SEXUAL MEDICINE REVIEWS REVIEWS

Controversies in Testosterone Therapy

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ABSTRACT

Introduction: Testosterone prescriptions have increased dramatically in recent years, largely because of changes in expert guidelines. Concerns have been raised that testosterone therapy (TTh) may be associated with an increased incidence of conditions such as cardiovascular (CV) disease, thromboembolic events, obstructive sleep apnea (OSA), benign prostatic hyperplasia (BPH), and prostate cancer (PCa) and also may be a beneficial therapy in the management of prediabetes. As such, considerable debate remains regarding which hypogonadal populations are appropriate candidates for TTh.

Objectives: This systematic review aims to affirm or refute, using the most current evidence, the published concerns surrounding TTh and its potential increased risk of conditions such as CV disease, thromboembolic events, OSA, urolithiasis, BPH, and PCa, as well as its role as a potential tool for managing prediabetes.

Methods: A systematic review of literature surrounding TTh and its impact on increasing risk for the adverse conditions mentioned previously was performed. 62 publications were selected for inclusion based on their relevance to the effects and risks of TTh. Evidence is current through December 2019.

Results: Evidence demonstrates that positive associations exist between TTh and OSA, erythrocytosis, as well as urolithiasis. TTh may potentially be used to treat hypogonadal men with prediabetes. While low testosterone is positively correlated with adverse CV events, TTh in hypogonadal men either has no effect or decreases such risk. TTh is likely not associated with increased risk of PCa incidence or recurrence.

Conclusions: Despite historical beliefs that TTh increases the risk of CV disease, thromboembolic events, BPH, and PCa, recent evidence suggests that TTh conveys less risk than previously perceived. While caution should continue to be exercised, evidence suggests that TTh is a reasonable treatment option in many hypogonadal men who were previously excluded from TTh based on risk factors and prior health histories. **Twitchell DK, Pastuszak AW, Khera M. Controversies in Testosterone Therapy. Sex Med Rev 2020;XX:XXX–XXX.**

Key Words: Testosterone therapy; Testosterone; Cardiovascular; Prostate cancer; Hypogonadism; Diabetes

INTRODUCTION

Prescriptions for testosterone (T) have increased more than 3-fold between 2001 and 2011 across all age groups.[1–3] The cause of this significant increase in T prescriptions is largely attributed to changes in expert guidelines, as low T has been associated with increased cardiovascular (CV) risk and erectile dysfunction has become a part of the routine CV assessment.[4]

While testosterone therapy (TTh) is the primary treatment for hypogonadism, multiple studies[5,6] estimate that up to 25% of men receiving TTh do not have their T levels checked before treatment, almost 50% do not have their T levels checked after treatment, and up to 33% do not meet criteria for T deficiency. These data are further supported by a survey of nearly 250,000 American men who were treated with TTh in which only 72% had T level measured before being prescribed TTh and only 6% had T levels measured after treatment with TTh. These data are concerning because TTh has been reported to increase risk of conditions such as CV disease, myocardial infarction (MI), venous thromboembolism (VTE), erythrocytosis, obstructive sleep apnea (OSA), benign prostatic hyperplasia (BPH), and prostate cancer (PCa).

Following certain data about the potential risks of TTh, the United States Food & Drug Association recently required a label change which indicates that TTh may increase CV risk.[7] There are several potential pathophysiological mechanisms of TTh which could account for this increased risk of CV complications. Platelet thromboxane A2 is regulated by T, which could increase

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platelet aggregation. TTh is often reported to induce erythrocytosis, which can theoretically thicken the blood and make it more difficult to circulate blood through the body. In addition, TTh can worsen OSA and increase vascular cell adhesion molecule 1, which can increase monocyte recruitment. Thus, it is recommended that the benefits of TTh be carefully weighed against the potential risks. Given the rapid increase in T prescriptions worldwide and risk of adverse outcomes, recent debate has focused on which patient populations are appropriate to treat using TTh as well as the likelihood of TTh increasing risk for more serious health conditions.

This systematic review aims to affirm or refute published concerns, based on current data, regarding impacts of TTh on increasing risk for conditions such as CV disease, MI, OSA, VTE, erythrocytosis, BPH, or PCa as well as the potential use of TTh in the management of type 2 diabetes mellitus (T2D) and prediabetes.

MATERIALS AND METHODS

Included articles were identified using the PubMed database. Search criteria included the term "testosterone therapy", and articles published in English from January 1990 to December 2019 were identified. The initial search query yielded 19,310 publications. Of these, 62 articles were selected for review based on whether or not the abstract included TTh and its relationship to risk reduction or enhancement of conditions such as diabetes, CV disease, MI, stroke, VTE, erythrocytosis, OSA, PCa, BPH, or urolithiasis. Emphasis was given to more current publications and meta-analyses as well as to randomized controlled trials (RCTs).

