

Testosterone Therapy in Men: An Update **by Laurence Katznelson, M.D.**

Testosterone deficiency in men is manifested typically by symptoms of hypogonadism, including decreases in erectile function and libido. Testosterone also has an important role in the regulation of normal growth, bone metabolism and body composition. Specifically, testosterone deficiency is an important risk factor for osteoporosis and fractures in men. In men older than 65 years of age, the incidence of hip fracture is 4-5/1000 and approximately 30% of all hip fractures occur in men. Men with testosterone deficiency have significant decreases in bone density, particularly in the trabecular bone compartment. Testosterone deficiency has been reported in over half of elderly men with a history of hip fracture. Men with testosterone deficiency also have alterations in body composition that include an increase in body fat. Using quantitative CT scans to assess fat distribution, we have shown that testosterone deficiency is associated with an alteration in site-specific adipose deposition with increased deposits in all areas, particularly in the subcutaneous and muscle areas. Because truncal fat correlates with glucose intolerance and cardiovascular risk, hypogonadism may have important implications with regard to overall health and mortality. In one study, the alteration in skeletal muscle composition was associated with a decrease in muscle strength. Therefore, testosterone deficiency is associated with an enhanced risk for osteoporosis, altered body composition including increases in truncal fat, and, possibly, decreases in muscle performance.

Administration of adequate testosterone replacement therapy leads to improvements in libido and erectile function. Following testosterone replacement, men note an increase in energy and mood, which may reflect either direct behavioral effects of androgens, and/or, an elevation of hematocrit due to rising testosterone levels. Testosterone therapy also leads to important beneficial effects on the skeleton and lean tissue mass. Testosterone replacement increases bone density in hypogonadal men with the most dramatic effects seen in the trabecular bone compartment. These effects may be seen as early as 6 months following initiation of testosterone therapy. In one recent study of the long-term benefits of testosterone therapy, the greatest benefits in trabecular bone were seen in the first several years of therapy. With regard to body composition, testosterone replacement therapy results in a dramatic reduction in adipose content, with the greatest effects seen in the subcutaneous and skeletal muscle areas. Androgen therapy leads to a significant increase in lean skeletal muscle mass and strength. Therefore, there are beneficial effects of testosterone replacement on body composition and bone mineral density in adult hypogonadal men that may serve as indications for therapy in addition to libido and sexual function.

Because testosterone levels decline with age, and aging is accompanied by body changes including loss of muscle and increases in fat, there is great interest in the potential benefits of testosterone administration in elderly men. In a recent study, Snyder et al. (1999) administered testosterone via a scrotal patch in a randomized, placebo-controlled trial to 108 elderly men for 3 years. As shown in Figure 2, testosterone administration resulted in beneficial effects on lean and fat mass. Therefore, there may be a role for androgens in improving body composition and function in elderly men.

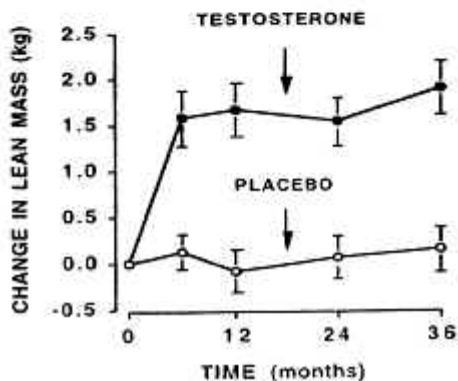
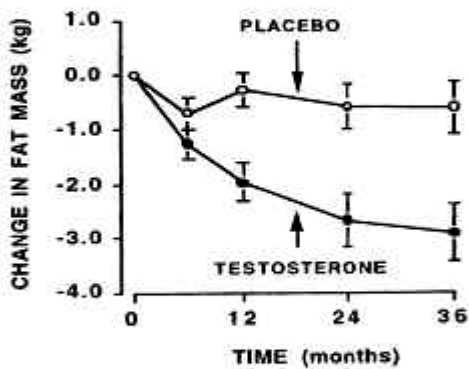
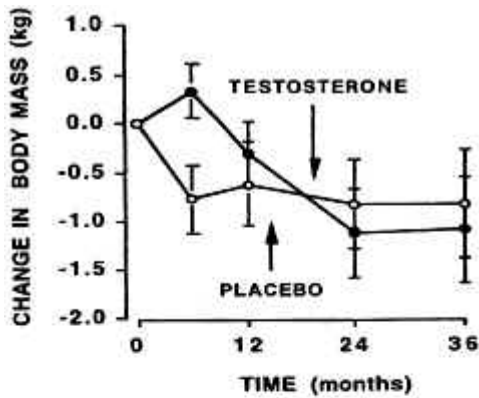


