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REVIEW

HOT TOPICS IN MALE INFERTILITY

# Testosterone and male rejuvenation

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## ABSTRACT

Testosterone has long been touted as the panacea for men wishing to restore their vitality, sexuality, and masculinity to that of their youth. While the benefits of testosterone are not mythical, they are definite. In this article we will review the various benefits of testosterone as it pertains to men's health and male infertility.

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Metabolic syndrome (MetS) is a worldwide public-health issue, which in the past has been largely confined to developed countries, yet now involves a growing number of developing countries undergoing industrialization as well. Industrialization has in turn led to the adoption of a Western diet, sedentary lifestyles, and increased obesity. This growing epidemic has garnered increased interest in the clinical application of testosterone therapy (TTh) for the improvement of MetS, weight loss, and muscle mass.

The relationship between testosterone, lean body mass, and athletic performance has long since been recognized. In 1935, Charles D. Kochakian, a pioneer in synthetic hormone research, reported that androgens stimulated the protein anabolic processes, leading to the belief that androgen therapy may restore protein tissue and stimulate muscle growth.[1] Clinical literature from the early 1940s comments on the correlation between androgens and enhanced muscularity, including speculation that the use of exogenous androgens may improve athletic performance.[1] In his 1945 publication of *The Male Hormone,* Paul De Kruif described the powers of TTh as "magical," with the potential to cure a variety of ailments, and is credited for popularizing the use of synthetic testosterone among body builders.[2]

While such claims about testosterone have not ceased, there is now a strong body of contemporary evidence supporting the clinical use of TTh to improve anthropometric parameters. Cross sectional studies demonstrate a proportional decrease in total serum testosterone concentration with age,[3, 4] a finding later corroborated by longitudinal studies.[5] Similarly, lean body mass decreases, while fat mass increases with age.[6] One consequence of these body composition changes that occur with aging is decreased muscle strength.[7] Bhasin *et al.* were among the first to report an improvement in lean body mass, body weight, and cross-sectional size of muscle in their observational study of seven hypogonadal men treated with 10 weeks of intramuscular testosterone enanthate.[8]

In 1999, Snyder *et al.* published the first randomized placebo-controlled double-blind study of men over age 65 who were randomized to transdermal testosterone or placebo for 3 years.[9] Authors selected for hypogonadal men, although admitted that mean baseline testosterone was

367 ng/dL, which is above the lower limit used by most modern studies to define hypogonadism. Subjects treated with placebo experienced no changes, while those in the treatment group benefited from a 3.8% improvement in lean body mass (P<0.001), 13.5% reduction in fat mass (P=0.001) and 6.3% reduction in insulin growth factor-1 (P=0.004). While the magnitude of improvement in lean body mass and insulin growth factor-1 is admittedly small, few would argue that a 13.5% reduction in fat mass is not clinically significant. With regard to muscle strength, the authors of this study chose to measure this parameter using knee extension angular velocity and hand grip as surrogates. Interestingly, they noted decreases in both groups, although not statistically significant compared to baseline or when compared between groups. Potential confounding factors included nutritional intake, physical activity level, exercise regimen, and precision of the tests used to assess muscle strength. Follow-up studies have reported similar improvements in physical performance and lean body mass.[10, 11]

## Insulin sensitivity

In addition to body composition, TTh appears to play a prominent role in the improvement of components of MetS. Strong evidence exists demonstrating that TTh improves insulin sensitivity, lowers blood glucose levels and $HbA_{1c}$ in addition to improving lipid profiles and blood pressure.[12-16] Improvement in lipid profiles includes a decrease in total cholesterol, low-density lipoprotein cholesterol, and triglycerides, while improving high-density lipoprotein.[17-19] A meta-analysis published by Ding *et al.* showed a 42% decreased risk of type 2 diabetes in men with a testosterone level greater than 450 ng/dL,[20] a finding which has subsequently been confirmed by additional studies.[17, 18] Meta-analysis by Corona *et al.* confirms that treatment with TTh reduces insulin resistance and improves $HbA_{1c}$, particularly in younger subjects.[14, 21]

