Adverse effects of testosterone replacement therapy: an update on the evidence and controversy

Ther Adv Drug Saf
2014, Vol. 5(5) 190–200
DOI: 10.1177/2042098614548680

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***Abstract*:** Testosterone replacement therapy (TRT) has been used in millions of men worldwide to treat diminished libido and erectile dysfunction, and to improve strength and physical function. The estimated likelihood of adverse effects of long-term TRT is still essentially unknown, as overall high-quality evidence based upon prospective randomized trials to recommend for or against its use in most men with testosterone deficiency (TD) is lacking. Evidence to suggest that TRT increases cardiovascular morbidity and mortality risks is poor, as results vary across study populations and their baseline comorbidities. While TRT may increase serum prostate-specific antigen levels in some men, it often remains within clinically acceptable ranges, and has not been shown to increase the risk of prostate cancer. Current literature supports that TRT does not substantially worsen lower urinary tract symptoms, and may actually improve symptoms in some men. Limited evidence suggests that TRT may initially worsen obstructive sleep apnea in some men, but that this is not a longstanding effect. TRT may result in erythrocytosis in some men, however long-term studies have not reported significant adverse events (e.g. cerebrovascular accident, vascular occlusive events, venous thromboembolisms). Future research will require dedicated focus on evaluation of large, multiethnic cohorts of men through prospective trials to better elucidate both risk and hazard ratios of TRT as it relates to cardiovascular disease, prostate cancer, lower urinary tract symptoms, obstructive sleep apnea, erythrocytosis, and other to-be-determined theoretical risks in men both with and without cardiovascular risk equivalents.

Keywords: testosterone, adverse effects, cardiovascular risk, prostate-specific antigen, mortality

Introduction

Testosterone deficiency (TD) in men has garnered substantial attention over the last decade due to an increased awareness by medical providers, increased direct-to-consumer advertising in the media, and the increasing age of the male population. Testosterone replacement therapy (TRT) has been used in millions of men worldwide to treat diminished libido and erectile dysfunction, and to improve strength and physical function [Shabsigh 2003; Page *et al.* 2005]. Between 2001 and 2011, prescriptions for TRT among men 40 years of age or older in the US increased more than threefold, from 0.81% in 2001 to 2.91% in 2011 [Baillargeon *et al.* 2013].

The trend of declining serum testosterone (T) in aging men has been well documented. The Massachusetts Male Aging Study, a community-based study of 3339 random men aged 40–79 years reported an annual decline in total and free T of 0.8–1.6% and 1.7–2.8% per year respectively in men over 40 years of age [Mohr *et al.* 2005]. Comparatively, the European Male Aging Study, a population-based prospective cohort study of 3369 men aged 40–79 years from the general population of eight European countries, reported an age-adjusted annual decline in total T of 0.4% per year [Wu *et al.* 2008]. Furthermore, the Hypogonadism In Men study, an observational study of 2162 men in primary care practices at least 45 years of age, reported a prevalence

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of hypogonadism of 38.7% [Mulligan *et al.* 2006]. The Boston Area Community Health Survey estimated a crude prevalence of symptomatic androgen deficiency at 5.6% [Araujo *et al.* 2007], while it was estimated that only 12% of symptomatic men are treated [Hall *et al.* 2008].

The 2010 Endocrine Society Guidelines define androgen deficiency as signs and symptoms of low T (e.g. decreased libido, decreased erections, decreased energy, decreased physical stamina, decreased lean muscle mass) in the setting of unequivocally low morning serum T levels of less than 300 ng/dl on two separate occasions [Bhasin *et al.* 2010]. TRT has been shown to increase serum T to physiologic levels, improve libido, improve erectile dysfunction, improve overall sexual function, increase energy, improve mood, increase bone mineral density, decrease body fat mass, and increase lean body muscle mass [Bhasin *et al.* 2010; Corona *et al.* 2013]. Currently, there are a variety of widely available T formulations, including topical gels and patches, intramuscular injections, subcutaneous pellets, and oral/buccal formulations that provide clinicians and male patients the opportunity to personalize replacement therapy.

