PATIENT'S GUIDE

to Low Testosterone

Sponsored by The Hormone Foundation

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(2003 Edition)

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Preface

It is estimated that four to five million American men may not produce enough testosterone. Most discouraging, research finds that most men know very little about testosterone, the potential consequences of having low testosterone levels, and the availability of therapies to increase testosterone and overall health.

A 1998 survey completed by Roper Starch Worldwide of 1,000 men found that 68 percent of participants could not name a symptom or condition associated with low testosterone. In addition, half of the participants admitted some knowledge of hormone replacement therapy, but only seven percent knew that it could be used in men.

This guide seeks to improve your awareness of testosterone, testosterone deficiency, and testosterone replacement therapy. Section 1, *Testosterone Overview*, provides comprehensive information on the hormone, its function, the diagnosis of low testosterone, and other related factors. Section 2, *Benefits and of Testosterone Replacement Therapy (TRT)* discusses some of the physical and psychological benefits associated with restoring testosterone. Section 3, *Treatments for Low Testosterone*, outlines treatment options that are available to increase testosterone levels. Section 4, *Potential Risks of Testosterone Replacement Therapy*, outlines the risks associated with prolonged testosterone therapy. Section 5, *Overview of Clinical Trials*, presents highlights of recent clinical studies evaluating testosterone and testosterone replacement therapy. Finally, Section 6, *Frequently Asked Questions* and Section 7, *Glossary of Terms* provide additional information and resources.

1. Testosterone Overview

Testosterone and Its Function

Testosterone is the most important sex hormone (otherwise known as androgen) produced in the male body. It is the hormone that is primarily responsible for producing and maintaining the typical adult male attributes. At puberty, testosterone stimulates the physical changes that characterize the adult male, such as enlargement of the penis and testes, growth of facial and pubic hair, deepening of the voice, an increase in muscle mass and strength, and growth in height. Throughout adult life, testosterone helps maintain sex drive, the production of sperm cells, male hair patterns, muscle mass, and bone mass.

Testosterone is produced mostly in the testes and a small amount of testosterone is produced from steroids secreted by the outer layer of the adrenal glands (called the adrenal cortex); in females, small amounts of testosterone are produced by the ovaries. While it is commonly perceived that testosterone is not a major factor in prepubescent male development, testosterone is active long before puberty begins. For example, while a fetus is still in the womb, testosterone and a product of its metabolism, dihydrotestosterone, cause the male genitalia to form.

Testosterone Production
The body carefully controls the production of testosterone. Chemical signals from two locations – the pituitary gland at the base of the brain, and a part of the brain called the hypothalamus – tell the testes how much testosterone to produce.

The hypothalamus controls hormone production in the pituitary gland by means of gonadotropin-releasing hormone (GnRH). This hormone tells the pituitary gland to make follicle-stimulating hormone (FSH) and luteinizing hormone (LH). LH signals the testes to produce testosterone. If the testes begin producing too much testosterone, this is sensed by the brain which sends signals to the pituitary to make less LH. This, in turn, slows the production of testosterone. If the testes begin producing too little testosterone, the brain senses this and sends signals to the pituitary gland telling it to make more LH, which stimulates the testes to make more testosterone.

Physical Symptoms Related to Low Testosterone
Signs of low testosterone in men may include decreased sex drive, poor erections by the penis [erectile dysfunction (ED)], lowered sperm count and reduced fertility, or increased breast size. Men also may have symptoms similar to those seen during menopause in women – hot flashes, increased irritability, inability to concentrate, and depression.

Some men may have a prolonged and severe decrease in testosterone production. As a result, they may experience loss of body hair and reduced muscle mass, their bones may be more brittle and prone to fracture, and their testes may become smaller and softer. In younger men, low testosterone production may reduce the development of body and facial hair, muscle mass, and genitals. In addition, their voices also may fail to deepen.

Conditions That Could Cause Low Testosterone

There are a number of specific medical conditions that can cause low testosterone. Often, such conditions are most evident in younger men and men with extremely low testosterone levels. Some of these conditions are associated with diseases or abnormalities of the testes, pituitary gland and hypothalamus. Other men experience low testosterone levels as a result of various genetic factors.

The effects of aging on testosterone production — Andropause
As men age, their ability to produce testosterone declines. Also, some men's production of LH decreases with aging, which lowers testosterone production. Moreover, a protein that binds up and holds onto testosterone called sex hormone binding globulin (SHBG) increases in older men. This reduces the amount of free (unbound) testosterone in the blood that is available to tissues, such as muscles. Aging also causes changes in the daily cycle of testosterone production. For example, younger men show a peak of testosterone in the morning, but this finding is blunted in older men.

The decrease in testosterone production as men age and symptoms associated with testosterone deficiency are sometimes referred to as andropause.

Testes-Based Conditions
Men whose testosterone deficiency is caused by an abnormality in the testes often display increased FSH levels, increased LH levels, and impaired sperm production. These conditions include:

- *Trauma* – A direct physical injury to the testes may damage the cells that produce testosterone.
- *Castration* – Surgical removal of the testes, e.g., for testicular cancer, results in severe reduction in testosterone production.
- *Orchitis* – Testicular inflammation can occur after a post-puberty bout with the mumps (there is a higher risk of risk of infertility than low testosterone).
- *Radiation treatment or chemotherapy* – These therapies for other diseases may damage the testosterone-producing cells of the testes.
- *Testicular tumors* – Treatment of testicular tumors may directly affect testosterone production.

