Testosterone deficiency syndrome: benefits, risks, and realities associated with testosterone replacement therapy

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Testosterone deficiency syndrome, which has sometimes been termed age-related or late-onset hypogonadism, is a syndrome characterized by both clinical manifestations as well as a biochemical deficiency of testosterone. This condition is associated with considerable morbidity and mortality, accounting for billions of dollars in health care costs. There is some evidence that suggests that restoring testosterone levels in these individuals may help to manage or delay progression of the associated morbidities. Furthermore, despite controversies in the literature and media, testosterone replacement has proven to be quite safe in most men with minimal if any adverse effects when dosing to achieve the eugonadal range. It is nevertheless very important for clinicians to be aware of the possible risks and contraindications of treatment to ensure proper patient selection and appropriate monitoring.

Key Words: testosterone deficiency syndrome, hypogonadism, testosterone replacement therapy

Introduction

Male hypogonadism is a clinical syndrome caused by androgen deficiency, which may adversely affect multiple organ functions and quality of life. It is due to the disruption of one or several levels of the hypothalamic-pituitary-gonadal axis and can be broadly classified, based on the level of disturbance, as either primary (testicular failure: biochemically associated with high gonadotropins-follicle-stimulating hormone (FSH) and luteinizing hormone (LH)), secondary (hypothalamic and/or pituitary failure: low FSH and LH, or mixed (combination of primary and secondary). Testosterone deficiency syndrome as it is termed in the recent Canadian Clinical Practice Guidelines1 is often age-related hypogonadism where testosterone levels are low, but the normal physiologic feedback pathway has been lost as demonstrated by the fact that FSH and LH levels are not elevated.

There are various clinical manifestations of hypogonadism, as shown in Table 1. While these signs and symptoms are characteristic of hypogonadal men, they are by no means specific, and thus biochemical parameters are necessary to establish a diagnosis.

It has been estimated that the crude Canadian prevalence of biochemical testosterone deficiency is 25% among men aged 40 to 62 years.2 A larger US-based biochemical prevalence study, the Hypogonadism in Males (HIM) study, estimated that 39% of men aged 45 and above are testosterone deficient based on a total testosterone cut off of 300 ng/dL.3 Far fewer men, however, are symptomatic and thus they are not
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Hypogonadism is more likely to be associated with certain medical comorbidities.3,5-10 Populations at high risk for low serum testosterone levels are shown in Table 2. The prevalence of symptomatic hypogonadism in these populations has been estimated to exceed 30%.11

Because of the expanding elderly population, the number of men that are hypogonadal will increase, and as a result, it will be more common for physicians to encounter these men in the clinic. Despite its widespread prevalence, however, it has been estimated that as few as 5% of hypogonadal men are receiving testosterone replacement therapy (TRT).5,32,13 This could be due to a poor understanding of hypogonadism and its implications in aging men.12,14 A study from Ontario showed that in men over the age of 65, one in 90 had been prescribed TRT but only 6% had conclusive biochemical evidence of hypogonadism.15 Controversies over treatment risk and benefit may also contribute to the low treatment rate.16-18

Benefits

A wealth of data accumulated over the past 70 years has revealed that low serum testosterone levels are associated with an increased risk of cardiovascular disease, diabetes, osteoporosis, and mortality.5-12,19,20

Although there are very few large, long term, randomized, placebo-controlled double-blind trials to be able to categorically prove the causal relationship and direct benefit of TRT, several smaller trials consistently reveal support for the benefits of TRT in the right patient.

A US-based public health impact study predicted that testosterone deficiency could be associated with as many as 1.3 million cases of cardiovascular disease, 1.1 million cases of diabetes, and over 600,000 osteoporosis-related fractures over a 20 year period. According to the study, this would translate into $190-525 billion dollars in health care costs.18

Fortunately, numerous intervention trials, some randomized and some not, have shown that repletion of testosterone in hypogonadal men with these conditions may reverse or delay their progression.21-29

Two recently published large prospective studies with long follow up, one in a veterans population and the other in men with diabetes, found that mortality was reduced by more than half in hypogonadal men who received TRT versus a control group of similar men who did not receive this therapy.19,20

Cardiovascular disease

Several studies have noted an inverse relationship with lower testosterone levels associated with more severe cardiovascular disease.8,30-33

