

Risks of testosterone replacement therapy in men

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ABSTRACT

Testosterone replacement therapy (TRT) is a widely used treatment for men with symptomatic hypogonadism. The benefits seen with TRT, such as increased libido and energy level, beneficial effects on bone density, strength and muscle as well as cardioprotective effects, have been well-documented. TRT is contraindicated in men with untreated prostate and breast cancer. Men on TRT should be monitored for side-effects such as polycythemia, peripheral edema, cardiac and hepatic dysfunction.

Key words: Hypogonadism, side-effects, testosterone replacement therapy

INTRODUCTION

Testosterone has many beneficial effects, including increasing bone strength and density, inducing hematopoiesis, driving sexual function and libido, providing a cardioprotective effect and increasing muscle strength.^[1] Testosterone levels are known to decline as men age. The Baltimore Longitudinal Study of Aging reported the incidence of hypogonadism as 20% in men over 60 years of age, 30% in men over 70 years and 50% in men over 80 years of age.^[2]

As men age, a decline in testicular production of testosterone are seen, as well as an increase in sex hormone binding globulin, both of which act to decrease bioavailable testosterone.^[3] With this gradual decline, the beneficial effects of testosterone could be diminished and negatively affect physical and emotional well-being. Testosterone replacement therapy (TRT) is a reasonable treatment option often discussed for men with low testosterone levels and symptoms of hypogonadism. When replaced, many of the positive effects of testosterone are regained.^[4]

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These positive results have led to a drastic increase in the use of testosterone replacement for men with symptomatic hypogonadism, though long-term data is lacking on the safety.

While the beneficial effects of testosterone are rarely disputed and widely publicized, there is a paucity of the literature on the risks of testosterone use. Any man who has a comorbidity that precludes TRT should be informed of all risks. Factors such as exacerbation of prostate cancer, male breast cancer, worsening benign prostatic hyperplasia (BPH), polycythemia and an increased risk of obstructive sleep apnea (OSA) should be considered when administering TRT to a patient. The goal of this review is to highlight the risks and summarize the current literature on safety of TRT.

EFFECT OF TRT ON BPH

One of the major risk factors associated with the administration of testosterone supplementation is its effect on the prostate. We know the prostate to be an androgen-dependent gland and conversely, anti-androgen agents can decrease prostate volume in patients with BPH. As the population continues to age, both the incidence of BPH and late-onset male hypogonadism will continue to rise and practitioners will need to be comfortable with counseling men on the effect of TRT on the prostate.^[5]

In a landmark randomized, double-blind, placebo-controlled trial of 44 hypogonadal men, Marks *et al.* showed that TRT for 6 months improves serum androgen levels, but had little effect on prostate tissue androgen levels, tissue biomarkers and/or gene expression.^[6] Testosterone supplementation has been shown to increase prostate size by 12%,^[7] but lower urinary tract symptoms (LUTS) and urinary retention do

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not worsen in men on testosterone therapy.^[8,9] Similarly, the presence of hypogonadism in 312 men with reportable LUTS was not predictive of worsening International Prostate Symptom Scores (IPSS) or maximal urinary flow rates.^[10]

In fact, some series report an improvement in LUTS after 1 year of TRT.^[11,12] In the most recent, randomized controlled trial, 52 men were randomly assigned to receive TRT. At 1 year, the 23 men randomized to 250 mg of testosterone enanthate every 4 weeks reported significant improvements in IPSS and maximal urinary flow rates compared with baseline and controls.^[12] At no point in this trial did any patient require additional medication or suffer urinary retention.

While older men on testosterone therapy do have an increase in overall prostate size, this increase in size does not differ from the increase in prostatic hypertrophy seen in elderly men not on testosterone therapy.^[13] Taken together, TRT does not appear to grossly worsen LUTS and is not contraindicated in men diagnosed with BPH.