Figure 2. Mean change from baseline in total body mass, fat mass, and lean mass, as determined by DEXA, in 108 men over 65 yr of age. The decrease in fat mass ($P < 0.005$) and the increase in lean mass ($P < 0.001$) in the testosterone-treated subjects were significantly different from those in the placebo-treated subjects at 36 months. (Reproduced with permission from The Endocrine Society – Snyder PJ, et al: The Journal of Clinical Endocrinology & Metabolism 1999; 84:2647-2653).

There are several modes of administration available for testosterone replacement. Until recently, the traditional form of testosterone therapy consisted of intramuscular injections of testosterone esters given at 2 to 4 week intervals. This mode of therapy leads to an increase in testosterone levels, but there are marked oscillations in serum testosterone levels with an early peak, often to supraphysiologic levels, followed by levels that fall in the subtherapeutic range. Therefore, men may note an improvement in sexual function only in the immediate period following the injection. Also, men may describe mood swings and behavioral alterations that may reflect these changing testosterone levels.

More recent advances have led to the development of novel delivery systems for androgens such as transdermal preparations of testosterone. These systems provide more physiologic testosterone replacement, with serum testosterone levels in the normal range throughout the day.

Therefore, transdermal systems are considered the first line therapy for men with hypogonadism. There are several patches currently available. There are two non-scrotal transdermal systems, Testoderm TTS and Androderm. Both of these patch systems are placed on the skin daily, Testoderm TTS in the morning and Androderm at night. Use of the patches leads to normal testosterone values, but Androderm in particular may be associated with local skin irritation. Testoderm TTS has an advantage because of a low incidence of skin irritation. The typical dose is 5 mg applied daily.

A newly available non-patch, transdermal testosterone delivery system is AndroGel. AndroGel comes as 2.5 or 5.0 gm testosterone packets, applied daily. Normal testosterone levels are usually achieved with 5.0 gm and there is a low incidence of skin irritation. This system therefore is another option for testosterone replacement therapy for men. Further studies are needed to assess long-term compliance and efficacy of this form of replacement therapy.

There are several possible adverse effects of testosterone administration that need to be closely monitored, including clinically significant benign prostatic hypertrophy (BPH) and prostate cancer. Despite the theoretical considerations that androgens will augment prostate size, there is no evidence that androgen replacement in elderly men will lead to the development of hyperplasia or aggravate its clinical status. There is also a concern that prostate cancer may develop during androgen therapy. There are no data available as to whether androgen therapy will enhance the progression of preclinical to clinical cancer. However, androgens may stimulate the growth of already existing prostate cancer. Therefore, prior to testosterone initiation, patients should be screened for BPH and prostate cancer with a clinical history, digital exam, and PSA (prostate specific antigen) level. Because androgens may stimulate erythropoiesis and precipitate sleep-related breathing disorders, a CBC should be followed and subjects queried for the presence of sleep apnea. To assess efficacy of replacement therapy using a transdermal system, a serum testosterone level should be obtained.

References

1. Katznelson L, Finkelstein JS, Schoenfeld DA, Rosenthal DI, Anderson EJ, Klibanski A. 1996 Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. *J Clin Endocrinol Metab.* 81:4358-65.
2. Simon D, Charles M, Nahoul K, et al. 1997 Association between plasma total testosterone and cardiovascular risk factors in healthy adult men: the Telecom study. *J Clin Endocrinol Metab.* 82:682-5.
3. Swerdloff RS, Wang C. 1993 Androgen deficiency and aging in men. *West J Med.* 159:579-585.
4. Snyder PJ et al. 1999 Effect of Testosterone Treatment on Body Composition and Muscle Strength in Men Over 65 Years of Age. *J Clin Endocrinol Metab.* 84:2647-53.
5. Wang C et al. 2000 Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in healthy men. *J Clin Endocrinol Metab.* 85:2839-53.