### TABLE 1. Signs and symptoms of hypogonadism

**Physical signs of hypogonadism**
- Change in body composition with more central body fat
- Gynecomastia
- Testicular atrophy
- Muscular atrophy
- Osteoporotic fracture
- Loss of height
- Loss of facial, axillary and pubic hair

**Symptoms of hypogonadism**
- Mood changes
- Sleep disturbances
- Reduced libido
- Decreased energy
- Fatigue
- Decreased muscle strength
- Muscle aches
- Hot flashes
- Decreased ability to concentrate
- Poor memory
- Lack of morning erections
- Less rigid erections
- Decreased ejaculate volume
- Infertility

considered hypogonadal. The Massachusetts Male Ageing Study (MMAS), estimated that the prevalence of hypogonadism is between 6%-12% among men aged 39 to 79 years based on the presence of both symptoms and a biochemical evidence of testosterone deficiency.4

### TABLE 2. Populations at high risk for low serum testosterone levels

- Type 2 diabetes
- Obesity
- Dyslipidemia
- Obstructive sleep apnea
- Coronary artery disease
- Congestive heart failure
- Rheumatoid arthritis
- Chronic obstructive pulmonary disease
- Osteoporosis
- HIV and antiretroviral therapy use
- Chronic opioid and corticosteroid use
- Chemotherapy and radiation treatment
A large community based meta-analysis by Araujo et al investigating a cohort of 16,184 men with a mean follow up period of 9.7 years revealed that low testosterone levels were associated with an increased risk of cardiovascular-related mortality with an HR of 1.35, (95% CI, 1.13-1.62; p < .001).34

Multiple randomized controlled trials have suggested that TRT has a protective effect on rates of myocardial infarction (MI) with an increased time to angina and cardiac ischemia during a treadmill test.21,22,35

Web et al showed that injection of physiological levels of testosterone directly into the coronary arteries led to an increase in mean coronary artery diameter and blood flow.36

Arterial intima-media thickness, a marker for atherosclerosis, has been shown in a dozen studies to be greater in men with lower testosterone levels.37-48 A randomized controlled trial by Aversa et al demonstrated significant reductions in carotid intima-media thickness with TRT versus placebo in hypogonadal men.48

In a study of severely obese hypogonadal men randomized to 54 weeks of diet and exercise alone versus diet and exercise with TRT, testosterone-therapy-treated men had significant improvements in cardiac ejection fraction, carotid intima-media thickness, endothelial function, and epicardial fat burden. Of note, cessation of testosterone therapy resulted in return of cardiovascular factors to baseline 24 weeks later, despite ongoing exercise and dietary measures.37

Diabetes
Large population-based studies have revealed that men with the lowest levels of endogenous serum testosterone concentrations have twice the risk of developing diabetes.49-51 Data from HIM study revealed that as many as 50% of diabetic men were testosterone deficient.50 In the Rancho Bernado study that followed a population-based cohort of 6629 men for up to 20 years, testosterone levels were inversely related to weight, body mass index, fasting glucose, and serum insulin levels.7

Several randomized controlled trials have noted consistent metabolic improvements with TRT, through decreases in total and visceral body fat, decreases in insulin resistance and improvements in glycosylated hemoglobin levels and glycemic control.52-55

Bone and muscle health
Osteoporosis is a source of considerable morbidity and mortality in elderly men. Almost 30% of all hip fractures are in men and men are twice as likely as women to die in hospital after a hip fracture.53,56-57 A nursing home study revealed that 66% of elderly men who had experienced a hip fracture were testosterone deficient.58 Repletion of testosterone to physiological levels has been shown to significantly improve bone mineral density. A randomized placebo-controlled study by Amory et al in hypogonadal men demonstrated bone mineral density increased 3% to 4% in the hip and there was an impressive 10% increase in bone mineral density of the spine with TRT over a 36 month period.59

Numerous randomized placebo controlled trials have revealed that TRT given to hypogonadal men results in increased lean muscle mass with improvements in strength and endurance.60-68 In some older, frail men with limited mobility, significant functional gains have been demonstrated with appropriate testosterone replacement.60 A study by Amory et al suggests that TRT in testosterone deficient men may be of use in populations that are at risk of developing a muscle-wasting catabolic state. Treating testosterone-deficient men with TRT before knee replacement surgery improved functional independence and thus recovery afterwards.69

