Testosterone Treatments: Why, When, and How?

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Testosterone treatment is controversial for men and even more so for women. Although long-term outcome data are not available, prescriptions for testosterone are becoming more common. Testosterone is used primarily to treat symptoms of sexual dysfunction in men and women and hot flashes in women. Potential benefits include improved libido, increased bone mass, and increased sense of well-being. In individuals with human immunodeficiency virus infection or other chronic diseases, testosterone has been shown to improve mood and energy levels, even in patients with normal testosterone levels. Testosterone can be administered by injection, patch, topical gel, pill, or implant. Side effects in men include polycythemia and acne. Side effects in women include acne, hepatotoxicity, and virilization and usually only occur when testosterone is used in supraphysiologic doses. Long-term studies of the effects of testosterone on prostate cancer, breast cancer, and heart disease have not been completed. Mammograms and monitoring of prostate-specific antigen, hematocrit, and lipid levels are recommended for patients taking testosterone. (Am Fam Physician 2006;73:1591-8, 1603. Copyright © 2006 American Academy of Family Physicians.)

▶ **Patient information:** A handout on testosterone therapy, written by the authors of this article, is provided on page 1603.

In the United States, approximately 43 percent of women and 31 percent of men experience sexual dysfunction.[1] It is not surprising that testosterone, primarily used to treat sexual problems, is being prescribed more often than in the past; a 500 percent increase in sales has been documented from 1993 to 2001.[2] However, testosterone therapy is controversial, particularly for use in women. The safety and effectiveness of testosterone supplementation have not been clearly defined, although there is an extensive review[3] by the Institute of Medicine outlining what is known about testosterone therapy in older men.

Testosterone in Men

PHYSIOLOGIC CHANGES IN TESTOSTERONE LEVELS

Testosterone levels in adult men decline at an average rate of 1 to 2 percent per year.[4] This change can be caused by the normal physiologic changes of aging, testicular dysfunction, or hypothalamic-pituitary dysfunction.[5] By 80 years of age, more than 50 percent of men have testosterone levels in the hypogonadal range.[6] Hypogonadism is defined as a low serum testosterone level coupled with any of the signs and symptoms outlined in *Table 1*.[7] The presentation varies from person to person.

TESTOSTERONE MEASUREMENT

Laboratory measures of testosterone include total testosterone, free testosterone, and steroid hormone-binding globulin. In addition, luteinizing hormone and follicle-stimulating hormone levels can be used to differentiate primary from secondary hypogonadism *(Table 2*[8]*)*. Approximately 98 percent of the circulating testosterone is bound to steroid

TABLE 1
Signs and Symptoms of Hypogonadism in Men

Anemia
Depressed mood
Diminished bone density
Diminished energy, sense of vitality, or sense of well-being
Diminished muscle mass and strength
Impaired cognition
Increased fatigue
Sexual symptoms, including decreased libido, erectile dysfunction, difficulty achieving orgasm, diminished intensity of the experience of orgasm, diminished sexual penile sensation

Adapted with permission from Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. N Engl J Med 2004; 350:483.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Testosterone supplementation should be considered when treating sexual dysfunction in hypogonadal men.	B	10-13
Testosterone combined with estrogen can improve sexual function and bone density in women, but is not FDA approved for this purpose.	B	32, 43, 45-48
Men with human immunodeficiency virus infection or acquired immunodeficiency syndrome; who also have diminished mood, strength, libido, and well-being; often benefit from testosterone use.	B	21-24
Until more consistent data are available, testosterone should be used with caution and only for those indications approved by the FDA.	C	3

FDA = U.S. Food and Drug Administration.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 1495 or http://www.aafp.org/afpsort.xml.

hormone–binding globulin or albumin.[9] The amount of bioavailable testosterone is the sum of the free testosterone and a portion of the bound testosterone. Total testosterone (normal range, 300 to 1,000 ng per dL [10.4 to 34.7 nmol per L]) is the most commonly used measure of testosterone in research studies and in clinical practice.[4] Changes in steroid hormone–binding globulin can affect the bioavailable testosterone. Because measures of bioavailable testosterone are not standardized, they are not used routinely. There are no consistent guidelines for the level of total testosterone that defines hypogonadism; however, many studies use the American Association of Clinical Endocrinologists (AACE) definition of a total testosterone level less than 200 ng per dL (6.9 nmol per L).[8]

Benefits of Testosterone Therapy in Men

Table 3[10-24] lists the possible benefits of testosterone therapy in men.