TD has been identified concomitantly with many comorbid health conditions in men, including cardiovascular disease (CVD), metabolic syndrome, diabetes mellitus, hypertension, and dyslipidemia, while positing an associative relationship. The exact physiologic mechanisms behind these proposed relationships remains to be determined, and has led to much speculation. It has also been proposed that TD may be a direct cause of some or all of these comorbid conditions, a simultaneous condition associated with another underlying process such as senescence, or even a protective evolutionary factor that decreases energy expenditure in men with poor or declining health status [Corona *et al.* 2011, 2013]. Despite such theories, men with TD are likely to have less favorable health outcomes compared with the general population and thus may be more susceptible to potential adverse effects associated with TRT, through an associative relationship [Bhasin *et al.* 2010].

To date, few studies have addressed potential long-term adverse effects associated with TRT. This paper will summarize the current evidence, focusing on potential associated risks of CVD, elevated prostate-specific antigen (PSA) and prostate cancer, lower urinary tract symptoms (LUTS), obstructive sleep apnea (OSA), and erythrocytosis, with a goal of analyzing the literature regarding the safety of TRT and to identify areas of needed future research.

A computerized literature search was performed using the MEDLINE database to identify all publications using the following MESH terms: testosterone/adverse effects, testosterone/deficiency, hormone replacement therapy/adverse effects, andropause/drug effects, andropause/physiology, morbidity, mortality, cardiovascular disease, myocardial infarction, prostate-specific antigen/blood, prostate neoplasm/blood, prostate neoplasm/mortality, lower urinary tract symptoms, benign prostatic hyperplasia, benign prostatic hypertrophy, obstructive sleep apnea, erythrocytosis, polycythemia, and elevated hematocrit. The search was limited to studies involving human subjects published in the English language. Abstracts and book chapters were excluded from the search, yet relevant case studies were included in the search given the specificity and nature of the search topics. Bibliographies from index citations were reviewed for additional relevant studies.

Potential adverse effects of testosterone replacement therapy

The estimated likelihood of adverse effects of long-term TRT is still essentially unknown, as overall high-quality evidence to recommend against its use in most men with TD is lacking. The highlighted studies addressed in this paper can be used to guide the clinician in how to best monitor patients on TRT, especially those with the comorbid conditions detailed below.

Risk of cardiovascular morbidity and mortality

Reduced serum T levels have been associated with an increased risk of the development of CVD, including ischemic heart disease and stroke, yet whether TD is directly linked to the pathogenesis of CVD, a marker of pre-existing CVD, or concomitant manifestation of another underlying disease remains unclear [Corona *et al.* 2011, 2013]. Low endogenous T levels correlate with an increased risk of adverse CVD events, and endothelial dysfunction and increased atherosclerosis are means by which male hypogonadism may contribute to an increased risk of death [Jackson *et al.* 2010]. The potential that TD may be involved in the pathogenesis of CVD would

create a notion that TRT would result in improved cardiovascular outcomes, yet no current evidence exists to support this claim.

To date, the literature has been conflicting, suggesting TRT has either no beneficial effect on reduction of cardiovascular morbidity or mortality, or even a detrimental effect. Two meta-analyses found no differences in cardiovascular events between TRT and placebo groups [Fernandez-Balsells *et al.* 2010; Calof *et al.* 2005], while a more recent meta-analysis found that TRT increased the risk of cardiovascular events, although the data seemed to vary by source of research trial funding. The authors concluded that overall, and particularly in trials not funded by the pharmaceutical industry, exogenous T increased the risk of cardiovascular-related events [Xu *et al.* 2013]. It should be noted that trials that were not supported directly by the pharmaceutical industry [Basaria *et al.* 2010] commonly used T doses of 100–150 mg in older and frail men.

In trials not explicitly funded by the pharmaceutical industry, the risk of a cardiovascular-related event on T therapy was greater [odds ratio (OR) 2.06, 95% confidence interval (CI) 1.34–3.17] compared with trials funded by the pharmaceutical industry (OR 0.89, 95% CI 0.50–1.60). While this finding is intriguing and could suggest underreporting by the pharmaceutical industry, it does merit further consideration. First, it is reasonable to assume pharmaceutical industry funded studies may be more robustly funded overall and should in theory report adverse events more diligently. Second, it is difficult to make firm conclusions from these figures as there were no consistent methods of reporting or quantifying adverse cardiovascular events. The authors reported that only two trials provided a comprehensive list of cardiovascular-related events while eight trials did provide a summary table of cardiovascular-related events, yet cardiovascular events reported in the remaining 17 trials were inferred but not explicitly stated, leading to some modest speculation.