CLINICAL OBJECTIVES OF TTH

TTh is used on-label for treatment of hypogonadism, and off-label in the treatment of a number of conditions.[8,9] A recent meta-analysis[10] reported that there were no particular T formulations which improved quality of life in hypogonadal men more than that of any other T formulation. In both sexes, T is used off-label to increase fat-free mass and aid in treating the effects of protein-wasting conditions such as cancer, burns, trauma, acquired immunodeficiency syndrome, anemia secondary to chronic renal failure, aplastic anemia, and hereditary angioedema.[8] In addition, TTh can aid in the gender transition of transgender men and can serve as a form of male contraceptive.

The desirable effects of TTh in hypogonadal men include increases in libido, muscle strength, fat-free mass, and bone density.[11] The objectives of TTh in transgender males vary somewhat from those in hypogonadal men and include development of secondary sexual characteristics, increased lean mass and strength, decreased fat mass, deepening of the voice, cessation of menses, clitoral enlargement, and reduction of gender dysphoria, perceived stress, anxiety, and depression. Of note, transgender men treated with TTh typically have a decreased risk of breast cancer with or without mastectomy.[12]

CONTROVERSIES IN TTH

Diabetes

Up to 40% of men with T2D and metabolic syndrome (MetS) have hypogonadotropic hypogonadism.[13] According to the Hypogonadism in Males (HIM) Study, men with diabetes had a higher likelihood of having hypogonadism (OR = 2.09) than men without diabetes.[14] As low T may be an independent risk factor for development of T2D, it has been proposed that TTh alters the body composition in a metabolically favorable manner by increasing muscle mass and decreasing adipose tissue.[15] TTh has been used off-label in some cases for management of T2D and prediabetes.

Yassin et al[16] measured hemoglobin A1c (HbA1c) levels in 316 men with concomitant hypogonadism (total T $<$ 12.1 nmol/L) and prediabetes (HbA1c 5.7−6.4%) over 8 years and reported that treating this sample with TTh significantly reduced the likelihood of their conditions progressing to T2D (HbA1c $>$ 6.5%), as compared with controls not treated with TTh. In this sample, 90% of the TTh cohort achieved normal glucose regulation (HbA1c $<$ 5.7%) and had a mean HbA1c decrease of 0.39 ± 0.03% ($P < .0001$), whereas 40.2% of the non-TTh cohort progressed to T2D with a mean HbA1c increase of 0.63 ± 0.1% ($P < .0001$). Of note, mortality rates decreased over the follow-up period in the TTh group as compared to the non-TTh group, 7.4% vs 16.1% ($P < .05$), respectively. This study demonstrates that treating prediabetic hypogonadal men with TTh can significantly improve outcomes in terms of halting diabetes progression and reducing mortality.

However, the findings of Yassin et al[16] go against the findings of previous studies related to the effect of TTh in hypogonadal men with prediabetes. In a small sample of 39 hypogonadal men, Magnussen[17] reported that there was no association between degree of insulin resistance and change in insulin sensitivity during TTh and reported that the potential risks outweighed the potential benefit of using TTh as a treatment for T2D and prediabetes. A recent meta-analysis,[18] including 6 RCTs, stated that no studies have investigated the incidence of PCa, fertility, and CV disease after TTh in men with type 2 diabetes. The authors concluded that TTh could be considered in men with T2D, who are nonresponsive to phosphodiesterase-5 inhibitors or other therapeutic options, but also that the potential risks and benefits of TTh should be carefully considered as the data are very limited in the use of TTh as treatment for T2D.

It remains unclear regarding the extent of the TTh benefit in hypogonadal men whose disease has already progressed to T2D. While there may be some additional benefits of adding TTh to the diabetic pharmacologic regimen in this population, it is unlikely to replace metformin, insulin, and other currently used

pharmacologic therapies for T2D as the primary therapy. Furthermore, it is uncertain whether TTh has greater, or additional, benefit than exercise and healthy diet alone in hypogonadal men with prediabetes, especially since TTh has potentially serious CV outcomes as well as risk for other adverse effects. As such, it is debated whether the potential benefits of TTh outweigh the potential risks in the management of T2D and prediabetes based on current evidence (Table 1).

Erythrocytosis

Part of the controversial nature regarding the impact of TTh on CV outcomes lies in the poor understanding of the clinical significance of certain adverse effects of TTh, such as whether erythrocytosis in men receiving TTh increases the risk for stroke, MI, pulmonary embolism, or other VTE events.