EFFECT OF TRT ON PROSTATE CANCER

It has been over 60 years since Hodges and Huggins described a relationship between serum testosterone levels and prostate cancer progression.^[14] Later in 1982, Fowler and Whitmore reported that exogenous testosterone given to patients with metastatic prostate cancer had worse outcomes.^[15] Today androgen deprivation therapy remains a cornerstone of treatment for men with advanced prostate cancer, so it is no surprise that TRT is contraindicated in men with diagnosed prostate cancer, as well as high-risk patients, which includes men with first-degree relatives with prostate cancer and African-Americans who have a prostate-specific antigen (PSA) >3 ng/mL.^[4,16]

Recently, there has been a paradigm shift whereby TRT usage has increased despite this potential risk. Many longitudinal studies investigating the relationship of endogenous testosterone levels and subsequent risk of prostate cancer failed to find any association.^[17] As such, prostate cancer incidence in men on testosterone therapy is similar to men not on testosterone therapy.^[18,19] Similarly, in a 3-year prospective trial, the incidence of prostate cancer was similar among men receiving TRT and controls.^[20] In a large meta-analysis of 18 prospective studies that included over 3500 men, there was no association between serum androgen levels and the risk of prostate cancer development.^[21] Morgentaler *et al.* proposed a saturation theory where prostate growth becomes insensitive to changes at normal androgen levels due to saturation of the androgen-receptor; however, there is exponential growth at castrate levels.^[22] This theory may explain why testosterone does not directly cause prostate cancer,^[23] but it has been shown to accelerate the development of prostate cancer.^[24,25]

For premalignancy, prostatic intraepithelial neoplasia (PIN) appears to be a risk factor for developing prostate cancer, however this association has been mostly demonstrated for high-grade disease.^[26,27] There is a lack of long-term data on the use of TRT in men with PIN. In one study, 12 months after TRT, only one patient out of 20 men with previous PIN developed overt prostate cancer.^[28]

For men who have previously undergone definitive treatment for prostate cancer, the usage of TRT is becoming more accepted. TRT does not appear to increase cancer recurrence in hypogonadal men following radical prostatectomy.^[29] In the most recent study by Pastuszak *et al.*, the authors retrospectively reviewed a cohort of 103 men who underwent prior radical prostatectomy and were treated with TRT. Despite a significant increase in PSA in men receiving TRT, there were twice as many cancer recurrences in the control group after 36 months of follow-up.^[30]

For men with untreated prostate cancer on active surveillance, TRT remains controversial. However, several studies have shown that TRT is not associated with progression of prostate cancer as evidenced by either PSA progression or gleason grade upstaging on repeat biopsy.^[31,32] In the most recent study by Morgentaler *et al.*, 13 men with symptomatic hypogonadism and untreated prostate cancer received TRT for a median of 2.5 years and no local prostate cancer progression or distant disease was observed.^[33]

While there have been reports of metastatic prostate cancer in older men who are on testosterone therapy,^[20] these are mostly anecdotal. Because of this potential risk, practitioners are often reluctant to administer testosterone in patients they believe may be at high risk for prostate cancer or whom they suspect may have the low-grade disease. Men on TRT should have frequent PSA monitoring; any major change in PSA (>1 ng/mL) within the first 3-6 months may reflect the presence of a pre-existing cancer and warrants cessation of therapy.^[34] Current guidelines on the frequency of PSA monitoring and role of pre-treatment transrectal ultrasound guided prostate biopsy are lacking.^[35] Taken together, there has been consistent rejection that TRT causes development of prostate cancer in men, however administration of TRT for hypogonadal men previously treated for high-risk prostate cancer should be taken with caution.

BREAST CANCER

While there is no known physiologic link of testosterone directly to the development of breast cancer, it has been suggested that high levels of testosterone may lead to increased aromatization to an active derivative of estrogen, which ultimately may stimulate breast tissue receptors and increase the risk of male breast cancer.^[36]

The role of testosterone in breast cancer development is yet to be fully understood.^[37] Currently, several case reports exist^[38] and one retrospective review sites an incidence 11% in 45 men on long term TRT over 10 years.^[39] Future prospective studies with longer follow-up will determine if such association between TRT and male breast cancer truly exists.

INFLUENCE OF TESTOSTERONE ON RED BLOOD CELL COUNT

Testosterone leads to an increase in hemoglobin by as much as 5-7%^[1,25] through its effect on the production of erythropoietin, which can dramatically improve symptoms of anemia in men.^[40,41]

Studies looking at the occurrence of polycythemia as a negative side-effect in men on testosterone therapy are rare. Despite this, polycythemia is an accepted side-effect of TRT. While testosterone exerts a positive effect in men with baseline anemia, it can lead to polycythemia in over 20% of men treated on TRT.^[42] Polycythemia may lead to an increased incidence of vascular events, including stroke, myocardial infarction and deep vein thrombosis with possible pulmonary embolus.^[42] While these complications are all possible with polycythemia, their theoretical occurrence has not been demonstrated to occur in men on TRT.^[43]

