Benefits and Health Implications of Testosterone Therapy in Men With Testosterone Deficiency

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ABSTRACT

Introduction: Testosterone (T) deficiency (TD; hypogonadism) has deleterious effects on men’s health; negatively affects glycometabolic and cardiometabolic functions, body composition, and bone mineral density; contributes to anemia and sexual dysfunction; and lowers quality of life. T therapy (TTh) has been used for the past 8 decades to treat TD, with positive effects on signs and symptoms of TD.

Aim: To summarize the health benefits of TTh in men with TD.

Methods: A comprehensive literature search was carried out using PubMed, articles relevant to TTh were accessed and evaluated, and a comprehensive summary was synthesized.

Main Outcome Measures: Improvements in signs and symptoms of TD reported in observational studies, registries, clinical trials, and meta-analyses were reviewed and summarized.

Results: A large body of evidence provides significant valuable information pertaining to the therapeutic value of TTh in men with TD. TTh in men with TD provides real health benefits for bone mineral density, anemia, sexual function, glycometabolic and cardiometabolic function, and improvements in body composition, anthropometric parameters, and quality of life.

Conclusion: TTh in the physiologic range for men with TD is a safe and effective therapeutic modality and imparts great benefits on men’s health and quality of life. Traish AM. Benefits and Health Implications of Testosterone Therapy in Men With Testosterone Deficiency. Sex Med Rev 2017;X:XXX—XXX.

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Key Words: Testosterone; Testosterone Deficiency; Testosterone Therapy; Sexual Function; Metabolic Syndrome; Diabetes; Bone Mineral Density

INTRODUCTION

Testosterone Is a Metabolic Hormone and Plays a Vital Role in Human Physiology

Testosterone (T) and its metabolite, 5α-dihydrotestosterone, regulate energy metabolism, nitrogen retention, muscle growth and maintenance, inhibit adipogenesis, and modulate male reproductive and sexual function.1—14 T exerts an important metabolic and functional role in many tissues and organs (Figure 1). Among the well-documented physiologic roles of T is its regulation of muscle growth and function and inhibition of adipogenesis.15—24 The role of T in the regulation of bone metabolism, erythropoiesis, endothelial and liver functions, and hair growth is well established.25—55 The wide distribution of androgen receptors in various tissues, including the central nervous system, strongly supports the premise that T plays a key physiologic role in regulating human physiology and that T is an integral hormone in maintaining human health.1—14

Hypogonadism (Testosterone Deficiency)

In an effort to use terminology that promotes accuracy and clarity of T deficiency (TD) and T therapy (TTh), this review has adopted the language recommended by an international expert consensus panel.7 Testosterone deficiency is used instead of the older term hypogonadism. Also, testosterone therapy is used instead of testosterone replacement therapy.7 TD is characterized by low levels of circulating plasma T concomitant with a host of clinical signs and symptoms attributed to decreased physiologic T levels and function.7,8,56—62 TD is a well-established significant medical condition, which has been recognized since 1940.6,7,63,64 TD negatively affects men’s health and is associated with increased body weight, adiposity, waist circumference (WC), insulin resistance (IR), type 2 diabetes mellitus (T2DM), hypertension, inflammation, atherosclerosis and cardiovascular disease (CVD), infertility, erectile dysfunction, and increased incidence of mortality (for
Clinically, TD is divided into primary (testicular dysfunction), secondary (pituitary or hypothalamic failure), or mixed hypogonadism (a combination of testicular failure and pituitary hypothalamic failure). Signs and symptoms associated with TD include sexual dysfunction, depressed mood, decreased motivation, fatigue, and diminished quality of life. Signs and Symptoms of TD