Although the definitions of erythrocytosis vary somewhat by institution, it is typically defined as a hemoglobin level greater than 18.5 g/dL or a hematocrit (Hct) level higher than 52% in men.[19] Calof et al[20] performed a meta-analysis of randomized, placebo-controlled trials and found that of 651 men who were treated with T compared with 433 men treated with placebo, the T-treated men were nearly 4 times as likely to have Hct > 50% as placebo-treated men (OR = 3.69; 95% CI, 1.07 - 2.95). In this analysis, Hct increase was the most frequent adverse event associated with TTh.[20] Fernández-Balsells et al[21] later conducted a meta-analysis of 51 studies investigating the effects of TTh on blood composition and similarly reported that TTh patients are at a higher risk of developing erythrocytosis than the placebo/nonintervention groups. Pastuszak et al[22] retrospectively compared the incidence of erythrocytosis according to the form of T administration and reported that erythrocytosis (Hct > 50%) was more common with injectable T (66.7%) than with T pellets (35.1%) or T gels (12.8%; $P < .0001$).

Although TTh increases the risk of erythrocytosis, the clinical implications, such as its association with VTE, remain debated. While it is logical to assume a connection between erythrocytosis and VTE, there is a paucity of data available showing a link between TTh and VTE. Two recent meta-analyses,[7,23] including both observational studies and RCTs, found that there was no significant association between TTh and VTE. Despite this, several recent individual studies with large sample sizes have indicated otherwise. Sico et al[24] assessed the relationship between Hct levels and poststroke mortality by retrospectively analyzing medical records from 3,965 American Veterans who presented with acute ischemic stroke. The authors reported that patients with Hct levels >48% were at increased risk (OR = 2.9; 95% CI, 1.4 - 6.0) of in-hospital mortality as compared with stroke patients with mid-range Hct levels. However, poststroke mortality at 1 year was significantly lower for patients who presented with Hct > 48% (10.8%) than for patients with Hct < 27% (43.6%; $P < .0001$). This suggests that high Hct levels may provide some protective mortality benefit relative to anemic Hct levels in the posthospital stroke setting, although this association has yet to be proven.

In an attempt to identify whether TTh is associated with an increased risk of VTE independent of erythrocytosis, Walker et al[25] conducted a case-crossover study in 39,622 men with a mean age of 57.4 years in which filled T prescriptions were measured along with the first-time occurrence of VTE. In this cohort, 3,110 men (7.8%) had evidence of hypogonadism. The authors reported that TTh was associated with a higher risk of VTE in men both with (OR = 2.32; 95% CI, 1.97 to 2.74) and without (OR = 2.02; 95% CI, 1.47 to 2.77) hypogonadism. However, current literature demonstrating that erythrocytosis, secondary to TTh, increases the risk of VTE is lacking.

Obstructive Sleep Apnea

Liu et al[26] analyzed the effect of TTh on sleep and breathing in a small double-blind, placebo-controlled, RCT, in which 17 men older than 60 years received either 3 intramuscular (IM) T injections (500 mg, 250 mg, and 250 mg) or placebo followed by the T regimen after 8 weeks of washout. The authors reported that T treatment reduced total time slept by ~1 h/night, increased the duration of hypoxemia by ~5 min/night, and disrupted breathing during sleep (total and nonrapid eye movement respiratory disturbance indices both increased by ~7 events per hour) (all $P < .05$). The authors concluded that short-term administration of high-dose T shortens sleep and worsens OSA in older men, but does not alter physical, mental, or metabolic function. These changes did not appear to be due to upper airway narrowing.

Killick et al[27] also analyzed the association between T and breathing quality during sleep in a randomized, double-blind, placebo-controlled, parallel group trial in which 21 obese men received either 3 IM 1000-mg T undecanoate injections or placebo. Awake chemoreflex testing was performed at baseline, during week 6, and after completion of week 18. The authors reported that TTh worsened sleep-disordered breathing at 6-7 weeks, but not at 18 weeks, citing changes in ventilatory chemoreflexes as a potential cause. The data from these studies[26,27] provide supporting evidence that there is a positive association between TTh and development of OSA.

Cignarelli et al[28] conducted a meta-analysis of 12 studies which included 388 men who were either eugonadal or hypogonadal and had OSA to assess the effect of continuous positive airway pressure (CPAP) utilization on T levels in this cohort. The authors reported that CPAP use was not associated with a change is serum total T levels (mean difference = 1.08 nmol/L; 95% CI, -0.48 to 2.64; $P = .18$). Despite the observation that serum T levels appeared to increase more in hypogonadal than in eugonadal men, these increases also failed to reach statistical significance. Thus, while TTh may be associated with increased risk of OSA, treatment of OSA via CPAP does not appear to be associated with subsequent increases in serum T levels.