Because of this risk of polycythemia, men undergoing TRT should not only have their complete blood count (CBC) monitored during their therapy, but should also have a baseline CBC drawn before testosterone therapy is initiated. While on testosterone therapy, if the hematocrit (HCT) rises greater than 54%, testosterone therapy should be held until the HCT normalizes. If it is restarted after normalization, it should be performed so at a lower dose with continued careful monitoring.^[16]

RELATIONSHIP BETWEEN OSA AND TRT

OSA is a risk associated with TRT in men, but its' etiology is not particularly well understood. While some studies suggested that there is no association between OSA and TRT,^[44] others have demonstrated that that OSA occurs in men undergoing TRT and when supplementation is stopped, the OSA resolves.^[45]

While no clear link has been established, men on TRT should be counseled on the risk of potential OSA when therapy is started. They should be monitored for increased symptoms, such as snoring while sleeping or fatigue. If patients starting TRT already carry a diagnosis of OSA, physicians should counsel these patients that TRT may worsen their symptoms. While, OSA remains to be a relative contraindication to initiation of TRT, more research needs

to be completed on this association in order to gain a better understanding of its etiology if there is one at all.

SYSTEMIC EFFECTS OF TESTOSTERONE

The systemic effects of TRT may be exacerbated in men with limited cardiovascular reserve. Previous dogma held that androgens could have atherogenic potential. In a randomized, placebo-controlled trial, Basaria *et al.* reported an increased risk of cardiovascular events in men randomized to TRT; however, this small cohort had a high prevalence of chronic disease.^[46] Today, current literature suggests that TRT has a neutral to beneficial effect on reported cardiovascular events.^[47,48] Because some men may have a limited cardiovascular capacity, clinicians prescribing TRT must be cautious with respect to its ability to cause edema.^[49] Until date, no longitudinal studies examine the impact of TRT on the cardiovascular system, however some studies suggest that TRT may serve as an adjunct rehabilitative therapy in patients with congestive heart failure (CHF).^[50-52]

While topical testosterone delivery systems avoid first-pass hepatic metabolism, there remains concern regarding TRT in patients with chronic liver disease. The majority of reports of liver toxicity and jaundice are limited to orally-administered alkylated forms of testosterone.^[53] However, a small prospective study representing a cohort of cirrhotic patients demonstrated topical gels to be safe and efficacious.^[54] It has also been shown that TRT may improve hepatic function in patients with end-stage liver disease.^[55] Because of these mixed results, clinicians should be aware of the possible risks associated with TRT in men with hepatic dysfunction and counsel these men accordingly.

Because TRT is known to cause water retention, caution with testosterone use in patients with chronic renal insufficiency is often advised. In patients with end-stage renal disease (ESRD) on dialysis, fluid shifts are less of a concern in patients on TRT since the fluid retention can be handled with dialysis. While polycythemia may be an adverse side-effect, this is a potential benefit in patients with chronic renal failure and anemia.^[56] Furthermore, the half-life of testosterone elimination after withdrawal appears similar between patients with and without ESRD.^[56] Few studies have assessed the effects of TRT in patients with chronic kidney disease; however, small studies have suggested that TRT has anabolic effects among ESRD patients, even in the absence of hypogonadism. Aside from frequent monitoring of congestive symptoms and peripheral edema in this select population, TRT appears to be safe for patients with chronic kidney disease without dose adjustment.^[57]

When testosterone reaches supra-therapeutic levels, aggressive behavior and increased rates of suicide among adolescent users have been reported;^[58] however, no study has documented a negative impact on cognition in men patients

receiving TRT. In fact, studies have shown that testosterone replacement to eugonadal levels may improve or stabilize cognitive function.^[59-61] Lower levels of testosterone have a negative impact on spatial and verbal abilities, as well as cognitive function; therefore, it is no surprise that normalizing testosterone levels results in cognitive improvements.^[62,63]

With exogenous testosterone supplementation, the pulsatile release of gonadotropin-releasing hormone is blunted and the release of follicle-stimulating hormone and luteinizing hormone are depressed. As such, a decrease in spermatogenesis is seen.^[64] While this effect may not be of importance to many men who have completed their families, physicians prescribing TRT need to be aware.