The signs and symptoms of TD encompass several domains (sexual, physical, psychological, and cognitive). Sexual dysfunctions such as decreased or lost sexual desire, diminished nocturnal and morning erections, and erectile dysfunction are often among the most recognized symptoms of TD. Other recognized symptoms of TD include decreased physical vigor, sarcopenia, energy, and motivation, fatigue, depressive mood, and sleep disturbances. In addition, visceral obesity is often observed, and muscle mass and bone mineral density (BMD) are often reduced. Other signs are the presence of smaller testicles, decreased body hair, and gynecomastia. It must be noted that owing to interindividual variability, not all these manifestations must be present simultaneously to determine the signs and symptoms of TD. Several comorbidities are associated with TD. These include metabolic syndrome (MetS), obesity, diabetes, hypertension, and hyperlipidemia. Thus, it is not surprising that there is an association among obesity, MetS, and TD. It is reasonable to suggest that obese men exhibit increased risk of TD and have similar signs and symptoms of TD.

Adverse Effects of TD on Men’s Health

TD is associated with decreased lean body mass (LBM), increased fat mass (FM), increased state of inflammation, MetS, dyslipidemia, IR, adiposity, T2DM, bone loss, and anemia. TD and T2DM are often diagnosed together in the same patient, and men with TD are at a greater risk of developing T2DM. Acute T withdrawal markedly decreases insulin sensitivity in young healthy men with idiopathic hypogonadotropic hypogonadism in the absence of changes in BMI or detectable changes in body composition. Decreased T levels predict IR and incident T2DM in older adults and increased risk of MetS and T2DM even in initially non-obese men. An inverse relation between circulating T levels and inflammatory cytokines has been reported and TTh in men with TD has been shown to rebalance the relation between T and inflammatory cytokines. Men with MetS have increased fasting insulin levels and decreased total T compared with men without MetS. TD is a stronger risk factor in the
development of increased insulin and glucose levels compared with overweight or obesity.100 TD is associated with adverse plasma levels of triglycerides, insulin, and high-density lipoprotein cholesterol in young men.114,115 Low T levels are associated with an unfavorable lipid profile.114–121

TD is associated with increased cardiometabolic risk.101,122–124 Total T levels are inversely associated with risk of CV events, and this association remains significant even after adjustment for traditional CV risk factors.125 Patients with coronary artery disease exhibit significantly lower mean T levels than healthy subjects.126 Men with coronary artery disease have significantly lower levels of free T and free androgen index than controls, even after adjusting for age and BMI.127–130 These findings suggest that men with TD could be at greater risk for coronary atherosclerosis.131 Men with an unfavorable lipid profile have significantly lower levels of total T.114–119 Men with TD exhibit greater intima-media thickness compared with controls and carotid intima-media thickness correlates inversely with T levels after adjustment for age, total cholesterol, BMI, blood pressure, and smoking.91,92,110,121,123,132–137 TD contributes to endothelial damage and dysfunction and androgen therapy enhances endothelial repair and function and increases synthesis and release of endothelial nitric oxide in the vasculature.12,44,45,47,138–147 T levels are inversely associated with systolic blood pressure and increased arterial stiffness.80,148–150 TTh is associated with a significant decrease in blood pressure.151–156 Shores et al14 reported increased mortality in men with decreased T levels compared with men with normal T levels. Men with total T levels in the lowest quartile are 40% more likely to die than those with higher T levels, independent of age, adiposity, and lifestyle.62,79,110,157–162

The relation between TD and sexual function has been recognized for decades and a large number of basic science and clinical studies have documented that androgens are critical for the development of male sexual organs and maintenance of sexual function in men.138,163–178