Pituitary/Hypothalamus-Based Conditions
Men whose low testosterone levels result from defects in the pituitary or hypothalamus generally have a low or low-normal FSH level and low or low-normal levels of LH. These conditions include:

- *Pituitary tumors* – The growth of abnormal tissue in the pituitary can disrupt the gland's normal functioning and interfere with hormone production. Some tumors produce hormones that can interfere with LH production.
- *High prolactin levels* – High levels of the pituitary hormone prolactin from a hypothalamic or pituitary tumor, certain medications, and other causes inhibit LH and FSH production, resulting in low testosterone levels.
- *Medications* – Certain drugs used to treat medical conditions that affect the brain (e.g., opiate pain medications such as morphine) and hormones (e.g., cortisone-like medications such as prednisone, and anabolic steroids) may inhibit LH and FSH secretion by the pituitary, and in turn, testosterone production by the testes.
- *HIV/AIDS* – Viruses or other infectious agents may directly or indirectly affect the hypothalamus, pituitary or testes and can decrease testosterone levels; as many as 50 percent of men infected with the human immunodeficiency virus (HIV) may have low testosterone. Severe malnutrition that occurs with AIDS and other wasting conditions may also inhibit LH and FSH production, resulting in low testosterone levels.
- *Immune and Inflammatory Pituitary Disease* – Conditions such as sarcoidosis, tuberculosis, fungal infection, and autoimmune disease may also impair the pituitary's ability to make hormones.

Genetically-Based Conditions
Men may have low testosterone as a result of chromosomal abnormalities or genetically-based conditions. These conditions include:

- *Klinefelter's syndrome* – A genetic condition in which an extra X chromosome is present (about one in every 400 men have this); testosterone production is low to low normal; men with this syndrome also may have markedly reduced bone density and learning disabilities.
- *Hemochromatosis* – A common genetic disorder in which there is excessive depositing of iron into body tissues, most notably the liver, pancreas, heart, skin, and pituitary gland, resulting in reduced functioning of these organs. Iron deposition in the pituitary gland causes impaired production of LH and FSH, which results in decreased testosterone production.
- *Kallmann's syndrome* – Usually a recessive genetic disorder associated with the X chromosome, which occurs in about one of every 10,000 men. A deficiency of gonadotropin releasing hormone (GnRH) impairs the release of LH and FSH, which

decreases testosterone production; men with the syndrome lack the sense of smell; testes do not enlarge at puberty.
- *Prader-Willi syndrome* – A genetic disorder characterized by decreased muscle tone in infancy that improves with age, underdeveloped genitals (including undescended testes in boys) and low sex hormone levels. An obsession with food and compulsive eating, also linked with this disorder, may begin before the age of six.
- *Myotonic dystrophy* – The most common adult form of muscular dystrophy, this genetic condition only occurs in men and is carried on the Y chromosome; because testicular failure usually occurs around the age of 30 to 40, men may have sons at risk for the disease.

Diagnosing Low Testosterone

Importance of the medical history
Sometimes physical symptoms can suggest a medical problem. For example, a man who, as he ages, has a progressive decrease in muscle mass, loss of libido, erectile dysfunction (ED) or reduced sperm count may have low testosterone. Similarly, a teenager who still has the appearance of a young boy – small testes, penis and prostate; scant pubic and body hair; and a high-pitched voice – shows clear signs of someone with inadequate testicular function. There are cases, though, that may involve some medical detective work. Therefore, it is extremely important to provide the doctor with a detailed medical history. Things that should be discussed include:

- past or present major illnesses;
- all prescription and nonprescription drugs currently being taken;
- family/relationship problems, such as sexual problems; and
- any major life events or changes that have occurred.

A family history also may help the doctor to pinpoint a genetic basis for the problem. The doctor can use these clues to identify the correct diagnosis.

Physical examination
During the physical examination, the doctor will look at:

- the amount and distribution of body hair;
- presence and degree of breast enlargement;
- size and consistency of the testes;
- abnormalities in the scrotum;
- size of the penis; and
- the ability to see in all directions (visual field test)

Measuring hormone levels
Testosterone levels vary from hour to hour, so the time at which blood is drawn for testing can affect the results. However, the generally acceptable range of values is 300 to 1,200 nanograms per deciliter (ng/dl) for total testosterone. Generally, the highest testosterone levels occur in the early morning hours; therefore, doctors will often measure testosterone levels at this time.

Testosterone circulates in the blood in three forms:

- About 40 percent of testosterone is bound tightly to a protein called sex hormone binding globulin (SHBG), and is not available to body tissues for action;
- About 58 percent is weakly bound to another protein called albumin and is available to many tissues for action;
- About two percent circulates freely in the bloodstream.

Determination of low testosterone may require more than one blood test. A normal total testosterone reading may not necessarily indicate that a man has normal levels of free testosterone. For example, some men with increased levels of SHBG and low blood levels of free testosterone may have normal levels of total testosterone. Therefore, labs often measure the total testosterone levels and its components.

Other tests

- Because low testosterone levels may affect bone mass, the doctor may want to assess any bone loss with bone density testing.
- Genetic testing can confirm the presence of an inherited condition.
- If tests cause the doctor to suspect a problem within the pituitary gland, he/she may want to examine the gland to see if a tumor is present. Two examination procedures are most common, and neither penetrates the skin. A computed tomography, or CT, is a computer-assisted X-ray process. Magnetic resonance imaging, or MRI, uses a combination of radio waves, high intensity magnetic fields, and computer technology to produce images of the body's interior. The MRI is often the preferred procedure; both tests are usually done before and after a minute amount of dye is injected into a vein.

2. Benefits of Testosterone Replacement Therapy

Men with low levels of testosterone generally complain of sexual and mood problems. Testosterone replacement therapy has been proven to improve both physical and psychological functioning.

Sexual Interest

- Testosterone replacement has been shown to increase sexual interest and the frequency of spontaneous erections.

Erectile Function

- Testosterone replacement restores erectile function in androgen deficient men in the absence of other diseases (such as blood vessel and nerve diseases that occur commonly in older men) that affect erectile dysfunction.

Mood

- Men whose condition makes them depressed, angry, tired, or confused prior to therapy may feel better after receiving supplemental testosterone.

Masculine Characteristics

- Men taking testosterone can maintain masculine characteristics such beard growth and pubic hair.

Bone Density and Muscle Mass

- Testosterone therapy can increase lean muscle mass and bone density in men and improve grip and leg strength.