A retrospective cohort study of men with serum T levels below 300 ng/dl who underwent coronary angiography in the Veterans Affairs (VA) healthcare system between 2005 and 2011 investigated the association between TRT and all-cause mortality, myocardial infarction (MI), and stroke in 8709 men [Vigen *et al.* 2013]. Men were excluded if they were started on TRT prior to angiography or prior to obtaining serum T levels, as 'time 0' was defined as time of angiography, not time of commencement of T therapy. Further exclusion criteria included receiving TRT after having an MI. In the study, 1223 men with low serum T levels received TRT while 7486 did not. Their results indicated that TRT was associated with an absolute risk difference of 5.8% (95% CI 1.4–13.1%) increased risk of mortality, MI, or ischemic stroke regardless of the presence of pre-existing coronary artery disease.

Several limitations of this study are noteworthy, as it is open to criticism given very complex statistical methodology [Traisch *et al.* 2014]. With regard to the T-treated group, the calculated absolute risk for all CV events was 10% (123 events in 1223 men) *versus* the group not treated with T with a calculated risk of 21.2% (1587 events in 7486 men). Next, this study excluded 128 hypogonadal men (originally reported as 1132, of whom over 100 were actually women) who had suffered either MI or stroke, prior to initiation of T therapy. Since these men were no longer in the T risk group, ideally they should have been more appropriately categorized in the non-T-treated group, which would have increased the number of events in this group by 70%. Additionally, these findings are in direct contrast with results from a similar VA population that yielded a mortality risk in men treated with T of 10.3% compared with 20.7% in untreated men ($p < 0.0001$), and a mortality rate of 3.4 deaths per 100 person-years for T-treated men compared with 5.7 deaths per 100 person-years in men not treated with T [Shores *et al.* 2012].

A prospective cohort study examined 581 subjects with type 2 diabetes mellitus and known T levels with the purpose of observing the impact of TD on mortality and effect of T replacement [Muraleedharan *et al.* 2013]. The cohort was divided into the low T group, with total T < 10.4 nmol/liter and the normal T group, with total T > 10.4 nmol/liter. Mortality was significantly higher in the low T group with a rate of 17.2% *versus* 9% in the normal T group ($p = 0.003$). Interestingly, there were no differences in cardiovascular or cancer mortality between the two groups. However, a subanalysis using a lower T cutoff (8.4 nmol/liter) demonstrated significantly higher cardiovascular mortality in the low T group with multivariate-adjusted hazard ratio (HR; $p = 0.021$). This study then evaluated the effect of TRT on mortality in men in the low T group that was divided into men who did and did not receive

TRT. Mortality was significantly higher in the untreated group, with a rate of 20.11% *versus* 9.38% in the TRT group ($p = 0.002$). These findings demonstrate an association between TD and increased mortality; however, the association between TD and cardiovascular mortality is only apparent at lower levels. The association between TD and mortality is strengthened with the observation of decreased mortality in men with TD undergoing TRT.

The Testosterone in Older Men (TOM) trial, a double-blind randomized-controlled trial of 209 men of mean age 74 years, was performed to assess the effects of TRT in men with low serum T and limited mobility [Basaria *et al.* 2010]. The primary outcome was to evaluate the change from baseline of maximal voluntary muscle strength in leg-press exercise with secondary outcomes measuring chest press, 50 m walking speed, and stair climbing. Although the study demonstrated significant improvements in leg press, chest press, and stair climbing in the TRT group compared with the placebo group, the study was discontinued early due to a higher incidence of adverse cardiovascular effects in the TRT group (HR = 2.4, $p = 0.05$). Of the 209 men randomized (106 in the TRT arm and 103 in the placebo arm), 23 of the TRT subjects experienced an adverse cardiovascular event compared with only five in the placebo arm. The predominant criticism of this study was that there was a high prevalence of hypertension, diabetes, hyperlipidemia, obesity, and metabolic syndrome among the participants, with a substantially advanced age. In addition, subject selection was based solely upon T values, rather than in combination with defined clinical symptoms of TD.