## Weight loss

The benefits of TTh on weight loss are heavily marketed directly to consumers and widely reported in the medical literature. Several large observational studies have established a consistent relationship between TTh in testosterone deficient (TD) men and weight loss.[12, 15, 22] A review of two independent observational registries published by Saad *et al.* identified 411 obese, TD men treated with TTh for up to 8 years.[15] Authors stratified subjects according to severity of obesity using Body Mass Index (BMI) into class I (BMI 30-34.9 kg/m$^2$), class II (BMI 35-39.9 kg/m$^2$), and class III (BMI >40 kg/m$^2$). Class III subjects achieved the greatest weight loss, 23.6% compared to baseline, while classes I and II reported 16.8% and 21.5% weight loss, respectively. While all classes also sustained improvements in waist circumference and BMI, similar trends among classes were noted, with class III subjects experiencing the greatest degree of improvement. Several subsequent studies have confirmed these findings.[14, 15, 23-30] Traish *et al.* recently published the results of their prospective observational study of 656 men, mean age of 60.7 years with a baseline testosterone <350 ng/dL and symptoms of hypogonadism.[12] Of the 656 men enrolled, 360 elected to receive TTh in the form of parenteral testosterone undecanoate 1000 mg every 12 weeks, while the remaining 296 subjects served as controls. At 8 years, subjects in the treatment group experienced a 16.4% weight loss, while those in the control group gained 0.7% compared to baseline (P<0.0001).

Most would agree that TTh is not a substitute for health-promoting lifestyle changes, but its effects may be complementary to diet and exercise. A randomized double-blind placebo-controlled trial published in 2016 sought to investigate the role of 56 weeks of TTh in addition to a very low energy diet in TD men.[31] Of the 82 men who completed the study, those in the TTh group had a greater reduction in fat mass and visceral fat. While both groups achieved approximately 11 kg of weight loss by the end of the study, the weight loss in the TTh group was almost exclusively due to loss of body fat, in contrast to the placebo group that lost fat mass and lean body mass. Although these results are promising, they are not indefinite; at follow-up of 82 weeks there were no longer found differences in body fat or lean body mass between groups, and the TTh group had lost more lean body mass than controls.[32] Interestingly, according to the results of one study, men with severe hypogonadism are more likely to demonstrate sustained weight loss of 3% or more after 1 year while on TTh compared to men with less severe hypogonadism.[33]

On the other hand, TTh has also been applied as a treatment for men who are frail or suffering from chronic illnesses. Treatment of testosterone deficiency in men with human immunodeficiency virus results in similar improvements in libido, fatigue, and muscle mass, renewing interest in its application for human immunodeficiency wasting syndrome.[34, 35] In 2010, Fleishman *et al.* reported the prevalence of testosterone deficiency as high as 48% among men with cancer unrelated to androgens, which

correlated with decreased quality of life and reduced sexual function.[36] A review of male patients with terminal cancer asserts that testosterone deficiency is an independent negative prognostic factor of life expectancy.[37] One report of community-dwelling men who were elderly and undernourished demonstrated reduced hospital admissions for men treated with TTh.[38]

## Bone mineral density

Testosterone and estradiol deficiency are risk factors for non-vertebral fractures and osteoporosis,[39-45] health conditions that coincide with aging. There is an abundance of evidence that TTh increases bone mineral density.[24, 46-48] The evidence supports improved bone mineral density of the lumbar spine, and the hip.[47, 49-54] Recent data suggests that after 1 year of treatment TTh increases bone density and bone strength, particularly in trabecular bone, in contrast to cortical-rich peripheral bone.[47] The mechanism by which TTh exerts its effects are largely mediated by conversion to estradiol.[55-60] A study of 45 testosterone deficient men with osteoporosis who were treated with parenteral testosterone undecanoate for up to six years demonstrated that bone mineral density improved progressively over time.[61] The majority of patients had a dramatic response, and at the end of 6 years only four subjects met criteria for osteoporosis. While the mean age of subjects in this study was relatively young at 53, nearly half of subjects had a diagnosis of Klinefelter's disease yet had a similar response to treatment compared to subjects with testosterone deficiency of a different etiology. A larger observational study of 428 testosterone-deficient men confirmed similar improvements in vertebral and femoral bone mineral density at a follow-up of 8 years.[62]