3. Treatments for Low Testosterone

There are four delivery methods of testosterone that have been approved by the U.S. Food and Drug Administration (FDA). Supplemental testosterone is typically used in one of the following forms:

Pills

	Manufacturer	Dosing	Administration
Andriol* (testosterone undecanoate)	Organon	80-160 mg daily	Orally

*Available in Canada, Mexico, and Europe

Injections

	Manufacturer	Dosing	Administration
Depo-Testosterone® (brand of testosterone cypionate)	Pharmacia Corporation	150-200 mg, every 10-21 days	Intramuscular injection
Delatestryl® (testosterone enanthate injection)	BTG Pharmaceuticals	150-200 mg, every 10-21 days	Intramuscular injection

Patches

	Manufacturer	Dosing	Administration
Testoderm®	Alza Pharmaceuticals	4mg/day, 40cm^2 patch or 6mg/day, 60cm^2 patch	Applied daily to scrotum
Androderm® (testosterone transdermal system)	Watson Pharmaceuticals	5 mg/day, using two 2.5 mg, 37 cm^2 patches, or one 5 mg, 44 cm^2 patch	Applied daily to back, abdomen, upper arms, or thighs

Gel

	Manufacturer	Dosing	Administration
AndroGel® 1% (testosterone gel)	Unimed Pharmaceuticals/Solvay	5-10 g/day, using clear, colorless, water/alcohol mixture	Applied daily to shoulders and upper arms and/or abdomen
Testim®	Auxilium Pharmaceuticals	5-10 g/day, using clear, colorless, water/alcohol mixture	Applied daily to shoulders and upper arms and/or abdomen

Buccal

	Manufacturer	Dosing	Administration
Striant® (testosterone buccal system gel)	Columbia Laboratories, Inc.	Single dose/strength; no dose titration required	Applied to the buccal mucosa (where the gum meets the upper lip)

Once a doctor has diagnosed low testosterone on the basis of physical symptoms and medical test results, he/she should determine if the low testosterone levels are due to testicular, pituitary, or hypothalamic etiology. Individuals with low testosterone and normal or low serum LH levels may require further evaluation. After resolving these issues, treatment with supplemental testosterone can begin. Many studies have demonstrated improved function with testosterone replacement. Investigators have found that treatment resulted in increased sexual interest and an increased number of spontaneous erections. Men taking testosterone replacement therapy also were less depressed, angry, and fatigued.

As seen in the accompanying chart, testosterone replacement therapy can be offered in a variety of forms. Together, the patient and his physician can select a mode of acceptable treatment.

Pills
Although methyl testosterone is manufactured in capsule or pill form, it is not recommended for testosterone replacement in men because it is a weak androgen and not as effective as other preparations, and it has potentially serious adverse effects on the liver and lipids. When capsules/pills are swallowed and absorbed into the bloodstream, they are quickly broken down by the liver and do not achieve high enough blood levels to be useful unless given in large doses (40-50 mg/day). At these doses, they may cause adverse changes in blood lipids (fats) and liver damage. Testosterone undecanoate is moderately effective, but it must be given in capsular form three times daily. It has unique properties that reduce rapid metabolism by the liver and has not been associated with serious adverse effects on the liver.

Injections
Deep muscle injections do not have to be taken daily but are instead given every 7–21 days. With injections, blood levels peak about two to three days after dosing and slowly decline during the next one to two weeks. The injections are painful, and fluctuations in serum levels of testosterone may be accompanied by changes in mood and a sense of well being. Injectable therapy usually is the least expensive way to provide testosterone replacement, and it requires the least patient motivation and compliance.

Transdermal (through the skin) delivery systems
Gel and patch systems offer other advantages. Both are easy-to-apply systems that provide continuous delivery of testosterone. The water/alcohol mixture in the gel system dries quickly and the testosterone is readily absorbed into the skin, which serves as a reservoir for the sustained release of testosterone into the bloodstream. The site of application should be covered, or direct contact with women and children should be avoided. Skin reactivity with the gel seems to be limited in studies at the present time. Patches may cause local reactions in some patients. Most common complaints consist of itching or irritation and

rarely blister formation at the application site and they may fall off when the individual sweats.

Buccal testosterone delivery system
A recently approved system, buccal testosterone treatment, provides a controlled and sustained release of testosterone through the buccal mucosa (tablet adheres to gum surface), where it is absorbed into the bloodstream. Tablets are replaced about every 12 hours. This system may cause gum or mouth irritation, bitter taste, gum pain or tenderness, headache, and taste perversion, but the majority of side effects were resolved within one to 14 days. Insignificant amounts of testosterone are present in the saliva, so transfer of testosterone to women and children in contact with saliva (e.g., with kissing or sharing of eating utensils) is negligible.

4. Potential Risks of Testosterone Replacement Therapy

With any testosterone delivery system, prolonged use may result in breast enlargement or increased risk of prostate enlargement or cancer in older men. Men receiving testosterone replacement therapy should be monitored carefully for prostate cancer, e.g., with a rectal examination and prostate specific antigen. In addition, patients with preexisting heart, kidney, or liver disease may experience fluid accumulation with or without heart failure. Men with breast cancer or known or suspected prostate cancer should not receive testosterone therapy. The patch and gel products are not indicated for use in women. Testosterone may cause fetal harm.

Physicians should instruct men taking testosterone to report any of the following:

- Breathing disturbances, especially those associated with sleep
- Too frequent or persistent erection

5. Overview of Clinical Trials

Testosterone and its effects on sexual function

1. A long–term prospective study of the physiologic and behavioral effects of hormone replacement in untreated hypogonadal men – A.S. Burris et al. *Journal of Andrology* 1992; 13(4):297–304.

   Men with low levels of testosterone who had not yet been treated with supplemental hormone showed significantly higher levels of depression, anger, fatigue and confusion than did men with acceptable testosterone levels. During testosterone replacement therapy, scores improved. Also during treatment, these **men reported increased sexual interest and greater numbers of spontaneous erections.** *(Design of Study: Hypogonadal men before and during testosterone treatment compared to untreated normal men and untreated infertile men; no placebo treated controls.)*

2. Effects of androgen on sexual behavior in hypogonadal men – J.M. Davidson et al. *Journal of Clinical Endocrinology and Metabolism* 1979; 48(6):955–958.