Subsequent evaluation of the TOM trial sought to evaluate changes in gonadal hormones and markers of inflammation and coagulation to determine risk factors associated with potential cardiovascular events. In 179 men of mean age 74 years, within the T treatment group, the 6-month increase in serum free T levels was significantly greater in men who experienced cardiovascular events than in those who did not [mean (95% CI), 10.6 (4.6–16.7) *versus* 5.2 (3.0–7.5) ng/dl, $p = 0.05$]. In multivariable logistic regression analysis, the change in the serum levels of free T was associated with cardiovascular events. Older men with limited mobility who experienced cardiovascular events had greater increases in serum free T levels compared with control subjects [Basaria *et al.* 2013].

A recent cohort study was conducted to assess the risk of acute nonfatal MI within 90 days following an initial prescription for TRT in a healthcare database of 55,593 US men [Finkle *et al.* 2014]. The authors also compared post/pre rates in 167,279 men prescribed phosphodiesterase type 5 inhibitors (PDE5I) (sildenafil or tadalafil). In men aged 65 years and older, the relative risks (RR) were 2.19 (95% CI 1.27–3.77) for those who received TRT and 1.15 (95% CI 0.83–1.59) for men who received PDE5I. The RR for TRT prescriptions increased with age from 0.95 (95% CI 0.54–1.67) for men under age 55 years to 3.43 (95% CI 1.54–7.56) for men aged 75 years and older. A limitation of this study centers on utilization of a healthcare database that did not include information on either serologic or diagnostic criteria for men who received TRT. The trial also identified only men with nonfatal MIs, based upon diagnosis of a physician. Additionally, the authors admit that they were unable to explore whether or not the increase in CVD mortality was directly related to serum T levels or baseline TD.

In June 2014, the US Food and Drug Administration (FDA) called for all T product labels to carry a warning about the potential risk of venous thromboembolism (VTE), despite rigorous evidence to support a link between risk and T supplementation. The Copenhagen City Heart Study, a prospective study of 4673 men, found no associations with extreme levels of endogenous T (defined as $>$ 95th percentile) and elevated risk of deep venous thrombosis, pulmonary embolism, or recurrent VTE [Holmegard *et al.* 2014]. Similarly, a prospective, population-based study of 1350 men aged 50–84 years yielded only 4.5 VTE events per 1000 person-years over 10.4 years of follow up with an insignificant HR of 1.06 (95% CI 0.83–1.35) [Svartberg *et al.* 2009]. This study also supports the claim of no elevated risk of VTE in men across the spectrum of endogenous serum T levels. To date, there are no prospective studies that have evaluated the risk of VTE in men receiving exogenous T supplementation.

Elevation of prostate-specific antigen

A European interventional trial of 200 men investigated changes in serum PSA in hypogonadal men treated with transdermal T over a 6-year period [Raynaud *et al.* 2013]. One hundred and sixty-one men completed the 1-year study and 115 entered into a 5-year study extension; 51 men

completed the sixth year of the study and reported a statistically significant increase from a mean baseline of 0.50 ng/ml to a mean level of 0.80 ng/ml (95% CI 0.19–0.41). Only seven men throughout the study were found to have PSA levels above 4.0 ng/ml, six of whom were treated for suspected prostatitis with a resultant interval decrease in PSA. PSA velocity was also reported, which ranged from 0.00 to 0.08 ng/ml. Overall 10 patients at one point in the study had a velocity greater than 0.4 ng/ml, yet no cases of prostate cancer were observed.

While TRT for treatment of TD may cause elevations in serum PSA in some men within safe parameters (as outlined in the Endocrine Society Guidelines), it has not been definitively shown to lead to a significantly increased risk of prostate cancer [Bhasin *et al*. 2010]. The Saturation Model postulates that the androgen receptors on the prostate are saturated at physiologic and even subphysiologic levels of T, such that there is minimal response of the prostatic tissue to TRT. This model also explains how castration results in dramatic regression of prostate cancer, as there is no longer an available substrate for the androgen receptors [Morgentaler and Traisch, 2008].