## Lower urinary tract symptoms

According to preclinical evidence, testosterone plays a vital role in promoting increased bladder capacity by restoring the ratio of smooth muscle to connective tissue,[63] a finding that has been confirmed in clinical studies.[64] This is contradictory to the concern among many providers that testosterone may fuel prostate growth and worsen lower urinary tract symptoms, which is based on historical studies. The European Association of Urology guidelines assert that once a man's lower urinary tract symptoms are appropriately treated, there is no longer a contraindication to TTh.[65] The effect of TTh with both testosterone deficiency and benign prostatic hyperplasia (BPH) appears to be beneficial. An experimental rabbit study by Vignozzi *et al.* demonstrated that testosterone supplementation may exert a protective effect by preventing some features of MetS in their model of high-fat diet-induced prostate fibrosis, hypoxia, and inflammation.[66]

In 2011, Shigehara *et al.* published a randomized controlled clinical trial of 52 men randomized to testosterone enanthate 250 mg every 4 weeks or placebo who were followed for 12 months.[67] Authors noted that the treatment group experienced improvement in maximum flow rate and voided volume ($P<0.05$), while no significant changes were observed in the control group. Neither group experienced a change in post void residual volume. In a larger retrospective study by Ko *et al.* compared 246 men treated with TTh and 17 men who were also treated with TTh but whom had moderate lower urinary tract symptoms and were not on any medical therapy BPH.[68] Mean baseline testosterone was less than 300 ng/dL for both groups, and while baseline characteristics were similar between groups, patients in the group without BPH medication had a higher Qmax than patients on BPH medication, 25 mL/s *versus* 17 mL/s, respectively ($P=0.056$). Subjects not on BPH medication also had a higher baseline post void residual compared to those on BPH medication, 21 mL *versus* 10 mL, respectively, although this value is unlikely to be clinically significant ($P=0.009$). At 1-year follow-up, subjects on TTh and BPH medication had no change in total international prostate symptom score, 13 and 14 pre- and post-TTh, respectively ($P=0.703$). Subjects not on BPH medication, but who were receiving TTh improved slightly from 9 to 7 ($P=0.028$). Further analysis revealed that subjects improved in both voiding and storage symptoms. It is important to note that there was no statistical difference in uroflowmetry parameters in either group on TTh.

The relationship between testosterone deficiency and lower urinary tract symptoms is not merely a function of age, but also of body habitus. Subgroup analysis of men enrolled in the Medical Therapy of Prostatic Symptoms Study evaluated 1896 men who had a testosterone level recorded at baseline. The overall prevalence of testosterone deficiency was 25.7%, which correlated with increasing BMI and was as high as 39.3% in men with a BMI >30 $kg/m^2$.[69]

## Cardiovascular disease

There is now a strong body of observational evidence that TTh decreases risk for overall mortality and myocardial

infarction.[70-75] An observational study by the Veterans Affairs medical center of 1031 TD men revealed that TTh was initiated in 398 men (39%).[71] The mortality rate of men treated was 10.3% compared to 20.7% in untreated men (P<0.0001), and TTh was associated with decreased risk of death on multivariate analysis. A retrospective analysis by Muraleedharan *et al.* of 581 men with type 2 diabetes similarly demonstrated that low testosterone predicts all-cause mortality with a similar reduction in mortality in the patients treated with TTh.[70] A meta-analysis by Araujo *et al.* also concluded that testosterone deficiency was associated with increased risk of all-cause and cardiovascular death, although there was considerable heterogeneity between cohorts making it difficult to rule out underlying health factors.[76] This observation highlights the fact that no studies have definitively established a direct relation between testosterone deficiency and mortality.[77]