   The study found that **the effect of testosterone replacement on sexual activity in hypogonadal men is rapid, reliable, and not due to placebo effect.** To maintain testosterone levels and adequate sexual function, testosterone replacement should be administered on an ongoing basis. *(Design of Study: Hypogonadal men during double blind, randomized, cross-over treatment with sub-replacement and replacement doses of testosterone; no placebo treated controls.)*

3. Improvement of sexual function in testosterone deficient men treated for one year with a permeation enhanced testosterone transdermal system – S. Arver et al. *Journal of Urology*, 1996; 155(5): 1604-1608.

   This study observed that **nocturnal erections occurred more frequently with longer duration and greater rigidity, and patient assessments of sexual desire and weekly number of erections were higher in hypogonadal men** when testosterone levels were normalized, as compared with measurements occurring during testosterone withdrawal. *(Design of Study: Hypogonadal men during open-label testosterone treatment; not a controlled study.)*

4. Androgen Replacement: Sexual Behavior, Affect and Cognition – A.W. Meikle, editor. *Hormone Replacement, Contemporary Endocrinology*. Humana Press, Totowa, NJ (in press).

   This chapter **reviews studies that evaluate the effects of testosterone replacement on erectile function in hypogonadal males**. *(A review article; not a controlled study.)*

Testosterone and its effects on mood and thinking

1. A long–term prospective study of the physiologic and behavioral effects of hormone replacement in untreated hypogonadal men – A.S. Burris et al. *Journal of Andrology* 1992; 13(4):297–304.

   Men with low levels of testosterone who had not yet been treated with supplemental hormone showed significantly higher levels of depression, anger, fatigue, and confusion than did men with acceptable testosterone levels. **During testosterone replacement therapy, scores for the previously untreated hypogonadal men improved indicative of less depression, anger, fatigue, and confusion**. *(Design of Study: Hypogonadal men before and during testosterone treatment compared to untreated normal men and untreated infertile men; no placebo treated controls.)*

2. Androgen–behavior correlations in hypogonadal men and eugonadal men. II. Cognitive abilities – G.M. Alexander et al. *Hormones and Behavior* 1998; 33(2):85–94.

   Reasoning abilities were assessed in 33 men with low levels of testosterone who were receiving supplemental testosterone, 10 men with normal levels of testosterone

who were given the hormone as part of a male contraceptive clinical trial, and 19 men with normal testosterone levels who did not receive supplemental testosterone. Prior to and after being given testosterone the men completed tests that measured visual–spatial ability, verbal fluency, perceptual speed, and verbal memory. **Men with low testosterone seemed to have lower levels of verbal fluency; these improved following treatment with testosterone.** These data suggest that **testosterone may play some role in influencing some aspects of reasoning and thinking**. *(Design of Study: Hypogonadal men before and during testosterone replacement treatment compared to normal men before and during high dose testosterone and untreated normal men; no placebo-treated controls.)*

3. Testosterone replacement therapy improves mood in hypogonadal men – a clinical research center study – C. Wang et al. *Journal of Clinical Endocrinology and Metabolism* 1996; 81(10):3578–3583.

   The study evaluated changes in mood for 60 days in 51 hypogonadal men. **Researchers found that testosterone replacement therapy in hypogonadal men improved their positive mood parameters including energy, well/good feelings, and friendliness. Testosterone replacement also decreased negative mood parameters including anger, nervousness, and irritability**. *(Design of Study: Hypogonadal men before and during testosterone treatment with a variety of testosterone formulations; not a controlled study.)*

Testosterone and its effects on body composition and bone density

1. Effects of testosterone replacement on muscle mass and muscle protein synthesis in hypogonadal men: a clinical research center study – I.G. Brodsky et al. *Journal of Clinical Endocrinology and Metabolism* 1996; 81(10):3469–3475.

   Researchers measured body composition and muscle protein synthesis in five men with low testosterone before and six months after beginning testosterone replacement therapy. **After testosterone therapy, all five men showed an increase in fat–free mass, a decrease in fat mass and an increase in muscle mass** (65 percent of the increase in fat–free mass could be attributed to increased muscle mass). The scientists also found that the **increased muscle mass was caused by the ability of testosterone to stimulate muscle protein synthesis.** *(Design of Study: Hypogonadal men before and during testosterone treatment; not a controlled study.)*

2. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men – C. Wang et al. *Journal of Clinical Endocrinology and Metabolism* 2000; 85(8): 2839-2853.

   This study evaluated the effects of 180 days of treatment with testosterone patch and testosterone gel on sexual function, muscle strength, lean body, and fat mass in 227 hypogonadal men aged 19-68. **The study found that sexual function and mood improved in all treatment groups; mean muscle strength in the leg press increased in all treatment groups; lean body mass increased greater in the highest dose of testosterone gel compared to lower dose gel and patch.** An increase in lean body mass and reduction in fat mass were correlated with the mean testosterone levels after treatment. *(Design of Study: Hypogonadal men*

before and during testosterone treatment with either testosterone gel or testosterone patch; no placebo treated controls.)

3. Effects of transdermal testosterone gel on bone turnover markers and bone mineral density in hypogonadal men – C. Wang et al. *Clinical Endocrinology* 2001; 54(6): 739-750.

   This study found that transdermal testosterone gel application in doses of 5-10 grams/day (delivering 50-100 mg of testosterone) for 6 months decreased bone resorption markers and increased bone formation activity markers (transiently) in 227 men aged 19-68 years. The highest dose gel resulted in increased bone mineral density in the spine and hip only in the higher treatment group. At the time of the articles the authors indicated that longer term data would determine if the positive effects on bone would persist. The same authors reported at the 2002 Endocrine Meetings that positive effects on bone continued to increase with continued treatment up to 42 months. *(Design of Study: Hypogonadal men before and during testosterone treatment with either testosterone gel or testosterone patch; no placebo treated controls.)*

4. Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism – L. Katznelson et al. *Journal of Clinical Endocrinology and Metabolism* 1996; 81(12):4358–4365.