Table 1. Primary evidence regarding effects of low testosterone and testosterone therapy in men with prediabetes/diabetes

Authorship	Year	Sample size	Study type	Significant findings
Mullligan et al[14]	2006	2,162	Multi-center	Men with diabetes are twice as likely to experience hypogonadism than men without diabetes.
Magnussen et al[17]	2017	43	RCT	TTh does not impact insulin resistance or sensitivity; risks of TTh do not outweigh benefits for treating prediabetes and T2D.
Algeffari et al[18]	2018	587	Meta-analysis	TTh can be considered in men with T2D, but the risks and benefits should be carefully weighed.
Yassin et al[16]	2019	316	Observational	TTh halted progression, and even moderately reversed, the course of disease in hypogonadal men with prediabetes.
Hackett[13]	2019	37 studies	Review	Up to 40% of men with T2D & metabolic syndrome have hypogonadotropic hypogonadism.

TTh = testosterone therapy; T2D = type 2 diabetes mellitus; RCT = randomized controlled trial

CV Events

In 2011, 3 independent meta-analyses[29–31] investigated the association between low T levels and incident CV diseases and CV mortality. Of these analyses, 2 reported a significant correlation between low T levels and increased CV-associated mortality,[29,30] while the other analysis reported no such correlation.[31] A more recent meta-analysis[32] of 37 observational studies including 43,041 subjects reported that low endogenous T was predictive of overall mortality and CV mortality with a OR = 1.26 (CI, 1.17-1.36) and OR = 1.54 (CI, 1.25-1.89), respectively. Another recent meta-analysis[33] by the same authors was conducted using 15 pharmaco-epidemiological studies and 93 RCTs. The analysis of pharmaco-epidemiological studies documented that TTh reduces overall mortality and CV morbidity. Conversely, in the RCT analyses, TTh had no clear effect, either beneficial or detrimental, on the incidence of CV events. A separate meta-analysis[10] of 51 studies reported that TTh in hypogonadal men improved quality of life, depression, libido, and erectile function, with no increase in CV death or other major adverse events, such as MI or stroke. Thus, these

Table 2. Primary evidence regarding effects of low testosterone & testosterone therapy on cardiovascular disease & mortality risk

Authorship	Year	Sample size	Study type	Significant findings
Araujo et al[29]	2011	16,184	Meta-analysis	Low endogenous T levels are associated with increased risk of all-cause and CVD death.
Ruige et al[31]	2011	19 studies	Meta-analysis	No association between endogenous T level and risk for CVD in middle-aged men. In elderly men, T may weakly protect against CVD.
Corona et al[30]	2011	70 studies	Meta-analysis	Hypogonadism correlates with increased risk of CVD and mortality,; this risk is reduced by TTh.
Etminan et al[34]	2015	150,330	Observational	Chronic or previous TTh is not associated with an increased risk of MI.
Anderson et al[35]	2016	4,736	Prospective cohort	Normalization of T levels in hypogonadal men may decrease risk of MI, but increases risk of stroke.
Elliott et al[10]	2017	138 studies	Meta-analysis	TTh in hypogonadal men improves quality of life, depression, and sexual function without significantly increasing adverse events.
Cheetham et al[36]	2017	44,335	Retrospective Cohort	Hypogonadal men treated with TTh have decreased risk of both MI and stroke.
Cole et al[37]	2018	6,844	Retrospective Cohort	Hypogonadal men treated with TTh have mildly decreased CVD risk.
Corona et al[32]	2018	43,041	Meta-analysis	Low endogenous T is predictive of overall mortality and CV mortality.
Corona et al[33]	2018	8,479	Meta-analysis	TTh reduces overall mortality and CVD morbidity in hypogonadal men.

CVD = cardiovascular disease; MI = myocardial infarction; T = testosterone; TTh = testosterone therapy

Table 3. Primary evidence regarding effects of testosterone therapy on prostate-specific antigen levels, prostate cancer risk, and prostate cancer recurrence