Other
Repletion of testosterone in hypogonadal men has been shown to improve several domains of sexual function, including libido, erectile function, and sexual performance.5,24,70-75 When regular TRT was added to therapy with “on demand” phosphodiesterase-type 5 (PDE-5) inhibitors, hypogonadal men who were refractory to treatment with a PDE-5 inhibitor alone recovered the ability to have an erection.73 Improvements in cognitive function, mood, vitality, and quality of life have also been accredited to TRT.76-82

Risks and realities
Restoring testosterone to physiological levels is generally very well tolerated and associated with few if any side effects. The intention is to bring the testosterone level back to the normal or high-normal range. Dosing to achieve levels above the normal range, however, can be cause for more serious concern and potential side effects.

Cardiovascular morbidity
Only four trials to date have suggested an increased risk of cardiovascular morbidity with TRT. Two of these studies used supra-physiologic doses of testosterone.83,84 The other two had major design
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and interpretation flaws.\textsuperscript{85,86} The Food and Drug Administration (FDA) confirmed these inaccuracies after official review. In fact, when the raw data was properly reinterpreted, TRT was actually shown to have a protective effect.\textsuperscript{87}

The largest meta-analysis to date which examined 75 placebo-controlled studies suggested that TRT was not related to any increase in cardiovascular risk and instead demonstrated a benefit in those with metabolic derangements.\textsuperscript{88}

A recent study reported results in more than 300 men who were randomized to placebo or TRT. The Testosterone’s Effects on Atherosclerosis Progression in Aging Men (TEAAM) was a placebo-controlled, double-blind, parallel-group, 1:1 randomized trial involving 308 men 60 years or older with low or low-normal testosterone levels (100 ng/dL to 400 ng/dL; free testosterone < 50 pg/mL), who were recruited at three US centers. Coprimary outcomes included common carotid artery intima-media thickness and coronary artery calcium. There was no increase in coronary artery calcium or carotid intima-media thickness (CIMT) after 3 years of testosterone therapy in the TRT arm compared to placebo.\textsuperscript{89}

**Congestive heart failure**

There is a concern for instigating volume overload in treating patients with a history of congestive heart failure (especially those with poorly controlled disease). Fluid retention is a possible side effect of TRT.\textsuperscript{16,90,92} Perhaps more concerning though, is that a link between untreated testosterone deficiency and increased mortality due to congestive heart failure has been suggested.\textsuperscript{93,94} Furthermore, several small prospective randomized controlled trials have demonstrated significant functional improvements in exercise capacity and peak oxygen consumption, without any adverse cardiovascular effect, in hypogonadal men given testosterone replacement over placebo.\textsuperscript{95-99} However, until there are larger trials to dictate otherwise, in patients with poorly controlled congestive heart failure, testosterone treatment is contraindicated.\textsuperscript{1,90}

**Lipid profiles**

With respect to serum lipids, the available data is inconsistent, but effect on lipids seems to depend on the amount of testosterone administered. While supraphysiologic doses of testosterone may have a negative effect on serum cholesterol through a reduction in high-density lipoprotein (HDL), dosing to achieve the eugonadal range of testosterone does not seem to affect lipid profiles.\textsuperscript{28,76,100,101}

**Polycythemia**

Erythropoiesis is stimulated by increased testosterone concentrations in boys at puberty, so that adult males, on average, have higher hemoglobin levels than adult females. The decrease in hemoglobin levels seen in elderly men is hypothesized to be secondary to declining testosterone levels.\textsuperscript{102} Canadian clinical practice guidelines recommend testosterone replacement in hypogonadal men with anemia of unknown origin. Although the restoration of hemoglobin levels to normal values may be beneficial, elevation to concentrations above the physiological range may lead to a dangerous increase in blood viscosity that could cause thrombosis. This is particularly important in those who are at high risk, such as elderly men with atherosclerosis and vascular insufficiency. The Endocrine Society recommends against testosterone replacement in those men with a baseline hematocrit > 50 for fear of worrisome erythrocytosis.\textsuperscript{90} Of note, it has been demonstrated that the incidence of erythrocytosis is often directly related to the dosage of testosterone administered, so that usually only supra-physiologic concentrations of testosterone are of significant concern.\textsuperscript{103} Studies suggest that these higher levels are more commonly seen with intramuscular (IM) dosing.\textsuperscript{24,76} One multicenter, randomized, parallel-group study demonstrated that 43.8% of hypogonadal men receiving IM testosterone injections versus 15.4% of hypogonadal men who received a testosterone patch had at least one documented elevated hematocrit value over a 24 week study period.\textsuperscript{76} Another prospective study observed erythrocytosis in only 5.5% of patients using a testosterone patch over 36 months with most changes in hemoglobin and hematocrit values limited to the first 3 months of treatment.\textsuperscript{23} Continued follow up screening is nevertheless recommended, with cessation of treatment if levels are concerning (hematocrit > 54).\textsuperscript{90}

