogen and progesterone have beneficial effects on the quality of life after menopause. When both ovaries have been removed, production of testosterone is reduced by half - this can affect sexual function and well-being!

Unfortunately very little is known about the role of testosterone and what effect testosterone deficiency has on pre-menopausal women. However, this dissertation demonstrates that women who received combined treatment of estrogen and testosterone for 6 months experienced a significant improvement in certain aspects of their sexual function. This also shows that endogenous testosterone plays a role in sexual desire, arousal, and satisfaction. Testosterone supplementation increased women's interest and joy in sex and their satisfaction with their frequency of sexual activity.

Causes of Testosterone Deficiency

- ?? **Elevated Prolactin levels** are a cause of hypogonadism and testosterone deficiency. In psychiatric patients, this is 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.
- ?? **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 up to 25% of healthy older men¹⁶ 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 brain, where it apparently can be neuroprotective or neurotoxic depending on the dose.

- ?? **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 supplement 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.
- ?? **Exogenous glucocorticoids** like prednisone suppress DHEA release by negative feedback suppression of adrenocorticotrophic hormone (ACTH) at the anterior pituitary. To protect against sex hormone deficiency, DHEA should be taken 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.

Diagnosing Low Testosterone (hypogonadism)

Hypogonadism is usually diagnosed by clinical and biochemical findings. 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 and free serum testosterone concentrations in blood withdrawn before 9 a.m. 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 a.m.—and lowest levels in the evening—typically 7 to 8 p.m.. Morning concentrations of serum and salivary testosterone decline an average 50% to 60% from high to low levels. When the 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 (Sex Hormone Binding Globulin) and albumin.

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.

- ?? **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 (a.m. 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 Lab Tests

If the patient is testosterone-deficient, we also like to assess other endocrine systems. If one system 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. If testosterone deficiency is established, we like to measure circulating pituitary hormones LH, FSH, and prolactin to determine if hypogonadism 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.

?? Serum prolactin concentrations are measured when evaluating hypogonadism because hyperprolactinemia is a cause as we mentioned above.

Treatment

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 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

In men, testosterone itself is normally used to increase testosterone levels - there are several recommended agents for testosterone replacement. **In women**, I prescribe DHEA (discussed below). In young men and women with secondary hypogonadism, pulsatile use of hormones may be necessary to induce sperm production or ovulation—interventions outside the scope of this guide.

Contraindications

Several reasons exist to avoid testosterone replacement including elevated testosterone levels, prostate cancer, antisocial personality, current mania (elevated mood), 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. I like to be cautious when replacing androgens in patients with benign prostatic hypertrophy, hypomania, or a history of mania or hypomania.

Dosage Forms

?? **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 above physiologic levels.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 poorly absorbed (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 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 “nutritional supplement.” However, many of these preparations, which are not regulated by the FDA, are unreliable because of poor quality control, so they should be **purchased from a reputable company with documented quality control**²²
- ?? **Aromatase inhibitors** were developed as anti breast 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

Testosterone replacement under medical supervision with appropriate laboratory monitoring is generally low-risk. 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 testosterone levels being above physiologic levels.⁸ Short-term testosterone replacement is extremely low-risk. Acne is the most common adverse effect.

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

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 caution must be exercised when testosterone is given to men with an enlarged prostate.

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 (enlarged breasts) during testosterone replacement, perhaps because of testosterone aromatization to estradiol. Testosterone may increase blood hematocrit levels and cause associated problems, but testosterone's cardiovascular risks are unclear. Testosterone deficiency also has been linked to increased atherosclerosis risk in older men so lipid levels should be closely followed along with other lab parameters.²³

Risks in women: Overtreating women with testosterone or DHEA can promote hirsutism (hair growth including facial hair), loss of hair on scalp, voice lowering, clitoromegaly, breast regression, and muscle hypertrophy (growth). Testosterone levels must be followed to attain "normal" levels equivalent to the values of a 20 year old.