TABLE 2
Causes of Hypogonadism in Men

Type	*Possible causes*
Primary (decreased testosterone, increased luteinizing hormone and follicle-stimulating hormone)	Klinefelter syndrome; androgen receptor defects; 5-alpha reductase deficiency; myotonic dystrophy; cryptorchidism; hemochromatosis; mumps orchitis; aging; HIV; AIDS; other chronic diseases
Secondary (decreased testosterone, normal or decreased luteinizing hormone and follicle-stimulating hormone)	Kallmann syndrome; fertile eunuch syndrome; pituitary disorders; HIV; AIDS; other chronic diseases

HIV = human immunodeficiency virus, AIDS = acquired immunodeficiency syndrome.

Information from reference 8.

SEXUAL DYSFUNCTION

Men with low testosterone levels commonly complain of decreased sex drive or erectile dysfunction. Treatment with testosterone gel, transdermal patch, or intramuscular injection is indicated for men with low total testosterone levels who have these symptoms. Regardless of the route of administration, studies have shown improvement in libido and sexual function in hypogonadal men.[10-13] Other small, short-term trials of sexual function in men, including some with men who have normal testosterone levels, show mixed results. The optimal delivery method has not been determined.

BONE DENSITY, BODY COMPOSITION, AND MUSCLE STRENGTH

The bone mineral density of hypogonadal men decreases as testosterone levels decrease, potentially increasing the risk of fractures.[25] Bioavailable testosterone and estrogen levels are more correlated with density changes than total testosterone. Testosterone replacement may stop bone loss and increase bone density[14]; however, many studies demonstrate equivocal results, and none have shown a decreased rate of fractures with testosterone therapy.[15,16] Lean body mass increases consistently occur with testosterone treatment in healthy men; however, muscle strength does not significantly increase.[15,17]

DEPRESSION, MOOD, COGNITION, AND WELL-BEING

The indications for the use of testosterone in cognitive and psychological impairment are still unclear; however, studies of healthy older men with testosterone deficiency have yielded interesting results. Neuropsychological testing has revealed

TABLE 3
Possible Benefits of Testosterone Therapy for Men

Increased libido,[10-13] including patients with HIV or AIDS[23,24]
Increased lean muscle mass[15]
Improved cognition[10,18-20]
Improved mood[10,18-20]
Increased sense of well-being,[10,18-20] including patients with HIV or AIDS[22,23]
Decreased erectile dysfunction[10-13]
Increased bone density[14-16]
Increased muscle strength[17]
Increased muscle mass in patients with HIV or AIDS[21-24]

HIV = human immunodeficiency virus, AIDS = acquired immunodeficiency syndrome.

Information from references 10 through 24.

improvements in spatial cognition[26] and spatial and verbal memory[27] with testosterone replacement. No positive effects on mood or depression have been clearly demonstrated for hypogonadal men.[10,18] Two trials[19,20] (not placebo controlled) have demonstrated improvements in quality of life.

HIV AND AIDS

Most men with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) have decreased androgen levels, although the levels may remain in the low-normal range.[21] Testosterone replacement has been shown to increase mood and sense of well-being in this population.[22,23] Improvements in libido, energy, and muscle strength also have been demonstrated.[23,24]

TABLE 4
Potential Risks and Side Effects of Testosterone Treatment

Risks/side effects	*Comments*
Benign prostatic hypertrophy[28-30]	No clear evidence
Cardiovascular[31,32,36]	No clear effect on these cardiovascular risk factors: total cholesterol, high-density lipoprotein cholesterol, C-reactive protein, or insulin sensitivity
Liver toxicity[35]	Usually does not occur at physiologic doses; oral formulations should be avoided in men for this reason
Polycythemia[11,19]	More common in men taking higher doses
Virilization (i.e., alopecia, hirsutism, acne)[32-35]	Men and women: usually dose and duration related

Information from references 11, 19, and 28 through 36.