Randomized placebo-controlled trials expanded on the beneficial effects of TTh on mortality. English *et al.* reported a reduction in exercise-induced myocardial ischemia in men with chronic stable angina, although lipid profiles did not change with TTh.[78] Malkin *et al.* tested the efficacy of TTh in 76 men with heart failure, and found improvements in exercise capacity and symptoms from baseline compared with placebo (P=0.006).[79]

## Sexual function

Several studies have demonstrated a relationship between erectile dysfunction (ED) and testosterone deficiency.[80-82] Testosterone deficiency is associated with symptoms of decreased sexual desire, ED, and ejaculatory dysfunction. The role of TTh in the management of these symptoms is hotly debated, yet critics would largely agree that the effect of TTh differs with each sexual symptom.

Early research on the benefits of TTh for the improvement of ED produced mixed results. A meta-analysis by Jain *et al.* included 16 studies from 1966 to 1998 focusing on the effects of TTh on ED in men with primary and secondary hypogonadism.[83] Authors concluded that compared to men receiving placebo, men on TTh experienced a greater improvement in ED, particularly in patients with primary testosterone deficiency. A review by Isidori *et al.* of 656 men randomized to TTh or placebo demonstrated that the magnitude of improvement in erectile function was inversely related to baseline serum testosterone.[46] TTh also significantly improved the frequency of sexual thoughts and sexual motivation with, although authors noted that improvement in erectile function was only significant in men with an initial testosterone levels below 361 ng/dL, and did not have an effect in eugonadal men. Another review of 17 randomized placebo-controlled trials including 862 men failed to produce significant and consistent effects on ED and sexual satisfaction in men on TTh, although did produce a large albeit nonsignificant effect on libido.[84] In a meta-analysis by Corona *et al.*, men treated with TTh showed a significant, although modest, improvement of an average of 0.20 points on the IIEF-15 libido domain.[85]

While systematic reviews and meta-analyses have produced conflicting results, several individual studies present a strong case of the application of TTh in for the treatment of ED. A prospective observational study of 261 men diagnosed with late-onset testosterone deficiency who were treated with long-acting intramuscular testosterone undeconate for an average treatment time of 4.25 years reported a 71% improvement in IIEF-5 score, and 31% improvement in AMS score within the first 3 months of treatment with TTh.[86] At the completion of the study, participants showed an improvement in IIEF-5 score to 21.96 from a baseline score of 7.8. Khera *et al.* also showed significant improvement in erectile function in a prospective observational study comparing testosterone to placebo, with Brief Male Sexual Function Inventory scores improving in the erectile function domain from 8.0 to 9.4 at 6 months and was sustained to 12 months.[87] Subjects also saw a significant, though mild, improvement in ejaculatory function. The Testosterone Trials Study also offers support for the use of TTh in the treatment of ED in TD men. This double-blinded, placebo-controlled study included 790 men 65 years and older with a baseline testosterone level less than 275 mg/dL. Authors showed an improvement in erectile function in the TTh group of 2.64 points at 12 months compared to only 1.0 point in the placebo group.[88] Several other studies have produced similar results.[64, 89-92]

Paduch *et al.* published one of the few studies directly examining the effect of TTh on ejaculatory function in their randomized double-blinded placebo-controlled trial, which included 76 men age 26 and older with a baseline testosterone level less than 300 ng/dL.[93] Subjects were randomized to treatment with 60 mg testosterone solution 2% *versus* placebo for a 16-week period, and changes in ejaculatory function were assessed using the Men's Sexual Health Questionnaire (ejaculatory dysfunction questions 1 through 4). No changes in frequency, force, or perceived volume of ejaculation were observed, while measured ejaculate volume did not increase significantly from baseline after TTh.