One double-blind, placebo-controlled, randomized, parallel-group study using IM testosterone suggested testosterone may stimulate thromboxane A2 (TXA2), a vasoconstrictor and platelet pro-aggregatory agent. It was hypothesized that this may contribute to the thrombogenicity and RBC adhesion of androgenic steroids.\textsuperscript{104} Of note however, the treatment duration was short, the sample size was small and the patients were not testosterone deficient at baseline. Furthermore, this was purely a biochemical analysis with no clinical end points. Larger long term randomized controlled trials are therefore necessary to confirm this hypothesis.
Benign prostatic hyperplasia (BPH)

Although it is well recognized that benign prostatic growth is stimulated by the presence of androgens, multiple studies including several randomized controlled trials have failed to show an increase in voiding symptoms or other complications such as urinary retention during TRT in hypogonadal men.24,25,55,59,60,76,104-111 A slight increase in prostate size was seen in some trials of TRT, but flow rates and post void residual volumes did not change significantly when the normal physiological range of testosterone was achieved. This paradox may be due to the poor correlation between prostate volume and urinary symptoms. Clinicians should nevertheless be aware of this slight increase in prostate size with TRT, and AUA symptom scores should be monitored. It is suggested that caution be exerted with TRT for patients with severe lower urinary tract symptoms (IPSS > 19) at baseline.90 If voiding symptoms should arise during treatment with TRT, one may consider additional medical management (with a 5-alpha reductase inhibitor or alpha blocker) and/or a urological consultation.

Prostate cancer

Huggins and Hodges demonstrated, over 70 years ago, that suppression of testosterone levels leads to a regression of prostate cancer.112 It has since been the practice to reduce blood levels of androgen to castrate values in men with metastatic prostate cancer in order to delay cancer progression. Despite this relationship, however, years of research have failed to demonstrate any compelling evidence that TRT in hypogonadal men increases the risk of prostate cancer above that in the general population.24,25,76,100,103,113-118 In fact, it has been hypothesized that untreated hypogonadal men, in contrast to eugonadal and castrated men, may be at an increased risk of prostate cancer.73,119-124 This relationship has been described through a saturation model, which describes that prostate cancer growth is exquisitely sensitive to variations in serum testosterone levels below a certain threshold.125,126 This is based on the fact that the availability of binding sites for testosterone to androgen receptors is limited. When androgen receptors are saturated, further increases in testosterone levels do not lead to further androgen receptor binding, and thus this fails to stimulate prostate cancer growth. The approximate threshold beyond which androgen receptors are saturated was suggested in a series by Morgentaler and Rhoden who reported that the risk of a positive prostate biopsy was 21% in men with a testosterone level < 250 ng/mL versus 12% in men with a testosterone level > 250 ng/mL.124 Furthermore, in a retrospective analysis by Park et al, testosterone deficiency (< 300 ng/mL) was noted to be an independent risk factor for high-grade prostate cancer on biopsy.127 Low preoperative testosterone levels have also been associated with poor prognostic factors at the time of radical prostatectomy, including higher Gleason score, positive surgical margins, extraprostatic extension, and seminal vesicle invasion. Postoperative biochemical failure has also been linked to low pre-treatment testosterone levels.120,122,128-135

It is well accepted that metastatic prostate cancer is a contraindication to TRT.130 There is evidence, however, to suggest that TRT is safe in hypogonadal men who have been “cured” of prostate cancer with surgery or radiation treatment for localized disease. Among with multiple benefits of feelings of well-being and increased energy, improvements in erectile function, a common post-treatment difficulty, have been noted with TRT.135 Although most of the evidence comes from small case series, results demonstrate that even men with poor prognostic features such as higher Gleason scores (8-10) can be successfully treated for long durations without biochemical recurrence of prostate cancer.136-143 It has been suggested that a disease-free interval of at least 1 year or more should precede any TRT. It has also been recommended that these patients be referred to a specialist for expert assessment and close follow up.1

