

Testosterone Replacement Therapy in Males

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Testosterone today is considered to be a lively topic for discussion among adolescents, adults, and health care professionals. When prescribed for conditions other than male menopause (andropause), testosterone replacement therapy is a controversial topic, especially regarding its use as an "antiaging" agent and its popularity among men who wish to build muscle mass. Polemics range from the artistic purity of the chemical structure to the role that testosterone plays in promoting male dominance in the animal kingdom.¹ Even though people are aware of this hormone, most have a vague understanding of its function and only a few have a reasonable knowledge of its role in the mammalian system. It is probably safe to assume that most individuals believe that testosterone is the principal guiding hormone in the development of the male embryo (embryogenesis) in all species. The charging bull and the sleek Arabian stallion are two examples of the phenotype and spirited behavior associated with this chemical. Not by way of coincidence, the greatest source of testosterone is in bull and stallion testes, and spermatid vein blood.²

Perhaps the finest example of the role that this powerful chemical evokes is exhibited in the adolescent male who seems destined to go through an unsettled period of life during the teen years; the adolescent male may demonstrate a lack of good judgment, including participating in some death-defying feats. He may also perceive himself to be immortal. The armed services have always recruited soldiers from this group. In some third world countries younger adolescents are highly publicized as soldiers. It is interesting that the cutoff age for Selective Service, except during times of all-out war, is 26, the age at which testosterone levels begin to decrease. Even during world conflicts, conscription of men older than 35 is highly unusual. (A rare exception to this was the formation of a German "home army" composed of middle-aged and older men—referred to as the Grandfather Defense Force—during the World War II battle for Berlin.)

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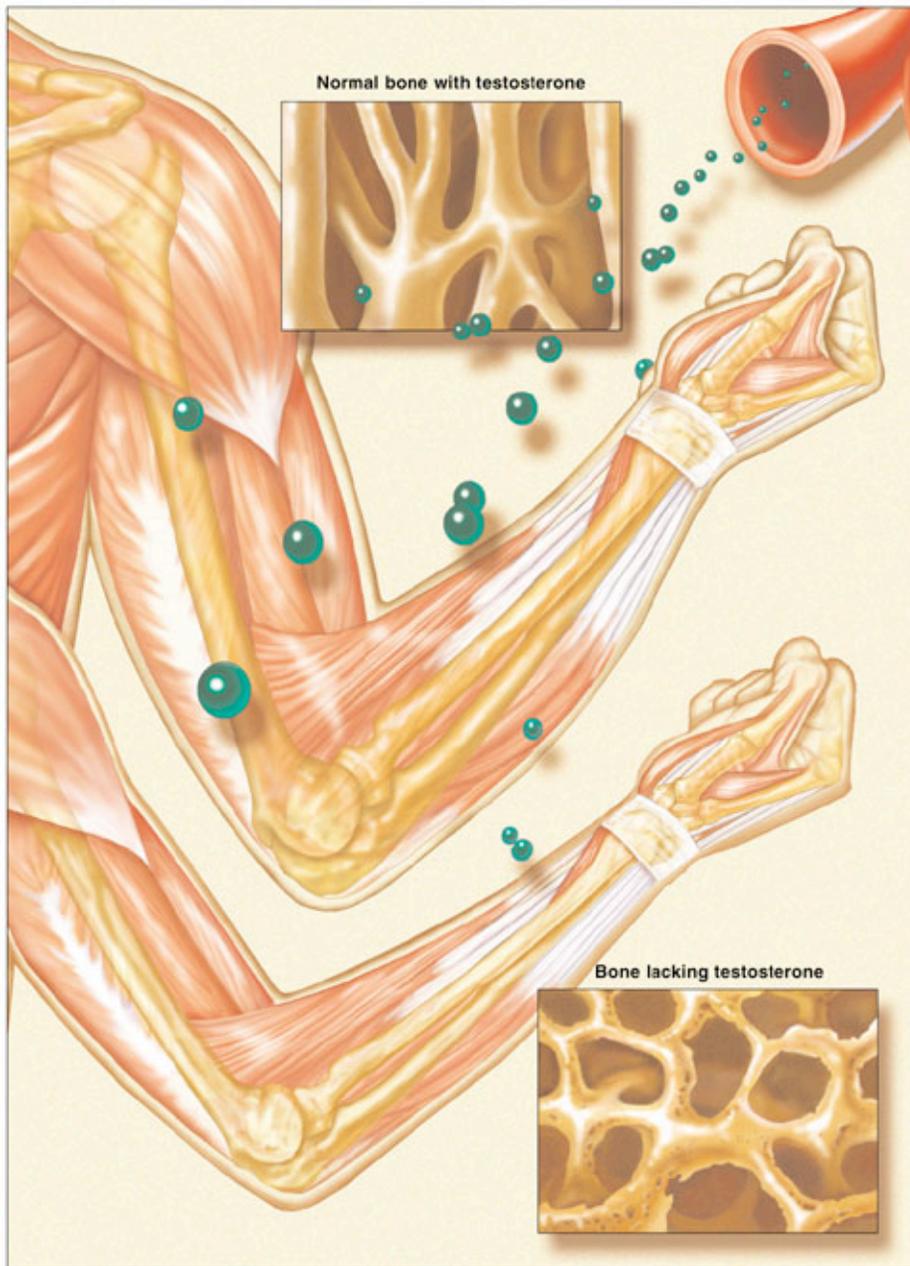
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Recent scientific studies suggest that patients suffering from low physiologic levels of testosterone and decreased bone density may benefit from testosterone replacement therapy.