Risk of prostate cancer

The theoretical relationship between an increased risk of prostate cancer development and TRT has been a robust debate for decades. It has been demonstrated in several trials that TRT increases serum PSA levels in some men, while androgen deprivation therapy can be used in the successful treatment of prostate cancer. The supportive argument posits that by treating men with TRT, thereby increasing PSA levels and administering T to a steroid responsive cancer, a man's risk of development of prostate cancer is significantly increased. However, prior literature has failed to definitively demonstrate an increased risk in a cause-and-effect relationship. A meta-analysis, looking at the adverse events associated with TRT in older men, found that men receiving TRT were 11 times more likely to undergo biopsy than the placebo group; however, there was no difference in the number of men diagnosed with prostate cancer between the two groups [Calof *et al*. 2005].

A retrospective study reviewed Surveillance, Epidemiology, and End Results Medicare data on nearly 150,000 men over a 15-year period and compared prostate cancer outcomes in men who had received TRT prior to prostate cancer diagnosis and those who did not [Kaplan and Hu, 2013]. The authors found no statistically significant difference in disease-specific survival (p = 0.2586), overall survival (p = 0.2882), or need for salvage androgen deprivation therapy (p = 0.5250). They also found favorable results with regard to prostate cancer specific outcomes, including tumor grade and clinical staging. Compared with men without prior TRT use, men who used TRT prior to diagnosis were more likely to have moderately differentiated cancer (64.6% *versus* 59.2%, $p < 0.001$) and less likely to have poorly differentiated cancer (28.3% *versus* 34.2%, $p < 0.001$). With regard to clinical staging, men with prior TRT use were more likely to be diagnosed with stage T3 disease (4.0% *versus* 3.1%, $p < 0.001$) and less likely to be diagnosed with stage 4 disease (4.3% *versus* 6.5%, $p < 0.001$).

A cumulative registry study aimed at investigating TRT effects on the metabolic syndrome followed 255 men with subnormal T levels treated with T undecanoate (TU) for a total of 60 months [Traish *et al*. 2013]. While the primary outcomes of the study focused on the metabolic syndrome, secondary outcomes included various prostate parameters. Mean PSA did significantly rise from baseline from 1.77 to 1.83 ng/ml ($p < 0.0001$); however, only three men were diagnosed with prostate cancer. This corresponds to an incidence of 30.3 cases of prostate cancer per 10,000 person-years (CI 0.9738–9.4052). This is lower than the incidence of prostate cancer in the general population reported in both the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial and the European Randomized Study of Screening for Prostate Cancer Patients, which reported prostate cancer incidences of 97.1 per 10,000 person years and 9.66 per 1000 person years respectively [Andriole *et al*. 2012; Schroder *et al*. 2012].

A prospective trial followed 81 men (mean age 57 years) for a mean (range) of 33.8 (6–144) months after starting TRT [Coward *et al*. 2008]. Only four men were found to develop prostate cancer over 5 years of observation, which is not greater than the incidence in the general population. The baseline PSA of men in this study was 1.32 ng/mL and among those not diagnosed with prostate cancer, there was no significant difference either at any 12-month interval or at 5 years relative to baseline (1.43 ng/ml, p = 0.82). However, among men diagnosed with prostate

cancer, there was a significant increase in PSA from baseline by a mean value of 3.2 ng/ml ($p < 0.05$). This finding led the authors to conclude that prostate cancer can be effectively diagnosed and treated while receiving TRT. These findings are consistent with prior data that demonstrated no influence of either T or other androgens on prostate cancer development [Morgentaler 2011].

The Testim Registry in the US (TRiUS) and the International, multicenter, Post-Authorisation Surveillance Study (IPASS) on long-acting-intramuscular TU investigated the safety of these forms of T and reported on both PSA and prostate cancer outcomes [Bhattacharya *et al.* 2012; Zitzmann *et al.* 2013]. Both studies demonstrated significant elevations in PSA from baseline in their study groups; however, the TRiUS study only demonstrated a nonsignificant increase in men over the age of 65 years. In TRiUS, the mean change from baseline was 0.33 ± 1.57 μg/liter with mean PSA level of 2.18 μg/liter for men 65 years and older, and the mean change in baseline was 0.17 ± 0.58 μg/liter with mean PSA level of 1.14 μg/liter in men under 65 years of age. In the IPASS study, PSA values increased from a baseline of 1.1 ± 0.9 ng/ml to 1.3 ± 1.2 ng/ml. Collectively in these trials, only one case of prostate cancer was observed during the study periods in over 2000 men. These studies together suggest that while TRT can significantly increase PSA levels, it remains within clinically acceptable ranges and does not increase the risk of prostate cancer.