   Scientists assessed the muscle and bone effects of testosterone replacement therapy in 29 men aged 22 to 69 with low blood levels of the hormone. The men were evaluated at six–month intervals for 18 months. The researchers found that body fat and subcutaneous fat significantly decreased while lean muscle mass and bone density significantly increased. The scientists concluded that **the beneficial effects of testosterone administration on body composition and bone density may provide additional indications for testosterone therapy in such men.** *(Design of Study: Randomized, placebo controlled study of older hypogonadal men before and during testosterone injections compared to before and during placebo injections.)*

5. Testosterone replacement in older hypogonadal men: a 12–month randomized controlled trial – R. Sih et al. *Journal of Clinical Endocrinology and Metabolism* 1997; 82(6):1661–1667.

   Researchers examined the year–long effects of testosterone replacement therapy in 32 men in their 60s (15 men received a placebo and 17 received biweekly injections of testosterone). They found that the **men who received testosterone showed improved grip strength in both hands and increased levels of hemoglobin, the blood component that carries oxygen**. The investigators concluded that **testosterone may have a role in treating frailty in older men**. *(Design of Study: Hypogonadal men before and during testosterone treatment; no placebo treated controls.)*

6. Long–term effect of testosterone therapy on bone mineral density in hypogonadal men – H.M. Behre et al. *Journal of Clinical Endocrinology and Metabolism* 1997; 82(8):2386–2390.

The researchers studied bone mineral density in 72 men who received testosterone replacement therapy for up to 16 years. Bone mineral density was measured annually. The **most significant increase in bone mineral density was seen during the first year of testosterone replacement therapy. Long–term treatment maintained bone mineral density at levels consistent for age in all men**. *(Design of Study: Randomized, placebo controlled study of older hypogonadal men treated with testosterone patches or placebo patches.)*

7. Effect of testosterone treatment on bone mineral density in men over 65 years of age – P.J. Snyder, et al. *Journal of Clinical Endocrinology and Metabolism* 1999;84:1966–1972.

   Researchers examined changes in bone mineral density in 108 men over 65 years of age who received testosterone for 36 months. The study found that **increasing testosterone to the midnormal range for young men did not increase lumbar spine bone density overall, but did increase it in those men with low pretreatment testosterone levels**. *(Design of Study: Randomized, placebo controlled study of older hypogonadal men treated with testosterone patches and placebo patches.)*

8. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age – P.J. Snyder, et al. *Journal of Clinical Endocrinology and Metabolism* 1999;84:2647–2653.

   Researchers examined changes in body composition and muscle strength in 108 men over 65 years of age who received testosterone for 36 months. The study found that **increasing testosterone concentrations in men over 65 years of age to the midnormal range decreased fat mass and increased lean mass, but did not necessarily increase muscle strength**. *(Design of Study: Randomized, placebo controlled study of men over age 65 treated with testosterone patches and placebo patches.)*

Testosterone and its effects on HIV positive men with low testosterone

1. Testosterone replacement in HIV illness – J.G. Rabkin et al. *Archives of General Psychiatry* 2000; 57(2):141-147.

   A total of 70 HIV–positive men with low testosterone levels completed a six-week trial of biweekly testosterone or placebo treatments. **Seventy four percent of men who received testosterone reported much or very much improved libido, compared to 19% of placebo-treated men. Of men with fatigue at baseline, 59% of testosterone-treated men had improved energy, compared to 25% of placebo-treated men. Of men with Axis 1 depression at baseline, 58% of men who received testosterone versus 14% of men treated with placebo reported improved mood. Testosterone improved muscle mass by 1.6 kg over 12 weeks in the entire group of men treated with testosterone, and 2.2 kg in those with wasting at baseline.** *(Design of Study: HIV-positive men with low testosterone levels before and during testosterone treatment; no placebo treated controls.)*

2. Effects of androgen administration in men with the AIDS wasting syndrome. A randomized, double–blind, placebo–controlled trial – S. Grinspoon et al. *Annals of Internal Medicine* 1998; 129(1):18–26.

   Fifty–one HIV–positive men with a mean age of 42 who had wasting and low testosterone were randomly assigned to receive testosterone or placebo every three weeks for six months. **Testosterone–treated men gained fat–free mass, lean body mass and muscle mass. These men also reported they felt better, had an improved quality of life and improved appearance**. *(Design of Study: Double-blind, randomized, placebo-controlled trial of testosterone versus placebo therapy in HIV-infected men with AIDS wasting syndrome.)*

3. Testosterone supplementation therapy for older men: Potential benefits and risks – D.A. Gruenewalk and A.M. Matsumoto. *Journal of the American Geriatric Society* 2003; 51(1):101-115.

   This study of men age 60 years evaluated one or more physical, cognitive, affective, functional, or quality-of-life outcomes. In general, these studies found increased lean body mass and decreased fat mass. Upper and lower body strength, functional performance, sexual functioning, and mood were improved or unchanged with testosterone treatment. **Testosterone improved exercise-induced coronary ischemia in men with coronary heart disease, but angina was improved or unchanged.** Compared to men with less marked testosterone deficiency, men with low testosterone levels were more likely to demonstrate improvements in bone mineral density, self-perceived functional status, libido and sexual function, and exercise-induced ischemia. No major unfavorable effects on lipids were reported, but hematocrit and prostate specific antigen often increased. *(Qualitative review of placebo-controlled trials.)*

6. Frequently Asked Questions

What is testosterone?
Testosterone is the primary sex hormone produced in men's bodies. Testosterone stimulates the development of the penis and testes, growth of facial and pubic hair, deepening of the voice, changes in body-shape, growth of bones, and increased muscle mass and strength. It helps maintain sex drive and the production of sperm cells, and it may play a role in balding. Mood is also affected by testosterone, and low levels of the hormone can cause severe and prolonged depression as well as fatigue. Testosterone is produced mostly in the testes and a small amount is produced from steroids secreted from the outer part of the adrenal glands called the adrenal cortex. Women's ovaries also produce a small amount of testosterone.