Authorship	Year	Sample size	Study type	Significant findings
Khera et al[53]	2009	57	Retrospective Cohort	TTh increased serum T levels in hypogonadal men without an increase in PSA levels or risk of PCa recurrence.
Pastuszak et al[54]	2013	152	Observational	Despite a significant increase in PSA levels following 28 months of TTh, PCa risk did not increase.
Rastrelli et al[43]	2013	2,967	Observational	More than half of the severely hypogonadal subjects had PSA < 0.65 ng/mL.
Pastuszak et al[55]	2015	98	Multi-center	TTh in men following treatment of PCa with radiation therapy had a low rate of biochemical recurrence.
Kang et al[45]	2015	1,124	Meta-analysis	TTh does not increase PSA levels in men being treated for hypogonadism.
Elzanty et al[44]	2016	119	Observational	After adjusted multivariate analysis, a positive association was detected between T and PSA levels.
Boyle et al[42]	2016	20,227	Meta-analysis	TTh for symptomatic hypogonadism does not appear to increase PSA levels nor the risk of developing PCa.
Loeb et al[47]	2017	1,662	Nested Case-control	TTh is not associated with an overall increase in PCa risk.
Teply et al[52]	2018	30	Clinical Trial	30% of metastatic, castration-resistant PCa subjects experienced a 50% decline in PSA levels following BAT therapy.
Cunningham et al[46]	2019	790	RCT	A small, yet significant, increase in PSA levels was noted following 12 months of TTh.
Zhang et al[48]	2019	776	Observational	TTh significantly reduces the risk of PCa associated with T deficiency at a young age.
Santella et al[49]	2019	12,779	Prospective Cohort	TTh is not associated with an increased risk of PCa as compared to absence of TTh.

BAT = bipolar androgen therapy; PCa = prostate cancer; PSA = prostate-specific antigen; RCT = randomized controlled trial; T = testosterone; TTh = testosterone therapy.

data from the different meta-analyses suggest that low T may increase risk of CV events, but TTh in hypogonadal men either has no effect or even potentially decreases CV morbidity and mortality risks.

There are many recently published individual studies examining the effect of TTh on the risk of adverse CV events, such as MI and stroke. Etminan et al[34] conducted a case-control study of 934,283 men aged 45 to 80 years and identified 30,066 MI cases and 120,264 corresponding controls. The authors reported that the current use of TTh was not associated with an increased risk of MI (risk ratio, 1.01; 95% CI, 0.89 - 1.16) and that history of previous TTh also demonstrated no association. However, the authors observed an increased risk of MI in first-time users of TTh (risk ratio, 1.41; 95% CI, 1.06 - 1.87). In addition, Anderson et al[35] compared the prevalence of adverse CV events in 4,736 hypogonadal men receiving TTh and grouped subjects according to serum T levels after at least 3 years of TTh. Comparing men with serum T > 742 ng/dl to men with serum T < 212 ng/dl, the authors reported multivariable hazard ratios (HR) at 1 year of 0.70 (95% CI, 0.27 - 1.78) for MI and 2.40 (95% CI, 0.81 - 7.09) for stroke. These data suggest that normalization of serum T levels through TTh may *decrease* risk of MI but likely *increases* risk of stroke. Cheetham et al[36] later conducted a retrospective cohort study of 8,808 hypogonadal men treated with TTh and 35,527 hypogonadal men not treated with TTh over a median follow-up of 3.4 years and reported a HR of 0.67 (95% CI, 0.62 - 0.73) for MI and 0.72 (95% CI, 0.62 - 0.84) for combined stroke events (stroke and transient ischemic attack) in men receiving TTh. Data from this study suggest that men with androgen deficiency who are treated with TTh have a *decreased* risk of both MI and stroke.

Cole et al[37] analyzed the link between TTh and incidence of thromboembolism, CV disease (stroke, coronary artery disease and heart failure) and OSA in 3,422 current and former military servicemen. Subjects who received TTh were matched on a 1:1 basis for age and comorbidities to men without a prescription for TTh. The authors reported no significant difference in event-free survival for VTE ($P = .239$). However, a small, yet significant *decrease* in CV risk was observed in men on TTh ($P = .004$), primarily due to a decreased incidence of coronary artery disease in this group ($P = .008$). This study adds to the evidence suggesting that the CV risk associated with TTh may be lower than that previously observed. By contrast, the 2-year absolute risk of OSA was higher in the TTh group (16.5%) than in the controls (12.7%) ($P < .001$).

Recent data (Table 2) suggest relative consensus that TTh has either no increased risk or even potentially a *decreased* risk of MI. However, data regarding the impact of TTh on stroke risk are less congruent, preventing a definitive conclusion at this time. Altogether, the evidence suggests that physicians should

Table 4. Primary evidence regarding genitourinary impacts of testosterone therapy

Authorship	Year	Sample size	Study type	Significant findings
Kristal et al[61]	2008	708	RCT	Serum T levels >593.7 ng/dl are associated with a reduced BPH risk.
Bhasin et al[59]	2012	102	RCT	Prostate volume and PSA levels did not change significantly in response to any T concentration of TTh cohort as compared with placebo cohort.
Vignozzi et al[62]	2012	66 mice	RCT	TTh normalized elevated mice prostate inflammatory markers and signs of histologic prostate damage.
Lee et al[60]	2014	2,308	Cross-sectional	TTh is not clearly correlated with development of BPH in middle-aged eugonadal men.
McClintock et al[56]	2019	53,172	Matched-cohort	TTh is positively associated with new-onset urolithiasis.