When serum levels of testosterone are increased, a concurrent increase in the secretion of sebum occurs, which can lead to acne. Despite this known association, this effect is typically minimal.^[65] Case reports regarding testosterone supplementation leading to changes in hair patterns have been documented; however no randomized, placebo-controlled trials exist. Various topical and intramuscular injectable forms of testosterone are associated with a variety of skin reactions, mainly erythema and pruritus in up to 60% of users.^[20]

EFFECTS OF TESTOSTERONE ON BODY HABITUS

TRT is associated with external, physical changes in the men. Exogenous testosterone is known to cause an imbalance in the hypothalamic-pituitary axis. As such, testosterone can be converted to estrogen by aromatization. Excess estrogens may lead to gynecomastia and/or breast pain, both of which may be seen in 10-25% of men on TRT.^[66] The ratio of estradiol to androgens is the key factor in the development of gynecomastia rather than absolute increases in androgens themselves.^[66] Clinicians must be aware of non-iatrogenic causes of gynecomastia and therefore the appropriate work-up should be sought out to rule out other pathology, especially if there is any breast tenderness or unilateral gynecomastia. Only a few case-reports describe a relationship between male breast cancer and TRT.^[38,39]

In addition, excess estrogens may cause an increase in visceral obesity. With vigilant monitoring of serum estrogen levels, TRT has been shown to promote weight loss.^[67] Well-known to many prescribers of TRT is a risk of water retention and/or edema. The etiology of this association remains unclear to date.^[68] The degree of retention is generally mild. As mentioned above, men on TRT with a history of CHF should follow closely.

CONCLUSIONS

TRT has numerous benefits that can greatly enhance a patient's quality-of-life. Before prescribing TRT, one must

be conscientious of its adverse effects. Data on the safety of TRT specific to our aging population is not currently available; however TRT has been linked to prostate cancer, BPH, polycythemia and OSA. A full assessment of the morbidity of TRT would require a large-scale, randomized, controlled trial. To date, physicians remain in a quandary about the best approach to care for men with symptoms of hypogonadism. TRT, when given to appropriately selected patients with vigilant monitoring as outlined in this review and in Table 1, can bring improvements in quality-of-life, energy level, libido, muscle mass, cognition and bone density.

Table 1: Potential risks of TRT and associated monitoring strategies

Potential risk	Suggested monitoring strategies
Cardiovascular disease	Baseline blood pressure checks and repeats at 3 and 6 months, then annually thereafter. For high-risk patients, consider cardiology referral
Erythrocytosis	Obtain baseline HCT then at 3 and 6 months, then annually thereafter. If HCT is >54%, stop TRT and restart at lower dose ^[69]
Fluid retention	Patient history and physical exam. Stop TRT if CHF is uncontrolled ^[69]
BPH	Patient questionnaire and history. Refer to urologist if: IPSS+above 19 and stop TRT ^[69]
Prostate cancer	Obtain baseline DRE* and serum PSA then again at 3 and 6 months. Continual monitoring depending on the patient's race/age. ^[69] Refer to urologist if PSA rises over 4 ng/mL Abnormal DRE If PSA rises more than 1 ng/mL in the first 6 months of TRT or by more than 0.4 ng/mL/year thereafter ^[34] If PSA velocity is more than 0.4 ng/mL/year ^[69]
Acne	Patient history and physical exam. Dose adjustment and/or referral to dermatology
Hepatotoxicity	Patient history and physical exam. Liver function tests are unnecessary in gel, pellet and IM preparations
Infertility	Patient history and physical exam. Reconsider alternative strategies if patient desires to father children
OSA	Baseline patient history and physical exam and again between 3 and 6 months. ^[20] Consider alternate causes of OSA ^[43]
Gynecomastia/ breast cancer	Exclude other etiologies with patient history and physical exam. Review all medications. Complete hormone evaluation may be necessary. Medications implicated to cause gynecomastia ^[66] Anti-androgens-finasteride, bicalutamide Antibiotics-isoniazid, ketoconazole, metronidazole Antihypertensives-amlodipine, captopril, diltiazem, verapamil, nifedipine GI agents-cimetidine, omeprazole Psychiatric-diazepam, haloperidol, tricyclic antidepressants

TRT=Testosterone replacement therapy, HCT=Hematocrit, BPH=Benign prostatic hyperplasia, DRE=Digital rectal examination, CHF=Congestive heart failure, IPSS=International prostate symptom score, PSA=Prostate-specific antigen, IM=Intramuscular, OSA=Obstructive sleep apnea, GI=Gastrointestinal,*Digital rectal examination,*International prostate symptom score

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