HEALTH BENEFITS OF TTH IN MEN WITH TD

TTh Increases LBM, Decreases FM, and Improves Body Composition

Clinical trials, meta-analyses, and observational studies suggest that TTh improves anthropometric parameters. TTh in men with medically induced TD results in a dose-dependent increase in muscle mass and a decrease in FM.15,15 It is widely acknowledged that TTh in men with TD increases LBM and decreases FM. Without exception, interventional and observational studies have clearly demonstrated that TTh in men with TD increases LBM, decreases FM, and improves body composition.6,7,9,11,16–18,22,23,27,31,78,154–156,179–187 Large observational registry studies of long-term TTh in men with TD have reported consistent and sustained weight loss and decreased WC and BMI.155,156,196 In a study of 411 obese men with TD, long-term TTh resulted in progressive and sustained weight loss and decreased WC and BMI in all classes of obesity.196 The greater the weight, BMI, and WC at baseline, the more profound the decreases in these parameters were in response to TTh. These findings were further corroborated by a recent study in which long-term TTh was compared in T-treated and non-treated groups.155 The decreases in WC (Figure 2), body weight, and BMI were accompanied by decreases in fasting blood glucose, glycated hemoglobin (HbA1c; Figure 3), blood pressure, total cholesterol, low-density lipoprotein cholesterol, and triglycerides (Figure 4) with a concomitant increase in high-density lipoprotein.155 These findings corroborate those reported previously by others.116,121,154–156,196

TTh in men with TD has been shown to ameliorate frailty and physical decline, such as sarcopenia, muscle strength, and physical function (reviewed in 16–18,179–183,198,201,208,209). In several meta-analyses, Corona et al10–21 reported that TTh was associated with a significant decrease in BMI and FM in uncontrolled and placebo-controlled trials. Although TTh consistently increased muscle mass in all reported studies, there were inconsistencies with regard to improvement in muscle strength and physical function.213–217

Figure 2. Changes in waist circumference in testosterone-treated and untreated (control) groups. Changes (yellow bars) were adjusted for baseline differences between testosterone-treated (green bars) and untreated control (red bars) groups. From T raish AM, Haider A, Haider KS, et al. Long-term testosterone therapy improves cardiometabolic function and reduces risk of cardiovascular disease in men with hypogonadism: a real-life observational registry study setting comparing treated and untreated (control) groups. J Cardiovasc Pharmacol Ther 2017;22:414–433.155 Reprinted with permission.

TTh Ameliorates Components of MetS, Increases Insulin Sensitivity, and Lowers Risk of T2DM

Considerable evidence exists from a large number of studies suggesting that TTh ameliorates components of MetS, improves lipid profiles, lowers blood glucose and Hba1c, improves insulin sensitivity, attenuates inflammation, decreases systolic and diastolic blood pressures, and improves cardiometabolic functions.154,155,184,185,196,218 Meta-analyses


Figure 3. Changes in fasting blood glucose and HbA1c in testosterone-treated and untreated (control) groups. Panel A shows changes in glucose levels (yellow bars) adjusted for baseline differences between testosterone-treated (green bars) and untreated control (red bars) groups. Panel B shows changes in HbA1c (yellow bars) adjusted for baseline differences between testosterone-treated (green bars) and untreated control (red bars) groups. From Traish AM, Haider A, Haider KS, et al. Long-term testosterone therapy improves cardiometabolic function and reduces risk of cardiovascular disease in men with hypogonadism: a real-life observational registry study setting comparing treated and untreated (control) groups. J Cardiovasc Pharmacol Ther 2017;22:414–433. Reprinted with permission.

have shown that TTh decreases total cholesterol, low-density lipoprotein cholesterol, and triglycerides and improves high-density lipoprotein and systolic and diastolic blood pressures.210–212 Higher T levels have been shown to produce a 42% lower risk of T2DM82 and T2DM has been associated with lower total T levels.210,211 In 2 meta-analyses, Corona et al184,185 showed that TTh significantly ameliorates hyperglycemia, HbA1c, and HOMA-IR index.