The Role of Testosterone

Throughout childhood both males and females constantly produce low levels of testosterone. Once puberty and adolescence begin in the male, the hormonal link between the hypothalamus, pituitary gland, adrenal gland, and the gonads is closely regulated in that supra or suboptimal levels of testosterone are readily manifested phenotypically. The adrenal cortex is responsible for producing androgens, including testosterone. In teenage boys, testosterone stimulates the growth of pubic and axillary hair, enlargement of the skeletal system, an increase in the musculature system, thickening of the vocal cords, and emergence of voluntary and involuntary sexual sensations.^{3,4} In men and women, testosterone serves as the basis for the sex drive (libido). (Although testosterone is considered the "male" hormone, it also serves to promote sexual activity in women.¹) It has been demonstrated that receptors exist in the central nervous system that respond to testosterone and its metabolite, dihydrotestosterone, establishing the neurochemical basis for libido. This mechanism is not completely understood.

The enzyme 5 alpha-reductase irreversibly catalyzes the conversion of testosterone to dihydrotestosterone, which has a greater affinity for androgen receptors.⁵

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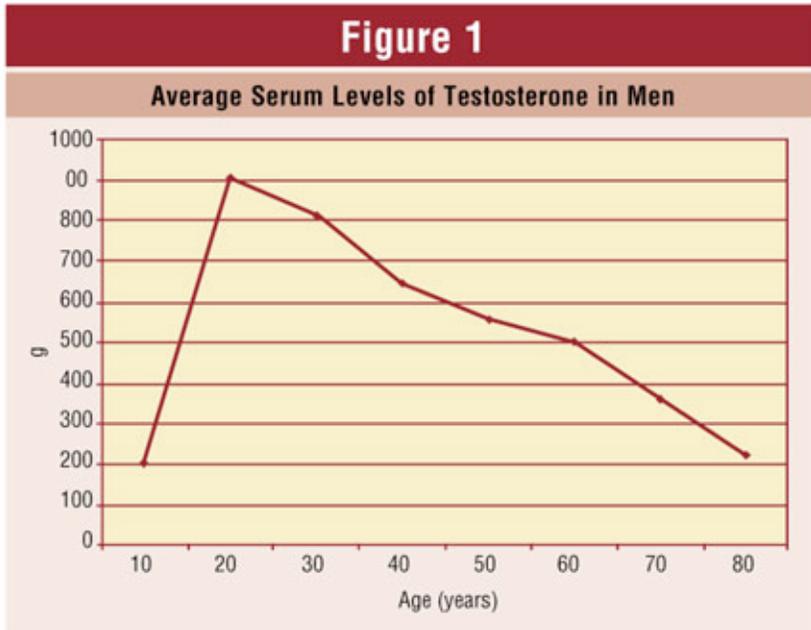
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Furthermore, the kinetics of receptor binding with dihydrotestosterone is such that it has a much slower dissociation from the receptor than does testosterone. This phenomenon allows for the amplification of the actions of testosterone in target cells. From this, testosterone is able to mediate effects in body tissues that express 5 alpha-reductase that otherwise would not be observed if only testosterone were present.⁶

The normal serum ranges of testosterone in a healthy teenager are between 500 ng/dL and 750 ng/dL, a lifetime high (FIGURE 1). These levels are fairly constant until ages 28 to 38. The decline, although variable and dependent on many interrelated factors, happens gradually over many years and is generally not noticed until later in life.