A recent randomized controlled trial conducted in Malaysia investigated the efficacy and safety of TU in the treatment of aging men with TD [Tan *et al.* 2013]. Their study demonstrated a significant elevation in PSA from baseline in the treatment arm compared with the control arm (0.44 *versus* 0.15 ng/ml, $p = 0.01$). However, although statistically significant, this elevation was within acceptable limits, with an increase in men receiving TU from a mean baseline of 0.80 to 1.25 ng/ml after 48 weeks.

While TRT is often a life-long treatment for many men, it is important to note that no randomized control trials to date have been large enough and adequately powered to detect differences in prostate cancer risk. One review reported that 6000 men with TD would need to be randomized both to the TRT and control arms and be treated for an average of 5 years to detect a 30% difference in prostate cancer incidence [Corona *et al.* 2013].

Lower urinary tract symptoms

In similar fashion to the potential increased risk of prostate cancer, it has long been postulated that TRT results in increased prostate volume and worsening due to benign prostate hyperplasia (BPH). Current literature has thus far been heterogeneous, yet tends to demonstrate that TRT does not worsen LUTS and may actually improve symptoms in some cohorts.

One randomized controlled trial of 46 men evaluated the effects of intramuscular T administration on LUTS in men with known BPH [Shigehara *et al.* 2011]. A significant decrease in International Prostate Symptom Score (IPSS) scores compared with baseline was observed in the group of 23 men who received TRT (baseline mean 15.7 with 12-month mean score of 12.5, $p < 0.05$), however no difference was observed in the control group (baseline mean 14.0 and 12-month mean score 13.5, $p = 0.345$). Additionally, compared with baseline, the TRT group was found to have significantly improved maximum urine flow rates (12.9 ml/s improved to 16.7 ml/s, $p < 0.05$) and voided volumes (253 ml to 283 ml, $p < 0.05$) whereas no differences were observed in the control group.

A prospective study of 120 men with TD receiving TRT observed that men who experienced improvement in symptoms had significantly higher baseline American Urological Association Symptom Index (AUASI) scores than those who experienced no change or interval worsening in symptoms [Pearl *et al.* 2013]. Overall, 55 men (45.8%) reported a less than three-point change in AUASI relative to either worsening or improvement of LUTS; 38 men (31.7%) had improvement in AUASI of three or more points, while 27 men (22.5%) had worsening of AUASI of three or more points. Nine men (7.5%) initiated a new medication for treatment of LUTS during the course of the study.

A randomized, double-blind, placebo controlled trial of 53 men aged 51–82 years old with symptomatic BPH, prostate volume 30 cm^3 or greater, and serum total T less than 280 ng/dl were randomized to daily transdermal 1% T gel plus oral placebo or dutasteride for 6 months [Page *et al.* 2011]. As expected, the TRT + dutasteride

(TRT+D) group had significantly smaller prostate volumes compared with the TRT only group (38.6 *versus* 58.3 cm^3, $p < 0.05$). While the TRT+D group demonstrated a significant decrease in prostate volume from baseline at 6 months (from 44.4 to 38.6 cm^3, $p < 0.05$), the TRT only group demonstrated a nonsignificant increase (from 54.2 to 58.3 cm^3, $p > 0.05$). Although significant decreases in IPSS scores were observed in both treatment groups at the end of the study period, there was no significant difference between the two groups (11.1 in TRT only *versus* 10.3 in TRT+D, $p < 0.05$). Additionally, there were no differences in urine flow measures or postvoid residual between the two groups. These results further suggest that TRT may offer some minor improvements in LUTS. While this study also demonstrates the desired effect of decreasing prostate volume, it failed to demonstrate any significant improvement in symptom scores or objective measures of urinary function.