SAFETY

Most studies of testosterone therapy in hypogonadal men have been on men younger than 65 years, but the Institute of Medicine examined the effectiveness and safety of testosterone treatment in older men.[3] The committee found no compelling evidence of major adverse side effects resulting from testosterone therapy *(Table 4*[11,19,28-36]*)*. However, because of the lack of well-done, long-term studies, the report[3] states that its use is appropriate only for those conditions approved by the U.S. Food and Drug Administration (FDA), and that it is inappropriate for wide-scale use of testosterone therapy to prevent possible future disease or to enhance strength or mood in otherwise healthy older men. Because of safety concerns, the Institute of Medicine recommended that well-constructed, short-term studies of testosterone in older men be conducted for conditions that do not already have effective therapies. If effective, they recommended that long-term studies be conducted to determine safety.[3]

PROSTATE DISEASE

Prostate cancer and benign prostate enlargement are thought to be stimulated by testosterone. Because treatments for both conditions include androgen suppression, the possibility of increased risk of these conditions with testosterone supplementation is of great concern. Testosterone treatment has been associated with increased prostate volume, although not necessarily above high-normal levels.[28] Multiple studies have not shown signs or symptoms of benign prostatic hypertrophy during testosterone treatment. In short-term studies,[18,29,30] there is no convincing evidence of an increased risk of prostate cancer from testosterone replacement treatment, as measured by prostate-specific antigen levels. Long-term studies need to be completed before it is reasonable to make a final determination.

CARDIOVASCULAR DISEASE

Few data show that testosterone replacement increases the incidence of cardiovascular disease. Most studies have focused on the effect on cardiovascular risk factors such as lipid levels, insulin sensitivity, and C-reactive protein. Although some studies have suggested that testosterone reduces high-density lipoprotein (HDL) cholesterol levels, there are many studies showing no effect on HDL cholesterol. No effect on C-reactive protein or insulin sensitivity occurs with replacement to

normal levels.[37] A meta-analysis[31] of the effect of testosterone replacement on cholesterol levels showed mixed results, indicating that the effect is unclear.

POLYCYTHEMIA

Because high levels stimulate erythropoiesis, testosterone can be beneficial for men with anemia. However, polycythemia can be an issue for nonanemic men who are at risk of vascular disease. Most studies of cardiovascular risks associated with testosterone demonstrate increases in hematocrit levels.[11,19]

Use of Testosterone in Women

PHYSIOLOGY

Testosterone, an essential precursor of estrogen in women, is made in the ovaries and adrenal glands. There is a steady decline in testosterone levels from the 20s through menopause. With surgical menopause, the level of testosterone drops precipitously. No clear lower limit of testosterone has been established; however 15 ng per dL (0.5 nmol per L) commonly is used. One study[38] found that women with 0 to 10 ng per dL (0 to 0.3 nmol per L) had markedly decreased sexual desire in all situations and absent or markedly decreased orgasms. Because of studies like this, supplemented with anecdotal evidence, many women have been started on testosterone therapy.

POTENTIAL USES

In December 2004, the FDA voted against approving a new testosterone patch for women because of safety issues. The advisory panel had concerns about the low numbers of women studied and the length of the studies. However, many physicians are prescribing testosterone in other forms. Oral esterified estrogen with methyltestosterone (Estratest) has been used extensively since the 1970s, though it has not been FDA approved. It is marketed for treatment of hot flashes, although there is marginal evidence to support its use for this.[32]

POSTMENOPAUSAL HORMONE THERAPY

Most women can expect to spend one third of their lives in the postmenopausal stage. With the new evidence that traditional hormone therapy using estrogen and progesterone can increase the risk of cardiovascular disease as well as uterine and breast cancer,[39] women with postmenopausal complaints of hot flashes, mood changes, and poor sexual functioning have been more interested in testosterone therapy as an option. Clinical guidelines for the use of androgens for female sexual dysfunction are being developed by the Endocrine Society.[40] There is little evidence in the literature for the benefit of estrogen plus testosterone over estrogen alone for the treatment of hot flashes.

Depression, anger, moodiness, insomnia, and lack of well-being are common complaints of postmenopausal women. A limited number of studies[33,41] have shown that psychological symptoms and memory are improved with the addition of testosterone to estrogen.

SEXUAL DYSFUNCTION

Testosterone replacement is prescribed most commonly to treat problems with libido, sexual enjoyment, and orgasm in patients who are postmenopausal or who have had an oophorectomy. As many as 50 percent of postmenopausal women have sexual dysfunction,[42] and a low testosterone level has been correlated with reduced coital frequency in these women.[43] A number of small studies done in postmenopausal women demonstrate effectiveness for sexual dysfunction; however, all used testosterone combined with estrogen *(Table 5)*.[32,36,43-48]

BONE DENSITY

Osteoporosis is a leading cause of morbidity and mortality in older women. Low circulating testosterone is correlated with hip fracture and height loss in postmenopausal women.[49] Estrogen alone has been used to prevent