BPH = benign prostatic hyperplasia; PSA = prostate-specific antigen; RCT = randomized controlled trial; T = testosterone; TTh = testosterone therapy.

cautiously consider extending TTh to patients with low serum T levels who are at increased risk of CV complications.

It is worthy to mention that there is a current phase 4 clinical trial (NCT03518034),[38] referred to as the Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy ResponSE in Hypogonadal Men (TRAVERSE) Study, across 389 centers of the United States and Puerto Rico which attempts to more definitively determine whether, and to what degree, TTh impacts risk of incurring a major CV event, defined as nonfatal stroke or MI. The study randomizes 6,000 middle-aged/elderly male hypogonadal subjects (serum T < 300 ng/dL) to either topical TTh or placebo and assesses the mean time between T administration and initial major CV event over 60 months with an expected completion date of July 2022.

T Effects on the Prostate

Historically, TTh has been reported to increase serum acid phosphatase levels,[39,40] which were the primary blood marker for PCa before the introduction of prostate-specific antigen (PSA).[41] Concern exists that exogenous T may stimulate prostate cell growth[42] and increase the risk of developing PCa or result in more rapid progression of current PCa and recurrence of previously treated PCa. However, recent data (Table 3) largely refute this concern.

Rastrelli et al[43] analyzed PSA levels as a predictor of severe hypogonadism, defined as T < 8 nmol/L, in a sample of 2,967 men with PSA levels < 4 ng/ml and reported that more than half (n = 141, 4.8%) of the severely hypogonadal subjects had PSA < 0.65 ng/ml. The authors proposed that PSA values are potential markers of T concentrations and may provide insights into not only the circulating levels of T but also of its active fractions. Elzanaty et al[44] later reported that after adjusted multivariate analysis, a positive association was detected between T and PSA levels in middle-aged, healthy men, which supports the work from Rastrelli et al.[43]

Kang and Li[45] performed a meta-analysis of 15 studies incorporating 739 TTh patients who were treated with TTh for 3-12 months and 385 non-TTh controls and reported that rates of elevated PSA levels after TTh were similar to those in controls

Table 5. Differences in American Urological Association & Endocrine Society testosterone therapy recommendations

Recommendation topic	American Urological Association	Endocrine Society
Contraindications of testosterone therapy	- History of CV disease within past 6 months - Desire to have children - No significant clinical improvement despite adequate trial of TTh	- History of CV disease within past 6 months - Desire to have children - History of prostate cancer - History of uncontrolled heart failure - History of myocardial infarction - History of stroke - History of male breast cancer - Severe untreated obstructive sleep apnea - Hematocrit > 48%
History of cardiovascular disease	- Low T increases CV disease risk - TTh is not recommended if recent history of CV disease	- Insufficient evidence linking TTh to CV risk
History of prostate cancer	- Consider TTh on a case-by-case basis	- Should not use TTh if history of prostate cancer - Should not use TTh if PSA > 4 ng/mL or > 3 ng/mL in high-risk patients - Should not use TTh if palpable prostate nodule or induration

CV = cardiovascular; PSA = prostate-specific antigen; T = testosterone; TTh = testosterone therapy.

(OR = 1.02; 95% CI, 0.48 - 2.20). The authors concluded that TTh does not increase PSA levels in men being treated for hypogonadism, yet noted a modest increase in PSA levels when TTh was administered IM. Boyle et al[42] conducted a meta-analysis of 37 studies analyzing the effects of TTh on PSA levels as well as its effects on risk of developing PCa. The authors reported the summary difference in PSA levels following TTh as 0.10 ng/ml (95% CI: -0.28 - 0.48) and the summary relative risk of developing PCa following TTh as 0.87 (95% CI, 0.30 - 2.50) based on 20 PCa cases. The authors thus concluded that TTh for symptomatic hypogonadism does not appear to increase PSA levels nor the risk of developing PCa. However, Cunningham et al[46] reported in a study of 790 hypogonadal men aged 65 years and older with average T levels $\leq$ 275 ng/dl that PSA levels demonstrated a small, yet substantially greater, increase after 12 months of TTh relative to placebo controls. In this cohort, mean serum PSA levels in the TTh group increased by 0.47 ng/ml compared with a mean increase of 0.06 ng/ml in the placebo group. This finding, combined with the data from the meta-analyses, suggests that PSA levels in hypogonadal men treated with TTh may initially increase but then plateau with time once T levels normalize.