Part II - DHEA

What it Does

Produced by the adrenal gland in both sexes, and in minimal amounts in the ovaries, DHEA, or dehydroepiandrosterone, is often referred to by gerontologists as the body's "mother of all hormones". DHEA is a pro-hormone that is converted to other active hormones. It is the most abundant steroid in the human blood stream. Regulated by a target organ such as your prostate or ovary, your physiology converts DHEA into such necessary hormones as estrogen, testosterone, progesterone, corticosterone, and others.

The adrenal glands make enormous quantities of DHEA when people are young, and the hormone courses through the bloodstream. DHEA production peaks between the ages of 25 and 30, then declines with age in both men and women, but an excessive decline may indicate that the age-related deterioration is

accelerated due to adrenal gland malfunction. Joints stiffen, bone mass decreases, sleep becomes restless and relaxation more difficult, moods often darken and stress becomes harder to handle.

DHEA is a steroid hormone and the precursor of androgens (testosterone) in women. The adrenal glands produce the majority of DHEA present in women while. Levels of this hormone decrease as we age to the point that by the time we are eighty years old the amount of DHEA produced naturally by the body is only about five to ten percent of the amount present at its highest level during youth and early adulthood.

Supplements

A search for 'DHEA' results in pages of vendors of supplements. It is important to note before buying any of these products either online or at your local store that DHEA supplementation has not been approved by the FDA for any use, and because DHEA is classified as a 'dietary supplement' the manufacturers do not have to prove the safety or efficacy of their products. To make DHEA supplements, vitamin and pharmaceutical companies extract sterols, most commonly diosgenin, from wild yams. Some supplements, however, are extracts of wild yams that haven't been processed into DHEA. These are marketed as containing natural precursors for the body's production of [DHEA](#), but they have not been found to boost DHEA levels. Therefore, anyone who is considering DHEA supplementation should consult their family doctor, and should only purchase supplements that are tested to prove that they contain the product they claim to provide in exact and consistent amounts.

Health Claims

Many health claims have been touted for DHEA – you will find references that it can increase your energy levels, help you lose weight, slow down the aging process, boost the immune system, and reduce your risk of cancer, heart disease²⁴, improve the memory, and a host of other symptoms. While scientists do not understand exactly how DHEA works, and whether DHEA is safe and effective as a supplement, it is also important to note that much of the DHEA research is based on animal data. Fortunately, more and more studies done in humans that are of good quality are confirming the benefits mentioned above.

Proven Benefits

Weight Loss, Blood Glucose, and Insulin Action

A recent study published in JAMA in November of 2004 proved that DHEA supplementation in older men and women helped them reduce abdominal or waistline fat that has been connected to heart disease and the metabolic

syndrome.²⁶ It also helped increase serum testosterone levels in these participants. Due to its effect on abdominal fat, and modulation of the metabolic syndrome, it may reduce the risk of type 2 (non-insulin-dependent) diabetes! Similar reports of enhanced glucose management and lipid lowering benefits were given at the 12th International Congress on Endocrinology by using a twice daily dose of 25mg of DHEA. These are indeed exciting news to support the benefits of DHEA in improved health!

Female Well Being

Similarly, a German study of 24 female patients (ages 23 to 59) with adrenal insufficiency on the effect of treatment with DHEA (dehydroepiandrosterone) was reported in the, September 30, 1999, issue of the *New England Journal of Medicine*. Researchers concluded that DHEA improves well-being and sexuality in women with adrenal insufficiency.

The double blind study found that women who took a single daily dose of 50 mg of DHEA reported significant increases in frequency of sexual thoughts, degree of sexual interest, level of mental satisfaction with sex, and their level of physical sexual satisfaction. Improvements were also seen in obsessive-compulsive traits, depression, anxiety, and other psychological symptoms.

The study participants were measured by their response to several questionnaires that related to their overall well-being and sexual response before the study, one month after the study began, and at four months.

Interestingly, these significant improvements were not seen until four months after treatment began. This delay in the action of dehydroepiandrosterone may explain why some recent studies found no psychological effects in normal subjects who were treated with dehydroepiandrosterone for two weeks, according to the *Journal*.