Fertility and secondary sex characteristics

Fertility is significantly compromised during TRT, as a secondary effect due to a down regulation of gonadotropins.14,91,92,144 Testicular size and consistency as a secondary effect due to a down regulation of FSH/LH stimulation. These effects are usually reversible with the cessation of therapy; however, it is recommended not to treat patients with TRT if they are interested in maintaining fertility more than in improving symptoms of hypogonadism.130

Gynecomastia and breast cancer

Breast tenderness and swelling may also occur due to the aromatization of testosterone into estradiol; however, the incidence is rare with doses used to achieve the normal range of testosterone.16,91,92 These effects are usually reversible with cessation of therapy. Interestingly, it is widely recommended not to give TRT to men with a history of breast cancer due to the fear that aromatized androgens may stimulate breast cancer proliferation.1,98 This direct causal effect, however, has never been studied in hypogonadal men who were given TRT. In fact, in-vitro studies have actually revealed that androgens have apoptotic and
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anti-proliferative effects on breast cancer growth. Furthermore, androgen therapy, both with or without an aromatase inhibitor, has been suggested to have a protective effect against breast cancer. Recent data has revealed that neoadjuvant therapy with testosterone and an aromatase inhibitor given to hormone positive breast cancer patients significantly reduces tumor size for a more successful surgical outcome.151 Given the current level of evidence in the literature, however, a history of breast cancer remains a contraindication to TRT in clinical practice guidelines.190

Sleep apnea
Testosterone levels play a role in sleep architecture, which is suggested to be related to centrally mediated breathing controls rather than anatomical factors. The Endocrine Society Clinical Practice Guidelines recommend against TRT in men with untreated, severe obstructive sleep apnea.90 Most of the data to corroborate this recommendation, however, comes from case reports and small studies. Given the available evidence, it appears that while supra-physiologic levels of testosterone may have a deleterious effect on sleep patterns, restoring testosterone to the eugonadal range does not seem to have these negative consequences. In fact, repletion of testosterone may be of benefit with regards to sleep, since sleep apnea has been suggested in several publications to be more common in the hypogonadal population versus eugonadal controls.114-128 Until further evidence is available through large prospective trials, however, severe untreated obstructive sleep apnea remains a contraindication to testosterone replacement.90

Hepatic effects
The risk of hepatotoxicity with testosterone supplementation is historical and limited to oral preparations that are metabolized by the liver. The newer oral forms of testosterone are absorbed by the lymphatic circulation, bypassing the portal system and subsequent hepatic metabolism that accounts for toxic effects. Routine monitoring of liver enzymes for Canadian and US approved formulations of TRT is therefore unnecessary.16 Although this route of delivery may seem ideal, the bioavailability of the dose administered depends on the ingestion of a fatty meal and therefore routine use can be impractical.

Skin reactions
Acne and oily skin are infrequent with physiological doses of testosterone. Local skin reactions at the delivery site are more commonly a concern with transdermal testosterone therapy. Erythema and pruritus are the usual reactions and are much more prevalent with patches (66%) than with gel preparations (5%) as demonstrated in a prospective multicenter double-blind randomized study by Wang et al.103

Conclusion
Testosterone deficiency syndrome is a syndrome related to low testosterone levels, which often occur later in life, which has been linked to considerable morbidity and health care cost burden. Due to the increasing life expectancy of the population, the number of symptomatic, hypogonadal men presenting to our clinics is also expected to increase. Fortunately, evidence suggests that TRT is quite safe and effective at helping to treat or delay time to progression of morbidities associated with this condition. It is crucial, however, that clinicians are aware not only of the benefits, but also of the possible risks associated with treatment so that patients are appropriately selected and follow up is adequate. Given our current level of evidence, contraindications to TRT include polycythemia (HCT > 54), metastatic prostate cancer, a history of breast cancer, poorly controlled congestive heart failure, untreated severe obstructive sleep apnea, as well as those desiring fertility over symptomatic treatment.

Disclosure
Dr. Jacob Hassan has no disclosure. Dr. Jack Barkin is a speaker and investigator for Glaxo, Actavis, Pfizer, Astellas, Merus Labs, Allergan, Janssen, Ferring, NeoTract and Merck.

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