Loeb et al[47] analyzed data from 284 men with PCa and 1,378 control cases which had filled prescriptions for TTh and reported no association between TTh and overall PCa risk (OR = 1.03; 95% CI, 0.90 to 1.17). However, men who received TTh had mildly increased risk of developing low- or intermediate-risk PCa (Gleason score $\leq$ 7; OR = 1.35; 95% CI: 1.16 to 1.56) as well as a *lower risk* of aggressive PCa (Gleason score $\geq$ 8; OR = 0.50; 95% CI, 0.37 to 0.67). The authors attribute the increase in lower-risk PCa to detection bias and the decreased risk of aggressive PCa as a novel finding which merits further investigation.

Zhang et al[48] analyzed data in 776 younger hypogonadal men to study the relationship between TTh and PCa and reported that TTh *significantly reduces* the risk of PCa associated with T deficiency at a young age (P = .00087). The authors proposed that this reduction in risk may be attributable to the ability of TTh to maintain serum T levels within the normal range. In addition, Santella et al[49] recently reviewed health data from 12,779 men treated with TTh for late-onset hypogonadism and reported that TTh was not associated (HR = 0.97; 95% CI, 0.71 to 1.32) with an increased risk of PCa in this population as compared with those subjects who did not have T supplementation.

This new body of evidence indicates that TTh is likely not associated with an increased risk of developing PCa and may perhaps even *reduce* the risk of developing PCa in men with low serum T levels. Although treatment of men with locally advanced or metastatic disease remains controversial,[50] a new approach[51] of using androgen deprivation therapy (ADT) combined with alternating injections of relatively high doses of T, termed bipolar androgen therapy (BAT), may be more effective in treating PCa than ADT alone. The concept behind BAT is that the PCa cells which survive the low-T environment of ADT are susceptible to damage from shock of alternating low and high T levels in semi-rapid succession.[51] Teply et al[52] conducted a phase 2 trial in 30 men with histologically and radiographically confirmed metastatic castration-resistant PCa who had increasing PSA levels after discontinuation of a progressive course of enzalutamide, an androgen receptor inhibitor used to treat metastatic PCa. The authors administered IM testosterone cypionate 400 mg every 28 days and continued luteinizing hormone agonist therapy and then rechallenged the men with daily doses of 160 mg of oral enzalutamide. The authors reported that 9 out of 30 subjects (30%; 95% CI, 15-49; $P < .0001$) achieved a 50% decline in PSA levels after BAT and that most subjects experienced a transient resensitization to enzalutamide after BAT. More research is needed to address how to prolong the resensitization to enzalutamide after BAT as well as identify the ideal treatment schedule of BAT, but these data show promise in more effectively treating castration-resistant PCa.

While TTh may not increase the risk of developing PCa, there have long been concerns that TTh could lead to recurrence of former PCa which has been treated and is presently clinically silent. Over the past decade, evidence has mounted which refutes this concern. In 2009, Khera et al[53] analyzed PSA levels in 57 men with a mean age of 64 years who had received TTh for an average of 36 months after radical prostatectomy. The authors reported after a mean 13 months of follow-up that mean serum T levels increased from baseline 255 ng/dl to 459 ng/dl after TTh without an increase in PSA levels and with no increased risk of biochemical PSA recurrence. In 2013, Pastuszak et al[54] performed a related study of 103 hypogonadal men with PCa, median age 61 years, who were treated with TTh after prostatectomy compared to 49 nonhypogonadal men with PCa treated with prostatectomy without TTh. The authors reported that after a median follow-up of 27.5 months, a significant increase in both T levels and PSA levels were noted in the TTh cohort, with 4 and 8 cases of cancer recurrence being observed in the treatment and reference groups, respectively. The authors concluded that despite the increase in PSA levels after TTh, PCa recurrence risk did not increase. In 2015, Pastuszak et al[55] assessed the association of TTh with PCa recurrence in 98 men with a median age of 70 years who were treated for PCa with radiation therapy. After a median 40.8 months of follow-up, the authors reported that median serum T levels increased from 209 ng/dl at baseline to a median of 420 ng/dl and that PSA levels showed a nonsignificant increase from 0.08 ng/ml at baseline to 0.09 ng/ml. In this sample, 6 men (6.1%) met criteria for biochemical recurrence. Thus, the authors concluded that TTh in men after treatment of PCa with radiation therapy had a low rate of biochemical recurrence. These studies collectively provide evidence that risk of PCa recurrence with TTh is likely much lower than once feared.