TTh Improves BMD

Several clinical trials and observational studies have demonstrated that TTh improves BMD.30,186,187,219–226 A significant increase in structural and mechanical properties of trabecular bone in response to TTh has been recently reported.219 The increase in structural and mechanical properties is concomitant with a parallel decrease in bone resorption markers and increases in osteoblastic activity markers are concomitant with a significant increase in BMD.220–222 Normalizing serum T in men with TD produced significant improvement of T scores after 6 years of TTh in men with osteoporosis to such an extent that 40 of 45 men (89%) no longer fulfilled criteria for osteoporosis at the last measurement.221 Furthermore, in a recent study with a follow-up of 8 years, mean T scores of vertebral and femoral BMD increased significantly.228 These findings confirmed that BMD is significantly improved with TTh in men with TD. In several meta-analyses, Corona et al210–212 showed a positive effect of TTh on improving lumbar BMD.

TTh Improves Sexual Function

The link between TD and erectile dysfunction, diminished libido, and lower sexual activity in men with TD is well-established.176,229 Experimental animal studies have unequivocally demonstrated a critical role for androgens in regulating sexual function.230,231 Clinical trials, observational studies, registry studies, and meta-analyses have demonstrated that TTh produces significant improvements in sexual function in men with TD. In placebo-controlled randomized clinical trials and observational studies, significant improvement in sexual function in men with TD has been reported in response to TTh (Figure 5).165,177,197,232–235 These findings strongly support the premise that T is an important physiologic hormone in sexual function. An 8-year study showed that TTh resulted in improvement in mean 5-item (P < .05) and 15-item (P < .05) International Index of Erectile Function (IIEF) scores (Figure 6). All subscale scores of the 5 erectile function domains, including orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction, significantly improved after TTh (P < .05).228 Findings from recent controlled randomized clinical studies have strongly suggested that TTh significantly improves all domains of sexual function.177,232 Because sexual health is an integral element of overall health, and sexual dysfunction is often associated with increased onset of depression, lower mood, and loss of self-esteem, TTh could be an important novel therapeutic approach to improve men’s overall health and quality of life.

TTh Attenuates Lower Urinary Tract Symptoms

Preclinical studies have shown that androgen deprivation decreases bladder capacity and alters tissue histologic architecture, with a decrease in the ratio of smooth muscle to connective tissue. T treatment has been found to improve bladder capacity and restore the ratio of smooth muscle to connective tissue.238 T treatment also has been shown to protect the lower urinary tract from MetS-induced alterations,239,240 and low T has been shown...
to correlate negatively with detrusor pressure at maximal flow and ureteral closure and could promote detrusor obstruction, suggesting that androgens ameliorate lower urinary tract symptoms (LUTS). Clinical studies have demonstrated that obese men with LUTS exhibit lower T levels.241 Chang et al242 reported that TD might contribute to the pathophysiologic mechanism of LUTS and that endogenous T levels correlate negatively with severity of LUTS. A registry study of 999 men with clinically diagnosed TD showed modest positive effects of TTh on LUTS243 with no significant changes in prostate volume. Several studies have reported that TTh attenuates LUTS.244–249 Patients with moderate LUTS who were treated with T for 1 year exhibited improvement in storage and voiding symptoms without clinical progression of benign prostatic hyperplasia or prostate-specific antigen.249 An 8-year study of TTh showed that mean IPSS decreased significantly from 8.54 ± 6.6 at baseline to 6.78 ± 5.44 (P < .05) at the end of the 8-year study period.248 In meta-analyses, Corona et al210–212 reported that significant improvement in the IPSS was noted in response to TTh. These findings support a role of TTh in ameliorating LUTS in men with TD.

TTh Ameliorates Conditions of Anemia

Anemia is a frequent symptom of TD and could contribute to the observed loss of energy and vitality observed in men with TD.250 Approximately 30% of all anemia cases in older patients are of unknown etiology. The prevalence of anemia in older men is significantly higher than in younger men.251–254 Although men with TD are not always diagnosed with anemia, the relation between TD and low hemoglobin is significant, suggesting that low T is one of the causal factors of anemia. Given that anemia has a negative functional outcome in elderly patients,253–256 TTh in men with TD could improve functional recovery in older patients, because it is well established that TTh in men with TD increases their hemoglobin levels.28