How does the body know how much testosterone to make and release?
The testes receive chemical signals from the pituitary gland, which is located at the base of the brain. The pituitary gland receives signals from the hypothalamus. The hypothalamus secretes gonadotropin-releasing hormone (GnRH). This signals the pituitary gland to produce and secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH). LH signals the testes to produce testosterone. If the testes begin producing too much

testosterone, the body sends signals to the pituitary telling it to make less LH. This, in turn, slows down the production of testosterone.

What is a "normal" level of testosterone?
Doctors check to see if a man's blood testosterone level falls into a generally acceptable range of values. Testosterone levels vary from hour to hour, so fluctuations can be seen in men with no apparent problems. Generally, the highest testosterone levels occur in the early morning hours, so measurements should be taken at this time. Normal ranges are determined in normal, healthy men between the ages of 20 and 40 or 45.

How is testosterone measured?
If a doctor suspects someone is not producing enough testosterone, he/she will check if the total blood testosterone level falls into the acceptable range. The doctor also may instruct the laboratory to measure the amount of free or loosely bound testosterone (about 40 percent of the total testosterone is strongly bound to a protein called sex hormone binding globulin, known as SHBG; about 58 percent is weakly bound to another protein called albumin) and the amount of free testosterone (only about two percent circulates freely in the blood). Blood levels of SHBG increase with age, so older men may have a higher percentage of bound testosterone and a lower percentage of free testosterone. Bioavailable testosterone includes the non-SHBG bound testosterone or the sum of the testosterone, which is bound to albumin and free (unbound) testosterone.

How does aging affect the body's ability to make testosterone?
Not only does the amount of testosterone produced decline with age, the morning spike of testosterone seen in young men is blunted in older men. The pituitary glands of older men also may produce less luteinizing hormone (LH), which decreases testosterone production. Testosterone in aging men is more likely to bind to sex hormone binding globulin (SHBG), which reduces the amount of bioavailable or freely circulating testosterone that is available to the body. However, aging also is frequently associated with increasing obesity, and obesity is associated with decreased SHBG levels. Thus, measurement of non-SHBG bound testosterone may be needed in aging, obese men.

Why would a doctor suspect that someone has a low level of testosterone?
Symptoms related to low testosterone include: decreased sex drive, erectile dysfunction (ED), lowered sperm count, increased breast size (a condition called gynecomastia), hot flashes, increased irritability, trouble concentrating, and depression. Men who have a severe and prolonged reduction of testosterone also may experience loss of body hair, reduced muscle mass and bone fractures due to osteoporosis. Certain medical conditions also can cause the condition.

Can low testosterone be seen in younger men, too?
Yes. Certain genetic conditions such as Klinefelter's syndrome, Kallmann's syndrome, and Prader-Willi syndrome can cause lowered testosterone production in boys and young men. In addition, testosterone production can be lowered by bilateral cryptochid testes injury, inflammation, and tumors. Chemotherapy and radiation therapy also may damage testosterone-producing cells. Finally, many patients who are HIV+ have low testosterone levels.

Can a low testosterone level cause other problems?
Studies have shown that men with low testosterone can become frail, lose muscle mass and suffer bone fractures due to osteoporosis. Some data have suggested that testosterone therapy can lead to increases in muscle mass and strength. Researchers also have shown

that men who are testosterone-deficient may be more likely to experience depression and reduced quality-of-life than men who produce adequate amounts of the hormone.

If someone has a low testosterone level, how do they get it increased?
Supplemental preparations of testosterone currently are available in gel and patch forms that deliver it through the skin, as pills, or as preparations that have to be injected into deep muscle about every 7–21 days.

What is the next step for a man who has low testosterone?
An endocrinologist is a doctor who is a medical expert in treating diseases with abnormal hormone secretion and tumors of glands that secrete hormones. Board-certified endocrinologists are ideally suited to evaluate, diagnose, and identify a wide spectrum of medical, physical and psychiatric abnormalities responsible for causing male sexual dysfunction including a low testosterone level. To find an endocrinologist near you, visit The Hormone Foundation's "Find an Endocrinologist" physician referral directory at www.hormone.org (The directory is comprised of over 2,500 members of The Endocrine Society, the parent organization of The Hormone Foundation and the largest organization of endocrinologists in the world.)

7. Glossary of Terms

Adrenal Cortex
The outer portion of the adrenal glands and one of the sites of steroid production.

Adrenal glands
Also known as the suprarenal glands, each of these two glands sits atop a kidney; the outer portion is a site of steroid production while the inner section produces other substances, such as epinephrine and norepinephrine.

AIDS-related wasting
A category of acquired immunodeficiency syndrome (AIDS). Signs and symptoms may include weight loss, fever, malaise, lethargy, oral thrush, and immunologic abnormalities characteristic of AIDS. Previously called AIDS-related complex (ARC).

Albumin
A simple protein that is widely distributed throughout the body.

Androgen
A hormone, such as testosterone, that is responsible for the development of masculine characteristics.

Andropause
A term used to describe the symptoms associated with aging in the setting of low testosterone levels in men as they age.

Bioavailable testosterone
Molecules of the male hormone circulating in the blood that is not bound to sex hormone-binding globulin (SHBG).

Bone mineral density
A measurement of bone that denotes its ability to resist fracture.

Buccal delivery system
Supplying medication in a form so it can be absorbed through the buccal mucosa (the gum surface) into the bloodstream).

Dihydrotestosterone
A derivative of testosterone that is responsible for many of testosterone's effects on the body.

Edema
Accumulation of excess watery fluid in cells, tissues, or serous cavities.

Endocrinologist
A medical expert in treating diseases with abnormal hormone secretion and tumors of glands that secrete hormones. He or she is trained to recognize hormonal problems and precisely restore the natural balance of hormones in the body's system.

Erectile Dysfunction (ED)
The total inability to achieve an erection, an inconsistent ability to do so, or a tendency to sustain only brief erections.