A recent prospective longitudinal observational registry of 259 men investigated the effects of TRT on LUTS in men with TD [Yassin et al. 2014]. Inclusion criteria were total T concentration less than 3.5 ng/ml and erectile dysfunction documented by International Index of Erectile Function scores less than 21. IPSS scores greater than 18 and history of obstruction due to BPH with residual urine volumes of greater than 40 ml were grounds for exclusion. All participants were treated with TU for a median duration of 42.3 months. Mean IPSS scores were significantly lower at the end of the study, decreasing from 10.35 at baseline to 6.58 ($p < 0.05$). There was no difference in IPSS scores when adjusted for weight loss during the study period or concomitant use of vardenafil. Furthermore, there were significant improvements in bladder wall thickness and postvoid residual volumes ($p < 0.001$; $p < 0.001$). Interestingly, despite improvement in symptom scores and objective measures of urinary function, there was a significant increase in prostate volume from 27.90 ml at baseline to 34.79 ml ($p < 0.05$). This study adds to the mounting evidence that suggests TRT may in fact improve LUTS; however, this study is limited in that men with severe LUTS by IPSS and evidence of obstruction were excluded.

Current evidence does not support an increased risk for worsening LUTS with TRT, and some men may in fact experience mild symptomatic improvement. However, these studies are of small sample size and of short duration of follow up. One observation that should be considered is the increase in prostate volume demonstrated in the studies by Page and Yassin and colleagues described above. Although IPSS scores were shown to significantly improve with TRT over the first 5 years of therapy, one might postulate that if prostate volume continues to increase with continued use of TRT, then LUTS may subsequently worsen after a period of improvement. More long-term randomized trials are needed before more definitive conclusions can be reached.

Obstructive sleep apnea

The potential risk of adverse effects of TRT on sleep, specifically OSA, has been a growing area of research and discussion. Our literature search retrieved five studies that evaluated this association [Barrett-Connor *et al.* 2008; Bercea *et al.* 2013; Hoyos *et al.* 2012a, 2012b; Killick *et al.* 2013]. However, only one trial addressed TRT in relation to the possible worsening of OSA.

An 18-week randomized, double-blind, placebo-controlled, parallel group trial in 67 men found that TRT in obese men with severe OSA mildly worsened sleep-disordered breathing in a time-limited manner, irrespective of initial T concentrations in the short term (7 weeks), but this worsening resolved after 18 weeks [Hoyos *et al.* 2012a]. In the trial, sleep and breathing were measured by nocturnal polysomnography at 0, 7, and 18 weeks. T, compared with placebo, worsened the oxygen desaturation index (ODI) by 10.3 events/h (95% CI 0.8–19.8 events/h; $p = 0.03$) and nocturnal hypoxemia [sleep time with oxygen saturation less than 90%, SpO(2) T90%] by 6.1% (95% CI 1.5–10.6; $p = 0.01$) at 7 weeks. TRT did not alter ODI (4.5, –5.4 to 14.4 events/h; $p = 0.36$) or SpO(2) T90% at 18 weeks (2.9, –1.9 to 7.7%; $p = 0.23$) compared with placebo. The authors also found that the TRT effects on ODI and SpO(2) T90% were not influenced by baseline T concentrations (T by treatment interactions, all $p > 0.35$). Moreover, serum T concentrations did not correlate with ODI or SpO(2) T90% (all $p > 0.19$) [Hoyos *et al.* 2012a].

The same authors, using the same cohort, also sought to evaluate body compositional and cardiometabolic effects of TRT with TU in men with obesity and severe OSA [Hoyos *et al.* 2012b]. This trial concluded that 18 weeks of TRT improved

several important cardiometabolic parameters, including insulin resistance, decreased liver fat, and increased lean muscle mass, but did not differentially reduce overall weight or the metabolic syndrome.

The remaining three trials did not adequately assess the relationship between TRT and OSA but offered some interesting results. One study of 1312 community-dwelling men aged 65 years or older from six clinical centers in the USA determined that low serum total T levels were associated with less healthy sleep in older men, explained by the degree of central adiposity [Barrett-Connor *et al.* 2008]. Another trial evaluated 40 men with severe OSA and 40 control subjects. Serum T in the OSA group was significantly lower compared with controls, and a statistically significant inverse correlation was found between serum T level and depressive symptoms [Bercea *et al.* 2013]. The third trial yielded positive correlations between changes in serum T and hyperoxic ventilatory recruitment threshold in 21 men with OSA ($r = 0.55$, $p = 0.03$), and between changes in hyperoxic ventilatory recruitment threshold and time spent with oxygen saturations during sleep less than 90% ($r = 0.57$, $p = 0.03$) at 6–7 weeks, but these changes had resolved by 18 weeks [Killick *et al.* 2013].