## Cognitive aging and psychologic health

While a strong body of evidence exists supporting the relationship of depression to ED, the association between depression and testosterone deficiency is less clear.[88, 94-99] Nearly 75% of patients with depression report a low libido,[100, 101] while 41% of men with depressive symptoms reporting moderate to severe ED in the Massachusetts Male Aging Study – double that of their nondepressed counterparts.[102] Notably, the Massachusetts Male Aging Study did not find a correlation between total serum testosterone and depression; these findings were further corroborated by the Baltimore Longitudinal Study of Aging, which also found no association.[103] Rizvi *et al.* concluded that major depressive disorder was a stronger predictor of ED than testosterone deficiency.[104] A review of 856 men age 50 to 89 revealed 17% lower bioavailable testosterone levels in men with depression compared to men who were not depressed independent of age, weight change, and physical activity.[105] Lastly, a larger study of 3987 men age 71 to 89 included 203 men with depression, who had significantly lower total and free testosterone concentrations than nondepressed men.[106] While these were observational studies, there are several randomized placebo-controlled trials examining the efficacy of TTh in TD men for the treatment of depression.

In 2014, Amanatkar *et al.* reported the results of their meta-analysis in which they included only randomized placebo-controlled trials and concluded that TTh had a significant positive impact on mood ($Z$=4.592; P<0.0001).[107] In a longitudinal study of men treated with testosterone gel for 36 months, mood improved compared to baseline, particularly in men younger than age 60.[108] Another observation study of 849 TD men who were also treated with testosterone gel demonstrated clinically meaningful improvements in Patient Health Questionnaire scores (P<0.01) as early as 3 months, while the number of patients with moderately severe to severe symptoms of depression decreased from 17.3% to 2.1% by 12 months.[87] Data from the Testosterone Trials confirmed similar benefits with men age 65 or greater deriving a slight improvement in mood and lower severity of depressive symptoms compared with placebo.[88]

The effect of testosterone deficiency on cognition is another area of interest, yet the heterogeneity in study design, methodology and outcomes measured makes it difficult to interpret these results. The Baltimore Longitudinal Study of Aging revealed an association between improved scores on visual and verbal memory, visuospatial functioning, and visuomotor scanning and a reduced rate of longitudinal decline in visual memory in men with a higher free testosterone index.[103] Though Huang *et al.* failed to demonstrate any treatment differences in cognitive parameters in 308 men randomized to TTh or placebo during a mean follow-up period of 29 months.[109] A recent systematic review by Hua *et al.* concluded that the evidence supporting TTh to improve cognition is promising, particularly in men with mild cognitive impairment or Alzheimer's disease in whom TTh may have a protective effect by slowing the rate of cognitive decline in men who are eugonadal at baseline.[110] The data is inconclusive at this point, and further long term follow-up studies are necessary.

## Impact on fertility

Infertility, defined as the inability to conceive after 12 months of unprotected intercourse, occurs to 15% of couples.[111] Testosterone production is necessary for normal spermatogenesis and is regulated by the hypothalamic-pituitary-gonadal axis vis pulsatile secretion of gonadotropin-releasing hormone.[112] Gonadotropin-releasing hormone stimulates the release of luteinizing hormone from the anterior pituitary, which in turn stimulates Leydig cells in the testicle to produce testosterone. Exogeneous testosterone can lead to atrophy of the germinal epithelium, suppressing spermatogenesis as early as 10 weeks after initiation.[113] Upon cessation of exogeneous testosterone, spermatogenesis will rebound in most men after a period of 6-18 months, potentially requiring up to 24-30 months to return to normal concentrations[114-118] and a remaining 4-10% of men may remain azoospermic.[119]

Urologists are the third leading prescribers of testosterone at 15.25%, preceded by endocrinologists (23.73%) and general practitioners (16.95%).[120] Despite the known detrimental effects that exogeneous testosterone has on spermatogenesis, 25% of urologists surveyed by the American Urological Association reported actually using TTh for the treatment of male infertility.[121] A semen analysis should be performed in men desiring to maintain fertility, prior to the initiation of TTh to rule out idiopathic male factor infertility.