A recent randomized placebo-controlled clinical trial found that TTh ameliorated anemia in men who were anemic with or
Benefits of TTh in Decreasing All-Cause and Vascular Mortality

7 observational studies reported that TTh was associated with decreased risk for overall mortality or myocardial infarction (MI). The Veterans Administration clinical database study showed a 39% lower risk for mortality in men with TD who received TTh compared with men with TD who remained untreated. An increased mortality risk (hazard ratio = 2.02, 95% CI = 1.2–3.4) was reported in men with T2DM and TD who did not receive TTh compared with men who received TTh. The relation between TD and increased risk of CV-related mortality was illustrated by a meta-analysis of which 16,184 community-dwelling men with mean follow-up of approximately 10 years. A significant increase in mortality is associated with TD. However, no studies have unequivocally established a direct relation between low T and mortality, but higher T levels have been correlated with lower mortality and the lowest T levels have been associated with increased mortality. All the evidence available to date suggests that low T, free T, and bioavailable T are associated with increased risk of CV-related and all-cause mortality.

TTh Improves Mood and Depressive Symptoms, Energy, and Quality of Life

TD adversely affects mood and depressive symptoms. Wang et al reported significant improvement in positive mood and decrease in negative mood with TTh over a period of 36 months. In a multicenter 12-month observational registry study (N = 849) of men with TD treated with 1% T gel, Patient Health Questionnaire (PHQ-9) scores improved significantly (P < .01) after 3 months of TTh and by 12 months PHQ-9 scores demonstrated clinically meaningful improvement, and the number of patients with moderately severe to severe symptoms decreased from 17.3% to 2.1%, respectively. A modest improvement in global cognition with TTh also was reported. Observational studies of 799 men on TTh showed a 22% decrease in fatigue scores over 6 months. A meta-analysis of 16 randomized trials, Amanatkar et al examined data from 994 subjects and found that TTh had a significant effect on mood in men with TD.

It is well recognized that TD significantly impairs quality of life. TTh promotes improvement of depression, BMD, energy, libido, erectile function, muscle mass, IR, and LUTS. Nian et al reported that TTh improved patients’ health-related quality of life as assessed by decreased Aging Males’ Symptoms (AMS) total score and psychological, somatic, and sexual subscale scores.

DISCUSSION

This review presents findings of the contemporary literature on TTh in men with TD and its positive benefits on men’s health. A large body of evidence is accumulating from...
randomized clinical trials, observational and registry studies, and meta-analyses supporting a therapeutic role for T in men with TD. The most recent data from several randomized placebo-controlled clinical trials have demonstrated that TTh in men with TD provides real health benefits for BMD, anemia, and sexual function.177,219,232

The findings reported in these recent trials showed that TTh produces significant improvement in sexual activity, sexual desire, and erectile function. Furthermore, men receiving TTh reported slightly better mood and lower severity of depressive symptoms.177,232 TTh is effective in correcting sexual dysfunction as demonstrated by improvements in erectile function and libido.177,232 Meta-analyses of pooled studies have demonstrated a strong and favorable response of TTh on sexual function.176,212

Animal studies have defined the critical importance of androgens in maintaining the biochemical and physiologic mechanisms of erectile function.230,231 In addition to improvement in sexual function, TTh has been shown to decrease LUTS and improve bladder functions by increasing bladder capacity and compliance and decreasing detrusor pressure at maximal flow in men with TD.247 These findings are congruent with data reported from a large number of observational and registry studies demonstrating benefits of TTh on sexual function.

One of the important benefits of TTh on men’s health is the improvement in metabolic and glycemic control. TTh in men with TD showed improved metabolic profiles with increased insulin sensitivity, lower blood glucose levels, and lower HbA1c levels.111,112 Data of meta-analyses strongly suggested that TTh lowered HbA1c in placebo-controlled and uncontrolled trials and showed a favorable glycometabolic profile as demonstrated by the significant effect of active treatment on glycemia and insulin sensitivity as detected by HOMA-IR index.230,231 In addition, data from long-term observational studies and meta-analyses demonstrated a positive effect of TTh on LBM and FM with parallel decreases in BMI, WC, and body weight and improvement in overall body composition.112,184–187,191,208,212,279 TTh attenuates components of MetS.154,184,185,211,212 This is of critical importance, because MetS is a risk factor for CVD.