Laboratory Testing / Hormone Levels

Traditional medical thinking accepts that imbalances of life-sustaining hormones are "normal" in aging people. Traditional practitioners almost never test hormone levels because they think that nothing should be done to restore hormone profiles to youthful ranges. More and more, however, aging people are seeking the health and vitality of a younger person. If you are 80 years old and are told that your hormone profile is normal for your age, tell your doctor that you would prefer the hormone profile of a 25-year-old because you perceive a 25-year-old as having more vitality and a reduced risk of contracting lethal diseases!

When it comes to assessing hormone status, the use of standard reference ranges may be failing aging people since reference ranges are adjusted to reflect a person's age. Since it is "normal" for an aging person to have imbalances of

critical hormones, standard laboratory reference ranges are not flagging dangerously high levels of estrogen and insulin or deficient levels of testosterone, thyroid, and DHEA. The following table shows standard hormone blood reference ranges for men (age 60) and compares them to what the "optimal" ranges should be.

Hormone	Standard Reference Range	Optimal Range
DHEA	42-290 mcg/dL	280-350 -500 mcg/dL
Insulin (fasting)	6-27 mcU/mL	Under 5 mcU/mL
Free testosterone	6.6-18.1 pg/mL	15- 22-25.5 pg/mL
Estradiol	3-70 pg/mL	10 15 -30 pg/mL
TSH*	0.2-5.5 mU/L	Under 2.1 mU/L

**Thyroid stimulating hormone*

DHEA Supplementation

DHEA acutely increases testosterone and estrogens in both men and women after a single physiologic 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. Some believe that DHEA is useful for hormone replacement therapy during menopause, and suggest taking low doses of this supplement.

DHEA is best taken early in the day or possible insomnia could result. DHEA is normally produced by the adrenal glands early in the day and then converted by the liver to DHEA-S by midday when the DHEA/DHEA-S ratio is usually stabilized (10% DHEA/90% DHEA-S).

Some people only need to take a small amount of DHEA to restore blood levels to that of a 21-year-old, although others need to take higher levels of DHEA. I recommend that those already taking DHEA should have a DHEA blood test to make sure they are taking the precise dose to suit their individual biochemistry.

Potential Side Effects

Almost nothing is known about DHEA's interactions with other drugs or its long-term effects. There may be some concerns with DHEA supplementation, especially in older patients. If you have an existing hormone-dependent tumor such as a testicular or prostate tumor in men, DHEA could be converted into the testosterone that the tumor needs to grow. The same may be true for endometrial, ovarian, and breast tumors in women. There is no research to

support these concerns, but also none to prove that DHEA supplementation is absolutely safe.

Testosterone replacement under medical supervision with appropriate laboratory monitoring is generally low-risk. The incidence of adverse events increases as testosterone concentrations are elevated above the normal range. Exogenous (external) hormone or high-dose DHEA suppresses endogenous (internal) gonadal function in men and pre-menopausal women. When a sustained course of exogenous (external) androgens is discontinued, gonadal suppression may not reverse completely for several months after it is stopped.

Androgenic side effects were reported by almost one-fifth of the study participants. Side effects included greasy skin, acne, and increased body hair—although hair loss has been described, and again modulated by adjusting hormone levels such as by every other day DHEA administration.

Liver Disease

Men or women with existing liver disease (such as viral hepatitis or cirrhosis) should consider taking DHEA sublingually (under your tongue) or using a topical DHEA cream to reduce the amount of DHEA entering the liver. DHEA is converted by the liver into DHEA-S. Those with liver disease should carefully monitor liver enzyme levels to be certain that DHEA therapy is not making existing liver disease worse.

In Men: about 5% experience an abnormal arousal of energy levels within 2 to 6 weeks of induced testosterone levels above normal values.⁸ Prostatic enlargement, commonly considered to be testosterone driven, may be a risk of testosterone replacement therapy. Urgent urinary retention or inability to pass urine during testosterone replacement therapy has been reported, so caution when giving testosterone to men with an enlarged prostate is essential.

In Women: Overtreatment with testosterone (either the hormone or DHEA) can promote hirsutism or hair growth in unwanted areas (including facial hair), loss of hair on scalp, voice lowering, clitoromegaly, breast regression, and muscle hypertrophy.

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