Follicle stimulating hormone (FSH)
A hormone produced by the pituitary gland; along with luteinizing hormone, it helps control production of sperm and semen and the development of secondary sex characteristics.

Free testosterone
Molecules of the male hormone that circulate freely in the blood and are not bound to proteins, such as SHBG or albumin.

Genetic testing
A process in which a person's DNA is examined to see if he has or is at risk of passing a condition on to his descendants.

Gonadotropin(s)
A group of hormones capable of promoting the growth and function of the sex glands (follicle stimulating hormone and luteinizing hormone are examples of gonadotropins).

Gonadotropin releasing hormone (GnRH)
A hormone produced by the hypothalamus that causes the release of gonadotropins.

Gynecomastia
Excessive development of the breast in the male.

Hormone
A chemical substance produced in one part of the body that travels through the bloodstream and exerts an effect on cells and tissues in another part of the body.

Hypogonadism
A condition characterized by inadequate functioning of the sex glands (insufficient sperm or egg production or insufficient production of sex hormones such as testosterone or estrogen).

Hypothalamus
A portion of the diencephalon of the brain, forming the floor and part of the lateral wall of the third ventricle. It activates, controls, and integrates the peripheral autonomic nervous system, endocrine processes, and many somatic functions, such as body temperature, sleep, and appetite.

Inherited condition
A disorder that results from a defect in genes or chromosomes; it may be apparent at birth or may not appear until years later.

Kallmann's syndrome
A condition characterized by the absence of the sense of smell and hypogonadotropic hypogonadism. It is caused by failure of the olfactory bulbs to develop and hypogonadism related to a decrease of luteinizing hormone-releasing hormone.

Klinefelter's syndrome
An inherited condition affecting males in which they are born with an extra X chromosome.

Luteinizing hormone (LH)
A hormone produced by the pituitary gland; along with follicle stimulating hormone, it helps control production of sperm and semen and the development of secondary sex characteristics.

Menopause
In women, the time when menstruation ceases.

Myotonic muscular dystrophy
A severe form of muscular dystrophy marked by weakness of facial muscles and difficulty speaking. Weakness of the hands and feet precedes that in the shoulders and hips. Muscle spasms of the hands are usually present.

Orchitis
Testicular inflammation, which can cause infertility or reduced production of testosterone; it can occur in conjunction with mumps or other infectious diseases affecting the testes in an adolescent or adult male.

Osteoporosis
A condition marked by abnormal loss of bone density and increased bone brittleness and fracture.

Ovaries
Female reproductive organs that produce eggs and female sex hormones.

Pituitary gland
An endocrine gland suspended beneath the brain, supplying numerous hormones that govern many vital processes. The pituitary hormones, controlled by hypothalamic releasing factors, include growth hormone (somatotropin), prolactin, thyroid stimulating hormone, follicle stimulating hormone, luteinizing hormone, adrenocorticotropic hormone, and melanocyte stimulating hormone.

Placebo
An inert substance given as a medicine for its suggestive effects.

Prader-Willi syndrome
A metabolic condition characterized by congenital reduced muscle tone, overeating, obesity and mental retardation. The syndrome is associated with below normal secretion of gonadotropic hormones by the pituitary gland.

Sex hormone binding globulin (SHBG)
A protein produced by the liver that binds testosterone in the blood, making it less available to the body; SHBG binds estrogen with less affectivity.

Testosterone
The male sex hormone in the body that stimulates key processes, including increases in muscle mass and strength, development of facial and pubic hair, enlargement of the voice box and deepening of the voice, increased size of the penis and testes, change in body shape, maintenance of sex drive, and sperm cell production. It also plays a role in maintaining energy and mood.

Total testosterone
The total amount of testosterone (bound and free) circulating in the blood.

Transdermal delivery
Supplying a medication in a form so it can be absorbed through the skin into the bloodstream.

Resources

Following are professional and patient care organizations that can provide you with additional information on low testosterone.

The Hormone Foundation
8401 Connecticut Avenue, Suite 900
Chevy Chase, MD 20815-5817
800-HORMONE (800.467.6663)
www.hormone.org

The Endocrine Society
8401 Connecticut Avenue, Suite 900
Chevy Chase, MD 20815-5817
301.941.0200
www.endo-society.org

American Academy of Family Physicians (AAFP)
11400 Tomahawk Creek Parkway
Leawood, KS 66211
913.906.6000
www.aafp.org

American Association of Clinical Endocrinologists (AACE)
1000 Riverside Avenue, Suite 205
Jacksonville, FL 32204
904.353.7878
www.aace.com

American Association for Klinefelter Syndrome Information and Support (AAKSIS)
c/o Roberta Rappaport
2945 W. Farwell Ave.
Chicago, IL 60645-2925
www.aaksis.org

American Foundation for Urologic Disease (AFUD)
1128 North Charles Street
Baltimore, MD 21210
410.468.1800
www.afud.org

American Society of Andrology (ASA)
11 North Plaza Drive, Suite 550
Schaumburg, IL 60173
847.619.4909
www.andrologysociety.com

American Society for Reproductive Medicine
1209 Montgomery Highway
Birmingham, Alabama 35216-2809
205.978.5000
Email: asrm@asrm.org

American Urological Association (AUA)
1120 North Charles Street
Baltimore, MD 21201
410.727.1100
www.auanet.org

Klinefelter Syndrome & Associates
P.O. Box 119
Roseville, CA 95678
916.773.2999
www.genetic.org/ks

Bibliography

1. Alexander GM, Swerdloff RS, Wang C, et al. Androgen-behavior correlations in hypogonadal men and eugonadal men. II. Cognitive abilities. *Hormones and Behavior* 1998; 33(2):85-94.

2. AndroGel Package Insert. Unimed Pharmaceuticals.

3. Basaria S and Dobs AS. Risks versus benefits of testosterone therapy in elderly men. *Drugs and Aging* 1999; 15(2):131-142.

4. Behre HM, Kliesch S, Leifke E, et al. Long-term effect of testosterone therapy on bone mineral density in hypogonadal men. *Journal of Clinical Endocrinology and Metabolism* 1997; 82(8):2386-2390.