To date, there are no randomized trials focusing on the long-term effects of TRT and OSA. It is recommended that clinicians inquire about symptoms of OSA in men with TD on TRT and to offer a referral for polysomnogram evaluation in men with hallmark symptoms, especially those who are starting T therapy [Bhasin *et al.* 2010].

Erythrocytosis

Erythrocytosis, or polycythemia, is a known side effect of TRT. A meta-analysis of adverse effects of TRT in men with TD found 11 trials that highlighted erythrocytosis as a prominent side effect of TRT. However, the mechanism behind what causes hemoconcentration and how this may affect men is poorly understood [Fernandez-Balsells *et al.* 2010]. Since 2008, there has only been one study that addressed elevated hemoglobin and hematocrit in patients receiving TRT. This study demonstrated that TRT caused statistically significant increased hemoglobin levels (0.86 ± 0.31 g/dl, $p = 0.01$). The authors then hypothesized that TRT increased serum erythropoietin, leading to erythrocytosis, yet this was disproven (-0.24 ± 2.16 mIU/ml, $p = 0.91$). Another proposed theory posits that T has a dose-dependent stimulatory effect on erythropoiesis in men that is more pronounced in older men [Coviello *et al.* 2008]. There were no 'serious' patient-centered adverse events (e.g. cerebrovascular accident, vascular occlusive events, venous thromboembolisms) reported during the study period of 36 months [Maggio *et al.* 2013].

To date, there are no other long-term studies that have adequately evaluated the potential risk of erythrocytosis from TRT. Clinicians are advised to check hematocrit at baseline, at 3–6 months, and then annually. If hematocrit is greater than 54%, then TRT should be stopped until hematocrit decreases to a safe level, the patient should be evaluated for hypoxia, underlying lung disease, and sleep apnea, then therapy can be reinitiated with a reduced dose [Bhasin *et al.* 2010].

Future directions

TRT will continue to offer the potential for substantial improvement in quality of life for many men around the world. Judicious and appropriate use of TRT will be imperative to minimize the theoretical risk of adverse events in high-risk populations. Future research should require a dedicated focus on the evaluation of large, multiethnic cohorts of men through prospective trials to better elucidate both risk and hazard ratios of TRT as it relates to CVD and metabolic disease, prostate cancer, LUTS, OSA, erythrocytosis, and other yet-to-be-determined theoretical risks in men both with and without cardiovascular risk equivalents.

Conclusion

The available evidence indicates that TRT is largely considered to be safe in most men, with a small inherent risk of adverse events in selected high-risk populations of men with multiple medical comorbidities. TD is associated with an increased risk of development of cardiovascular and metabolic disease; however, the nature of the relationship remains unclear and recent evidence suggests that TRT may increase risk of adverse cardiovascular events in men with significant comorbidities. TRT has been associated with occasional modest increases in serum PSA, yet within safe clinical parameters, and without substantial compelling evidence to support an increased risk of prostate cancer. LUTS appear to

remain stable or improve slightly with the use of TRT, which offers a differing viewpoint to previously held opinions. There remain little data on TRT relating to long-term OSA outcomes; however, current evidence suggests TRT may transiently worsen objective OSA parameters then resolve. TRT appears to be associated with erythrocytosis, yet data on the significance of this trend related to patient outcomes are lacking.

At this time, TRT remains a largely beneficial option in improving health-related quality of life in men with serum TD and associated symptoms. As of January 2014, the FDA stated they are investigating the potential link but have *not* concluded 'FDA-approved testosterone treatment increases the risk of stroke, heart attack, or death'. Clinicians should exercise caution when considering TRT for men with multiple cardiovascular comorbidities and utilize shared decision making with informed consent. As with any therapeutic intervention, clinicians should discuss the benefits and potential risks of hormone replacement therapy with men prior to initiating treatment, as well as discuss provisions for ongoing management and surveillance.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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