It should be noted that TTh produces improvements in obese and non-obese men with TD. 3 long-term observational studies of TTh in obese men with a follow-up duration of 5 to 8 years demonstrated significant benefits of TTh.156,196,228 In a study in which 255 men with TD treated with TTh were followed for up to 5 years, marked, sustained, and significant weight loss and marked decreases in WC and BMI were observed. A follow-up study with a pooled analysis of 411 men with various classes of obesity and TD found that long-term TTh produced significant and sustained weight loss and marked decreases in WC and BMI.196

Most importantly, TTh improved erectile function as assessed by the IIEF erectile function domain and improvement in quality of life as assessed by the AMS scale. Significant improvements were noted in blood pressure, markers of inflammation, and liver function test enzyme activities, and significant improvement in glycemic control was found as assessed by blood glucose and HbA1c. In addition, improvements in lipid profile were marked. In another long-term study, Permpongkosol et al228 followed patients on TTh for 8 years. They found that TTh in obese men significantly decreased WC, body fat, HbA1c, cholesterol, low-density lipoprotein cholesterol, and International Prostate Symptom Score (IPSS) and improved IIEF score and vertebral and femoral BMD. They lamented that some obesity parameters showed no improvements. It is becoming clear that benefits of TTh in men with TD are noted in non-obese and obese men and in men with diabetes or MetS. The benefits observed in men with various comorbidities suggest that TTh is of benefit to restore physiologic homeostasis in many tissues and organs.

It is well established that men with TD are at higher risk of osteopenia, osteoporosis, and bone fracture.280 TTh in the physiologic range to improve and maintain bone density in men with TD is a rational and logical approach.25,26,187,222 Several studies have demonstrated that TTh increases spinal bone density in men with TD and that bone density is maintained above the fracture threshold.25,281 Most importantly, TTh produces improvement in trabecular and cortical BMD of the spine independent of age and type of hypogonadism.282 The pooled results of a meta-analysis also support a beneficial effect of TTh on lumbar spine bone density. In a recent clinical trial, TTh in men with TD demonstrated significant improvements in volumetric BMD and estimated bone strength.219 These findings support TTh in men with TD to prevent bone loss and maintain BMD and decrease fracture and frailty.

In a recent clinical trial, TTh of men with TD produced improvements in men with anemia of known cause and in men with anemia of unknown cause.25 Most importantly, TTh in men with unexplained anemia resulted in a marked decrease in anemia at 12 months; 58.3% were no longer anemic compared with only 22.2% in the placebo group. The improvement in hemoglobin levels in men with known causes of anemia by restoration of T levels to the physiologic range suggests that TD contributes to anemia. The finding that TTh in men with TD and unexplained anemia increased hemoglobin concentration is a very relevant observation because no other treatment has been reported to correct unexplained anemia in older men.

Several studies have suggested that TD has a negative effect on mood and depressive symptoms.29,322,266–272,283 Men with TD are often bothered with loss of libido or diminished libido, dysphoria, fatigue, and irritability.29,283–285 These symptoms are often diagnosed with those of major depression. TTh in men with TD is associated with improved mood and well-being and decreased fatigue and irritability.29,283,286 In a meta-analysis of 16 randomized trials, Amanatkar et al260 reported that TTh had a significant effect on mood in men with TD. TTh improves depression, energy, libido, and erectile function.268 TTh improves patients’ health-related quality of life in terms of lower AMS total score and psychological, somatic, and sexual subscale
scores. In 2 studies, TTh improved PHQ-9 scores significantly ($P < .01$) after 3 months and by 12 months PHQ-9 scores demonstrated clinically meaningful improvement. Wang et al demonstrated significant improvement in positive mood and decrease in negative mood with TTh over a period of 36 months. Observational studies of 799 men on TTh showed a 22% decrease in fatigue scores over 6 months. TTh in older men resulted in some benefit in mood and depressive symptoms but no benefit in vitality.