Alternatives to TTh for TD men who desire to maintain fertility include human chorionic gonadotropin (hCG), selective estrogen receptor modulators (SERMs), and aromatase inhibitors (AIs). Intramuscular hCG can be prescribed in addition to TTh to minimize the deleterious effects that exogeneous testosterone has on spermatogenesis. A randomized, controlled trial of 29 healthy men assigned to

testosterone enanthate 200 mg weekly in addition to either intramuscular saline, 125, 250, or 500 IU hCG every other day demonstrated preservation of intratesticular testosterone levels in men who received 500 IU hCG.[112] In addition to preservation of intratesticular testosterone levels, hCG therapy can also maintain spermatogenesis. A retrospective study of 26 TD men treated with TTh and concomitant low-dose hCG demonstrated no differences in semen parameters at 1 year of follow-up and prevented azoospermia while on TTh.[122] Prospective, long term studies are lacking in the literature to determine the qualitative and quantitative benefits of this dual therapy.

SERMs function as an estrogen receptor agonist or antagonist depending on the tissue it is bound to. In the brain SERMs bind to estrogen receptors, antagonizing the effects of estrogen on the hypothalamus and anterior pituitary. Clomiphene citrate is a common SERM used off-label to treat testosterone deficiency and male infertility by increasing luteinizing hormone and follicle stimulating hormone production thus leading to increased production of intratesticular testosterone. Several small studies have demonstrated that clomiphene citrate effectively improves serum testosterone while preserving spermatogenesis.[123-126] Recently, more interest has emerged in using enclomiphene citrate, a potent trans-isomer of clomiphene citrate that inhibits negative feedback from estrogen on the hypothalamic-pituitary axis. A randomized, open-label, phase IIB study demonstrated that after 6 months of treatment with 1% testosterone gel, enclomiphene citrate restored both testosterone and sperm counts at 3 and 6 months.[127] A double-blind, placebo-controlled phase II study randomized 120 TD men to receive either 12.5 mg or 25 mg enclomiphene citrate, 1% testosterone gel, or placebo.[127, 128] Enclomiphene citrate was as effective as 1% testosterone gel in elevating total testosterone levels and maintaining sperm concentrations at a level comparable to the placebo group and higher than those of the TTh group. Larger placebo-controlled studies are needed to verity the efficacy of clomiphene citrate and enclomiphene citrate in improving testosterone levels while preserving semen parameters.

AIs inhibit the testosterone to estrogen converting enzyme aromatase, which is found in the testes, liver, brain, and adipose tissues.[129] Estrogen indirectly inhibits the hypogonadal-pituitary-gonadal axis; therefore, AIs decrease estrogen levels and increase gonadotropin production. Clinically, AIs are used off-label for the treatment of testosterone deficiency and male infertility, with a particular focus on men who are obese or who have a serum testosterone-to-estrogen ratio <10.[130, 131] Due to the increased adipose tissue in obese men, AIs are a logical treatment for testosterone deficiency in this population. While several randomized controlled studies have demonstrated a robust response in serum testosterone, they have failed to demonstrate a difference in body composition, strength, lipid levels, or psychological measures.[132-135] Additional concerns include the effect of deceased circulating estradiol on bone mineral density,[59, 136] sexual function, prevention of abdominal adiposity[137] and insulin sensitivity.[138, 139] AIs can be prescribed concurrently with TTh or hCG to mitigate the side effects of hyperestrogenemia.

## Conclusions

Men turning to TTh as the elusive fountain of youth need to adjust their expectations to avoid disappointment. While the benefits of TTh are not infinite, they are well defined by a strong body of evidence supporting the use of TTh for the treatment of testosterone deficiency. Users may unlock improvements in anthropometric parameters, bone mineral density, cardiovascular health, sexual function and urinary function. Prior to initiating TTh, clinicians should engage their patient in an informed conversation about the risks and benefits of therapy to ensure that they are a proper candidate with realistic expectations.

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