TABLE 5
Benefits of Testosterone Treatment for Women*

Indication	*Possible benefit*	*Formulations*
Bone strength	Increase bone mineral density[32,36,43]	Oral, supraphysiologic doses
Cognitive or psychological	Protective of memory, improved sense of well-being[44,48]	Physiologic doses
Sexual dysfunction	Increase desire/interest, frequency[45,46]	Oral
		Implants
	Increase frequency, satisfaction, orgasm[43,47]	Intramuscular, supraphysiologic dose
	Increase desire, orgasm[32]	Transdermal
	Increase frequency and pleasure[48]	

*—All studies of testosterone supplementation in women use testosterone in combination with estrogen.

Information from references 32, 36, and 43 through 48.

TABLE 6
Possible Uses of Testosterone Treatment

	Indication	*Formulation*	*Comment*
Men	Primary or secondary hypogonadism*	Transdermal, intramuscular	Indicated in symptomatic patients with low testosterone levels
	Patients with human immunodeficiency virus infection or acquired immunodeficiency syndrome who have muscle wasting, depression, or fatigue	Transdermal, intramuscular	Use if patient is symptomatic
Women	Poor sexual functioning in postmenopausal women	Oral, implant, transdermal	Consider if patient is symptomatic
	Prevention of osteoporosis	Oral	Not clear when to use testosterone
	Psychological symptoms such as depression	Oral, dehydroepiandrosterone†	Safety not ensured at high dosages

**—U.S. Food and Drug Administration approved for this indication only.*
†—Available without prescription.

loss of bone mass, but other studies have shown that oral estrogen-androgen hormone therapy promotes bone formation.[32,43,45] It is not known, however, if this prevents fractures or prolongs life.

PREMENOPAUSAL TREATMENT

Women with diminished sex drive have been shown to have lower free testosterone levels.[50] However, physicians are reluctant to use testosterone in premenopausal women because of concerns about masculinization. In a 12-week trial[51] of 34 women, testosterone therapy (1% cream, 10 mg per day applied to the thigh) improved well-being, mood, and sexual function in premenopausal women with low libido and low testosterone levels. No increase in hirsutism, acne, or voice change occurred.

OTHER USES

Testosterone is used for women with premature ovarian failure, Turner's syndrome, HIV infection, or chronic corticosteroid use. More research in the area of chronic illness has been completed in men than in women. Other uses such as the prevention of dementia and depression have been postulated.

SAFETY IN WOMEN

The controversy over using testosterone has primarily come from issues involving safety *(Table 4*[11,19,28-36]*)*. The typical side effects related to the estrogen-testosterone preparations are alopecia, acne, and hirsutism, although these are dose and duration dependent and are not common.[34] Controlled studies[32,35,48,51] have found low incidence of deep voice, oily skin, acne, and male-pattern hair loss. Virilization is not common, usually is reversible, and typically occurs only with supraphysiologic dosages. Reduced total cholesterol and HDL cholesterol levels have been demonstrated when used in women in addition to estrogen, although the long-term effects on heart disease are not known. Testosterone use in the short term has not been associated with an increase in cardiovascular disease or symptoms. Usual estrogen-testosterone doses in women have not been linked to hepatic damage.[35]

Anabolic Steroids and Testosterone Precursors

Anabolic steroids are testosterone compounds used by male and female athletes to improve performance and by others to treat depression and increase a sense of well-being. Their use has had a significant affect on international sports since the mid-20th century.[52] More recently, supplements such as dehydroepiandrosterone, a testosterone precursor, have gained popularity. A recent study[53] supports its use for depression in men and women. These substances can raise testosterone levels. Some athletes believe this will enhance performance, but no clear benefits have been demonstrated.[54,55] However, side effects such as gynecomastia, acne, and lowered HDL cholesterol levels have been noted. Over-the-counter supplements are not regulated, and wide variability exists in quality and content.[56] Testosterone precursors such as dehydroepiandrosterone may pose serious health risks.

Recommendations for Use of Testosterone

The AACE has issued guidelines for testosterone supplementation in men, and guidelines for women are being developed.[8,40] *Table 6* lists the indications and *Table 7*[57] shows the available forms of testosterone and their various costs. The goal in men is to restore the testosterone concentration to the normal range. Oral preparations should be avoided because of first-pass metabolism and the association of hepatotoxicity with the higher doses used for men. Injections of testosterone last 10 to

14 days, requiring frequent visits to the doctor or training in self-injection techniques. Pellets and transbuccal troches are the newest methods of delivery but have not been as well studied.