Typically, the levels at which this hormone are lost are at an average of 0.2% to 1% a year. By age 40, some men are experiencing andropause (male menopause) or hypogonadism with testosterone serum concentrations measuring only 200 to 300 ng/dL. Generally, the patient will go to a doctor, reporting loss of libido, sexual impotence, fatigue, hair loss, and dry skin. Further, he may experience hot flashes and mood swings, which are typical of the symptoms women may encounter during menopause (thus, the term "male menopause"). In addition, the patient may experience depression, muscular weakness, and loss of lean body mass.⁷ The time lapse between the first signal of change to the point where the individual cannot help but notice that his muscles are withering, energy is shrinking, and self-confidence is lacking, is generally 10 to 15 years.⁸

Loss of Bone Density

It has been demonstrated that as men age and their serum levels of testosterone decrease, there is concomitant loss of bone density. This decrease in bone density is also noted in men having low testosterone levels as a result of pituitary or testicular disease. Many studies have demonstrated that the use of testosterone replacement therapy may be beneficial in increasing bone density and lean body mass in men with acquired hypogonadism.⁹⁻¹¹ One of the longer studies to date involves a 16-year trial that evaluated bone mineral density in 72 hypogonadal patients undergoing testosterone replacement therapy.¹² This study demonstrates that long-term, effective testosterone therapy significantly increases bone mineral density in hypogonadal men. Such a finding is of particular importance when it is considered that osteoporosis is a significant problem in men; 30% of hip fractures occur in men.¹³ This form of bone structure loss accounts for an estimated \$2.7 billion per year in health care expenses.

Physiologic Actions

It is well accepted by the scientific and health care community that androgens have many important physiologic actions, including effects on sexual function, muscle, body composition, bone, prostate, and the central nervous system (including cognitive function and libido). In addition, low testosterone levels are associated with an increased incidence of coronary artery disease.¹⁴ However, as a result of the difficulty men have had in discussing this sensitive topic and the lack of sound clinical studies, treatment protocols are somewhat limited. The options available include testosterone and prohormones, which stimulate the production of testosterone. Agents that modify the metabolism of the precursors and metabolites of testosterone may also be used. However, for many patients, the only option that is viable includes testosterone replacement therapy.

For patients suffering from hypogonadism, testosterone replacement therapy increases muscle mass and strength, bone mineral density, cognitive function, and libido.¹⁴ Even though the latter finding is of paramount importance, one must bear in mind that simply increasing the levels of testosterone beyond the normal levels does not further increase libido. Furthermore, since serum levels of this androgen vary among individuals, it is impossible to create a standard dose-response curve that can be applied uniformly to all patients. Hence, for optimal effects, each patient should be evaluated for his specific needs.

There are three formulations of testosterone available: oral, intramuscular, and transdermal. There are advantages and disadvantages to each. Oral formulations tend to exercise liver enzymes beyond their normal limits. Over a period of time this may have serious consequences on the cytochrome oxidase system. Intramuscular preparations tend to bypass the liver and do not have as severe an effect on liver enzymes. This lack of first-pass metabolism is also noted with transdermal preparations.

Since the intramuscular forms generally consist of the fatty ester enanthane or cypionate, adverse effects cannot be quickly reversed due to their long duration of action. However, the transdermal formulations are easier to manage if adverse effects occur in the patient.

Adverse Effects

Although not an exhaustive list, the possible adverse effects of testosterone replacement therapy include breast soreness or gynecomastia, priapism, acute epididymitis, prostatic hypertrophy (leading to difficulty in urination), increased hair growth, facial oil, and acne. In addition, if the dosage involves an intramuscular injection, the patient may experience hives, infection, redness, and pain at the injection site. Furthermore, if a transdermal formulation is used, the patient may experience redness, itching, or other discomfort at the site of application.

Compounding pharmacists are often called upon to formulate an extemporaneously compounded testosterone ointment. This is a result of the margin of safety that is afforded by a transdermal preparation and its limited effect on metabolic enzymes that are present in the liver. Also, this facilitates the differing requirements that exist among patients as each individual can have his own "tailored" dose of this particular androgen, thus allowing for supraphysiological levels to be avoided. Through the relationship that exists between the physician, patient, and pharmacist, the patient's needs are determined and decisions are made regarding the appropriate level of hormone replacement therapy.

The similarities between menopause and andropause are striking in that reductions in serum levels of hormones play a role in the overall health of the patient. As with hormone replacement therapy in women, the health care provider is cautioned that further studies are needed to determine the benefits of testosterone replacement therapy in men suffering from hypogonadism. However, based on current studies, there seems to be an opportunity for improving the quality of life for many men suffering from reduced levels of testosterone. When the essential level of this hormone drops below normal, replacement therapy is a viable option that should be considered. Finally, it is an amusing paradox that in order to put a little zip into their lives, some lawmakers who made testosterone a CIII scheduled drug, due to its potential for abuse by body builders, are often themselves recipients of this valuable natural product.

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