Prostate Cancer Risk With TTh

One of the most serious concerns among physicians regarding TTh is the risk of prostate cancer (PCa). Since the landmark study in men with metastatic PCa suggesting that T activates PCa, it was believed that T would cause PCa and would promote its rapid growth. However, this was not demonstrated in a large prospective longitudinal study involving 3,886 men with PCa and 6,448 age-matched controls pooled from multiple individual studies that showed no significant relation between serum androgens and PCa risk. In addition, data from the placebo arm of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, in which 3,255 men underwent prostate biopsy at years 2 and 4 as part of the study protocol, and serum concentrations of T and 5α-dihydrotestosterone obtained at baseline showed no association with PCa risk. Similar findings were reported in the placebo arm of the Prostate Cancer Prevention Trial (PCPT). Specifically, men with the highest serum concentrations of T and 5α-dihydrotestosterone had no greater risk of developing PCa than men with the lowest concentrations. A plethora of clinical data has emerged contradicting the basic premise that T causes prostate cancer.

CVD Risk With TTh

The Testosterone in Older Men with Sarcopenia (TOM) study reported more CV events in men who received T gel than placebo and the study was terminated. This was a 6-month study ($N = 209$) in men at least 65 years old with limited mobility owing to frailty. The T-treated group experienced 23 CV events and the placebo group experienced 5 events. It should be noted that this study included events such as palpitations, syncope, pedal edema, and non-specific electrocardiographic changes, none of which were defined or captured systematically and were included whether they were noted by the study investigators, self-reported, or appeared in outside medical records. Basaria et al concluded that “The lack of a consistent pattern in these events and the small number of overall events suggest the possibility that the differences detected between the two trial groups may have been due to chance alone.” Interestingly, a similar UK study of frail men with limited mobility, Srinivas-Shankar et al reported only 2 major adverse cardiac events (MACEs), which were in the placebo arm.

Vigen et al published a retrospective study of 8,709 men in the Veterans Administration health care system who underwent coronary angiography and had T levels lower than 300 ng/dL. At baseline (date of angiography) none were treated with T. 2 groups were identified: one was composed of men who eventually received a prescription for TTh and the other was composed of men who did not receive a prescription. The initial publication reported that “the absolute rate of adverse events [cumulative for stroke, myocardial infarction (MI), and death] was 25.7% in the T-treated group and 19.9% in the untreated group.” However, after publication it was recognized these results were incorrect, and in fact the T-treated group had demonstrated a lower absolute rate of events, by half. The actual values for absolute rates of events were 10.1% for the T-treated group and 21.2% for the untreated group. The investigators published a correction and “absolute rate of events” was changed to “estimated cumulative probability of events” based on complex and non-validated statistical methods at the time. Months later, they published a second correction reporting a nearly 10% contamination rate of the all-male population by women.

A retrospective analysis from a large insurance database was published by Finkle et al suggesting an increase in non-fatal MI by 36% in the 90 days after a T prescription compared with the 12 months before the prescription. Because no control group was included, it remains impossible to determine whether the men with TD who did not receive a prescription would have had a greater, lower, or identical rate of MI. Studies based on flawed methodology yet claiming increased CVD risk must be viewed with extreme caution. Furthermore, their conclusions should be counterweighed against a considerable body of evidence suggesting that higher levels of serum T and TTh are associated with CV benefits.