5. Braunstein, G. Testes. *Greenspan & Strewler.*

6. Brodsky IG, Balagopal P, and Nair KS. Effects of testosterone replacement on muscle mass and muscle protein synthesis in hypogonadal men - a clinical research center study. *Journal of Clinical Endocrinology and Metabolism* 1996; 81(10):3469-3475.

7. Burris AS, Banks SM, Carter CS, et al. A long-term, prospective study of the physiologic and behavioral effects of hormone replacement in untreated hypogonadal men. *Journal of Andrology* 1992; 13(4):297-304.

8. Cherrier MM, Anawalt BD, Herbst KL, Amory JK, Craft S, Matsumoto, AM and Bremner WJ. Cognitive effects of short-term manipulation of serum sex steroids in healthy young men. *Journal of Clinical Endocrinology and Metabolism* 2002; 87(7):3090-3096.

9. Davidson JM, Camargo CA, Smith ER. Effects of androgen on sexual behavior in hypogonadal men. *Journal of Clinical Endocrinology and Metabolism* 1979;48:955-958.

10. Feldman HA, Longscope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ and McKinlay JB. Age trends in the level of serum testosterone and other hormones in middle-aged men: Longitudinal results from the Massachusetts male aging study. *Journal of Clinical Endocrinology and Metabolism* 2002; 87(2):589-598.

11. Ferrando AA, Sheffield-Moore M, Yeckel CW, Gilkison C, Jiang J, Achacosa A, Lieberman SA, Tipton K, Wolfe RR and Urban RJ. Testosterone administration to older men improves muscle function: Molecular and physiological mechanisms. *American Journal of Physiology, Endocrinology and Metabolism* 2001; 282:601-607.

12. Gray A, Feldman HA, McKinlay JB, and Longcope C. Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. *Journal of Clinical Endocrinology and Metabolism* 1991; 73:1016-1025.

13. Griffin JE and Wilson JD. "Disorders of the testes and the male reproductive tract," in Wilson JD et al, eds., *Williams Textbook of Endocrinology*, 9th edition, WB Saunders, Philadelphia, pp. 819-938, 1998.

14. Grinspoon S, Corocran C, Askari H, et al. Effects of androgen administration in men with the AIDS wasting syndrome. A randomized, double-blind, placebo-controlled trial. *Annals of Internal Medicine* 1998; 129(1):18-26.

15. Harman SM, Metter EJ, Tobin JD, Pearson J and Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. *Journal of Clinical Endocrinology and Metabolism* 2001; 86(2):724-731.

16. Janowsky JS, Chavez B and Orwoll E. Sex steroids modify working memory. *Journal of Cognitive Neuroscience* 2000; 12(3):407-414.

17. Katznelson L, Finkelstein JS, Schoenfeld DA, et al. Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. *Journal of Clinical Endocrinology and Metabolism* 1996; 81(12):4358-4365.

18. Kenny AM, Prestwood KM, Gruman CA, Fabregas G, Biskup B and Mansoor G. Effects of transdermal testosterone on lipids and vascular reactivity in older men with low bioavailable testosterone levels. *Journal of Gerontology* 2002; 57A(7):M460-M465.

19. *The Merck Manual of Geriatrics*, Abrams WB and Berkow R, eds. Merck, Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, N.J. ©1990.

20. Matsumoto AM. Andropause: Clinical implications of the decline in serum testosterone levels with aging in men. *Journal of Gerontology* 2002: 57a(2):M76-M99.

21. Matsumoto AM. "The testis," in Felig P and Frohman LA, eds., *Endocrinology & Metabolism*, 4th edition, McGraw-Hill, New York, pp 635-705, 2001.

22. Mooradian AD, Morley JE, and Korenman SG. Biological actions of androgens. *Endocrine Reviews* 1987; 8(1):1-28.

23. Morley J and Perry H. Androgen deficiency in aging men: Role of testosterone replacement therapy. *Journal of Laboratory & Clinical Medicine,* May 2000.

24. Petak SM, Baskin HJ, Bergman DA, et al. AACE clinical practice guidelines for the evaluation and treatment of hypogonadism in adult male patients. *Endocrine Practice* 1996; 2:440-453.

25. Physicians' Desk Reference. 53rd edition. ©1999 Medical Economics Company, Montvale, N.J.

26. Plymate S. Hypogonadism. *Endocrinology and Metabolism Clinics of North America* 1994; 23(4):749-772.

27. Pope HG Jr, Cohane GH, Kanayama G, et al. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. *American Journal of Psychiatry* 2003; 160(1):105-111.

28. Rabkin JG, Rabkin R, and Wagner G. Testosterone replacement therapy in HIV illness. *General Hospital Psychiatry* 1995; 17(1):37-42.

29. Sih R, Morley JE, Kaiser FE, et al. Testosterone replacement in older hypogonadal men: A 12-month randomized controlled trial. *Journal of Clinical Endocrinology and Metabolism* 1997; 82(6):1659-1660.

30. Snyder PJ, Peachy H, Hannoush P, et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *Journal of Clinical Endocrinology and Metabolism* 1999; 84:2647-2653.

31. Snyder PJ, Peachy H, Hannoush P, et al. Effect of testosterone treatment on bone mineral density in men over 65. *Journal of Clinical Endocrinology and Metabolism* 1999; 84:1966-1972.

32. Testosterone. The Columbia Encyclopedia, Fifth Edition ©1993, Columbia University Press. www.infoplease.com/ce5/CE051331.html

33. Tenover JS. Androgen replacement therapy to reverse and/or prevent age-associated sarcopenia in men. *Bailliere's Clinical Endocrinology and Metabolism* 1998; 12(3):419-425.

34. Tenover JS. Effects of testosterone supplementation in the aging male. *Journal of Clinical Endocrinology and Metabolism* 1992; 75(4):1092-1098.

35. Testoderm Package Insert. Alza. www.alza.com

36. Winters SJ. Current status of testosterone replacement therapy in men. *Archives of Family Medicine* 1999; 8:257-263.