Genitourinary Impacts of T

A recent study[56] has identified TTh as having a positive association with urolithiasis, which represents a novel finding in the literature surrounding TTh. McClintock et al[56] conducted a population-based matched cohort study with 26,586 pairs of hypogonadal men treated with TTh and non-TTh controls, all without history of urolithiasis, to determine the effect of TTh on risk of urolithiasis in hypogonadal men. The authors reported 659 stone-related events at 2 years in the TTh group and 482 stone-related events in the non-TTh group ($P < .0001$). This difference was observed for topical ($P < .0001$) and injection ($P = .004$) therapy-type subgroups of T, but not for pellet T ($P = .27$). A later study by Sueksakit and Thongboonkerd[57] identified that renal tubular cells treated with T significantly increased the number of calcium oxalate monohydrate crystals which adhered to the cell surface. However, the authors observed that while T treatment increased calcium oxalate monohydrate crystallization and tubular cell adhesion, it did not affect crystal growth or aggregation. It was reported that these crystals were completely abolished through administration of finasteride, a 5α-reductase inhibitor. These studies[56,57] indicate that TTh increases development of urolithiasis; however, more studies are needed to confirm these novel findings.

As the prostate gland is responsive to androgens,[58] there has also been concern that TTh may exacerbate inflammatory conditions, such as BPH. However, recent evidence (Table 4) suggests a different relationship. Bhasin et al[59] randomized 102 healthy men aged 18 to 50 years with normal T levels to either a 20-week regimen of T of varying doses ranging from subphysiologic to supraphysiologic doses or placebo and reported that changes in prostate volume and PSA levels were not significantly related to either T dose or T concentration and did not differ significantly from the placebo group. Lee et al[60] assessed whether T levels are related to prevalence of BPH by conducting a cross-sectional study in 2,308 eugonadal men with a median age and total serum T level of 49 years and 5.37 ng/ml, respectively. The authors reported that there was no significant correlation between T levels and BPH.

In addition, Kristal et al[61] conducted a case-control study of 708 men, aged 55 years and older, who were treated for BPH matched with 709 controls without BPH and reported that serum T levels > 593.7 ng/dl were associated with a *reduced* BPH risk (OR = 0.67; 95% CI, 0.48 to 0.93). Furthermore, Vignozzi et al[62] induced MetS, which parallels the effects of BPH, in male rabbits by feeding them a high-fat diet for 12 weeks. The authors noted that only treatment with T normalized all the high-fat diet–induced prostate inflammatory marker elevations and signs of histologic prostatic damage and concluded that T protects rabbit prostate from MetS-induced prostatic hypoxia, fibrosis, and inflammation. More data from animal and human trials are needed to confirm these findings.

Current Clinical Guidelines

The American Urological Association (AUA) and Endocrine Society (ES) have similar recommendations pertaining to appropriate usage of TTh. However, there are several important differences (Table 5) in their recommendations which reflect the considerations surrounding the controversies related to TTh. The AUA and ES agree on several contraindications for TTh including the desire to have children and history of a CV event within the past 6 months. However, the AUA adds no clinical improvement despite adequate trial of TTh to the list of contraindications and the ES adds history of PCa, uncontrolled heart failure, MI, stroke, male breast cancer, severe untreated OSA, as well as Hct greater than 48% as contraindications.[63]

The AUA recommends TTh be administered to patients with a history of PCa on a case-by-case basis while the ES recommends against the use of TTh in patients with a history of PCa or PSA levels above 4 ng/ml. The AUA states that low T increases CV disease risk and recommends against TTh if patients have a recent history of CV events. The ES states that there is insufficient evidence linking TTh to CV risk but recommends against TTh if baseline Hct levels are greater than 48%.[63]

CONCLUSION

TTh is the mainstay in hypogonadal men. Concerns regarding a potential increased risk of CV disease, MI, thromboembolic events, OSA, BPH, and the development and recurrence of PCa in men on TTh continue to be debated, although evidence suggests that TTh has a smaller impact on these conditions than initially perceived. In addition, TTh may potentially be used as an adjunct therapy in hypogonadal men with prediabetes, although data are somewhat limited on this topic and are not entirely congruent between studies.

Significant evidence now exists to suggest that TTh does not increase the risk, and may even *decrease* risk, of MI, BPH, and development of PCa. While TTh increases the risk of erythrocytosis, the clinical implications of erythrocytosis remain unclear. Recent evidence suggests that TTh is positively associated with VTE both in hypogonadal and eugonadal men, although more evidence is needed to confirm these findings. There appears to be a positive association between TTh and increased risk of OSA. Also, a recent novel association has been identified between TTh and the development of calcium oxalate urolithiasis, although additional work is needed to confirm this finding.

It appears that in many cases, TTh may be less harmful than once feared and can be more frequently used to treat hypogonadal men who were previously excluded from such therapy. However, some caution should still be exercised when administering TTh in certain populations as there is still a potential measure of increased risk for adverse outcomes.

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