A host of real-life observational studies have demonstrated that mortality is decreased by half in men who received TTh compared with untreated men with TD. In a study of 83,010 men with recorded low T levels, all-cause
mortality, MI, and stroke were significantly decreased in men who achieved adequate normalization of T levels compared with men who did not receive TTh or men who did not achieve adequate normalization of T levels. Interestingly, the risk of stroke and MI in men with inadequate TTh was similar to that of untreated men. Wallis et al.\(^{305}\) compared the effects of TTh in 10,311 men with a median follow-up of 5.3 years and compared the CV events recorded with those of 28,029 untreated men (controls). TTh produced a marked decrease in overall mortality (hazard ratio = 0.88, 95% CI = 0.84–0.93) compared with untreated men. Several other studies reported no increased CVD risk or protective effects of T on the vascular system, including a decrease in atrial fibrillation, against a major CVD event.\(^{306–308,311–313}\) Thus, conclusions on CVD risk should be viewed with extreme caution when based on contaminated data or use of non-validated statistical methods\(^{311}\) or meta-analyses that include studies that do not meet the inclusion criteria or studies that were not designed to investigate CVD risk as primary end point\(^{316}\) or comparing 2 groups that have nothing in common.\(^{317}\) The T Trials have provided the strongest pieces of evidence that TTh does not appear to be a risk for CVD.\(^{317,319,232,257,329,330}\) This multicenter, large prospective controlled T trial involving 790 men assigned to T or placebo gel for 1 year, with a second year of monitoring off treatment trial (sponsored by the National Institutes of Health), in men at least 65 years old demonstrated significant benefits for sexual desire, activity, and function and physical activity and mood. With regard to CV events, there were identical numbers (n = 7) of MACEs in the 2 arms. In the second year, there were only 2 events in the T arm and 9 in the placebo arm. Hospitalizations also were fewer in the T arm. Although this study did not provide a definitive statement regarding CV risk, one must recognize that no signal whatsoever of increased CV risk was reported in this large study of a relatively at-risk population (men > 65 years old). The number of MACEs over the 2-year study period was 16 for placebo compared with 9 for the T arm. Although one must remain cautious in drawing conclusions from small numbers of men, it is instructive to recall the powerful negative findings from the TOM study\(^{310}\) in which there were 4 MACEs in the T arm and none in the placebo arm.

A number of studies have suggested a potential association of TTh with CV events.\(^{310,311,317,328}\) However, an emerging body of evidence suggests that the conclusion of such studies is marred by methodologic and interpretational flaws and the CV risk is exaggerated (for review see 6,7,13,14). Several recent observational studies,\(^{2,155}\) clinical trials,\(^{322}\) and meta-analysis\(^{331}\) have not demonstrated an association between TTh and CVD. A recent review by Onasanya et al.\(^{332}\) found that 6 systematic reviews and meta-analyses showed no significant association between exogenous T and CV events. However, 2 of these 6 meta-analyses showed increased risk in subgroup analyses of oral T and men at least 65 years old during their first treatment year. As pointed out by Traish,\(^{13,14}\) only 1 of 9 meta-analyses reviewed showed an association between TTh and CV risk. Cheetham et al.\(^{364}\) described a retrospective cohort study in which 8,808 men who were prescribed T and 35,527 men never received a T prescription (median follow = 3.2 years). The rates of the composite CV end point were 23.9 per 1,000 person-years in the non–T-treated group vs 16.9 per 1,000 person-years in the T-treated group. It was concluded that men with TD who received TTh had a lower risk of CV outcomes over a median follow-up of 3.4 years. These findings support the suggestion that TTh is safe and effective and might be protective.\(^{307}\) Thus, the purported risks of TTh with regard to CVD are not supported by scientific or clinical evidence. Even the most recent reported T trial by Budoff et al.\(^{329}\) which showed some differences in plaque calcification between T-treated and untreated groups, did not report CV events. To this end, TTh seems to be safe and effective for the management of men with TD.

In summary, TTh in the physiologic range in men with TD imparts great benefits to men’s health as demonstrated by the improvement in glycometabolic and cardiometabolic function, improved sexual function, body composition, and BMD, amelioration of anemia, and improvement in overall quality of life.

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