Given the lack of long-term safety information, women who are interested in being treated with testosterone must understand the potential risks involved in using a powerful hormone. Clinical status of the patient is the best way to follow the effectiveness of testosterone therapy because normal levels are not well established. Oral treatment in combination with estrogen is the most readily available method of treatment for women, although some physicians prescribe the topical gel. Patients usually notice an improvement in libido and energy within days or weeks.

Monitoring Patients on Testosterone

Because of the uncertain safety of testosterone, monitoring patients during therapy is recommended *(Table 8[8,40])*. The AACE guidelines suggest routine monitoring of male patients by history and physical examination including a digital rectal examination and measuring prostate-specific antigen levels, testosterone levels in patients receiving injections, hematocrit, and lipid profiles.[7] Generally, women are watched for side effects rather than checking testosterone levels. It is recommended that physicians monitor women taking testosterone for virilization and do baseline and semiannual breast examinations, complete blood cell count, lipid levels, annual mammography, and endometrial ultrasonography.[40]

TABLE 7
Testosterone Replacement Modalities

Modalities	*Dosage*	*Side effects**	*Cost per month†*
For use in men			
Methyltestosterone‡ (Android)	10 to 50 mg orally per day	Hepatic effects, lower androgen response	$98
Fluoxymesterone‡§ (Halotestin)	5 to 20 mg orally per day	Hepatic effects, lower response	5 mg per day: $53 20 mg per day: $214
Testosterone buccal‡ (Striant)	30 mg applied to gums twice per day	Oral irritation	$190
Testosterone patch‡ (Androderm)	Applied to skin once per day	Site reaction	$96
Testosterone transdermal‡ (Testoderm)	Patch applied to shaved scrotum once per day	Site reaction, transfer to partner	$115
Testosterone cypionate‡ (Depo-Testosterone)	50 to 400 mg intramuscularly every two to four weeks	Urticaria, site reactions	$23 per injection
Testosterone enanthate‡§ (Delatestryl)	50 to 400 mg intramuscularly every two to four weeks	Site reaction	$28 per injection
Testosterone 1 % gel‡ (AndroGel)	5 gm topically once per day	Site reaction, transfer to partner	$209
Testosterone pellets†§ (Testopel)	150 to 450 mg implanted subcutaneously every three to six months	Site pain and inflammation	Varies
For use in women			
Esterified estrogen/ methyltestosterone (Estratest)	Orally once per day	Acne, change in voice, nausea	$70
Testosterone enanthate/estradiol valerate¶ (Valertest No. 1)	1 mL intramuscularly every four weeks (90 mg/4 mg per mL)	Site reaction	Varies

**—These side effects are in addition to those usual for testosterone: in men—polycythemia, acne, and edema; in women—acne, hirsutism, and deepening voice.*

†—Estimated cost to the pharmacist based on average wholesale prices (rounded to the nearest dollar) in Red Book. Montvale, N.J.: Medical Economics Data, 2005. Cost to the patient will be higher, depending on prescription filling fee.

‡—U.S. Food and Drug Administration approved for primary hypogonadism and hypogonadotropic hypogonadism (congenital and acquired).

§—Delayed puberty in males.

¶—Moderate to severe vasomotor symptoms of menopause.

Information from reference 57.

TABLE 8
Monitoring Patients on Testosterone Therapy

	Test/examination	*Frequency*	*Comment*
Men	History and physical	Every three to four months for the first year, then annually	—
	Testosterone levels	Until stable normal range	Only necessary with injections
	Liver function	Every three to six months	Only necessary with oral preparations
	Prostate-specific antigen	Every six to 12 months	Annually, if unchanging
	Digital rectal examination	Every six to 12 months	Annually, if unchanging
	Lipids	Annually	—
	Hematocrit	Every six months for 18 months, then annually	Discontinue treatment if there is more than a 50 percent rise.
Women	History and physical	Every six months (including breast examination)	Watch for virilization in skin, hair, and genitals.
	Lipid levels	Annually	—
	Complete blood cell count	Annually	—
	Mammography	Annually	—
	Endometrial ultrasonography	Annually	—

Information from references 8 and 40.

The authors thank Tanya Dougherty, Pharm.D., and Bennett Shenker, M.D., for reviewing the manuscript.

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Author disclosure: Nothing to disclose.

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