# Testosterone deficiency and replacement: Myths and realities

*Ethan D. Grober, MD, MEd, FRCSC*

Assistant Professor, Division of Urology, University of Toronto; Urologist, Mount Sinai Hospital and Women's College Hospital, Toronto, ON

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## Abstract

Testosterone deficiency, or hypogonadism, is common and may have deleterious effects on men, including decreased overall well-being, reduced sexual function and bone loss. Despite data demonstrating strong links between testosterone deficiency and significant comorbid conditions (including type 2 diabetes and metabolic syndrome as well as the health benefits of testosterone-replacement therapy [TRT]), some physicians are still hesitant to initiate these therapies. Their reluctance is based on a number of prevailing myths associating TRT with adverse prostate health and recent concerns highlighting the possibility of increased cardiovascular risk.

## Introduction

An estimated 25% of men have low levels of testosterone.[1] Besides being fundamental for the development and maintenance of male characteristics and male sexual organs, testosterone also has effects on most major organs, such as the brain, muscle, kidney, bone, liver and skin. Clinical consequences of testosterone deficiency, or hypogonadism, range from decreased libido and vitality, to osteoporosis[2,3] (Fig. 1), as well as increased mortality.[4]

Testosterone deficiency is more common in men with certain disease states, including obesity, diabetes, hypertension, hyperlipidemia, asthma, chronic obstructive pulmonary disease (COPD) and prostatic disease.[5] Indeed, the TIMES2 (Testosterone replacement In hypogonadal men with either MEtabolic Syndrome or type 2 diabetes) study showed that testosterone replacement therapy (TRT) improved glycemic control, lipid levels, sexual function and libido in men with type 2 diabetes and/or metabolic syndrome, with no corresponding increase in adverse events.[6] Despite such data, several prevailing myths surrounding the use of TRT may prevent physicians from considering its use in patients who might benefit from this type of therapy.

One myth is that TRT contributes to worsening benign prostatic hyperplasia (BPH) and to an increase in the risk of urinary retention. In a retrospective review of 120 hypogonadal men treated with TRT over a 10-year period, TRT was actually associated with a lower risk of worsening lower urinary tract symptoms (LUTS).[7] Among 52 men randomly assigned to receive TRT versus placebo for 1 year, investigators found that LUTS, flow rates and volumes voided were significantly better in the TRT group than in the placebo group.[8]

Another common misconception is that TRT increases a man's risk of developing prostate cancer. Importantly, TRT has not been associated with clinically significant increases in prostate-specific antigen (PSA) or an increased risk of prostate cancer.[9-14] In a systematic review of published studies of TRT in men with hypogonadism, the average PSA increase after initiation of TRT was 0.3 ng/mL in hypogonadal men under 65 and 0.4 ng/mL in men over 65.[15] The practice of using TRT as a "stress test" to determine whether PSA will rise or unmask clinically unapparent prostate cancer is not supported by science.[15] Consequently, significant increases in PSA among men on TRT should not be solely attributed to the use of TRT and should be investigated irrespective of TRT use.

No association has been established between endogenous testosterone concentrations and PSA, or the risk of developing prostate cancer.[16-20] However, among men with prostate cancer, low endogenous testosterone has been associated with adverse prognostic features, including higher stage cancer,[21,22] higher Gleason scores,[23-25] higher frequency of positive surgical margins,[26] and decreased overall survival with metastatic disease.[27]

Consistent with previous smaller investigations, in a review of 103 hypogonadal men with prostate cancer and a undetectable PSA following radical prostatectomy treated with TRT, there were no differences in the rates of biochemical recurrence compared to a reference group of 50 non-hypogonadal men. Among both groups, all biochemical recurrences were

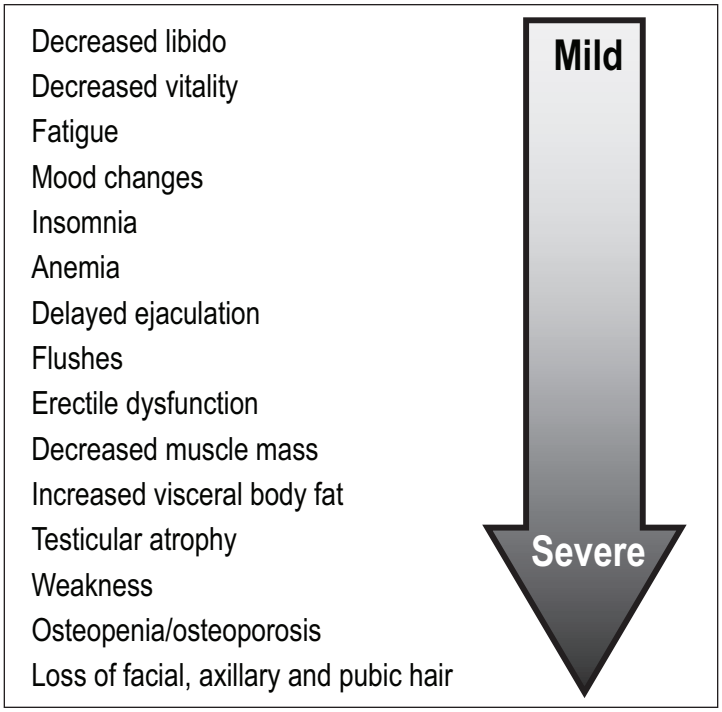


***Fig. 1.*** Clinical manifestations of testosterone deficiency.

seen in men with high-risk features (Gleason score 8 or higher, positive surgical margins or lymph nodes), suggesting that the characteristics of the cancer themselves drive recurrences versus testosterone levels or replacement.[28]

In a study of 13 hypogonadal men with untreated prostate cancer undergoing active surveillance, TRT for a median of 30 months was not associated with increased PSA levels or prostate cancer progression.[29]

Many healthcare providers hesitate to initiate men on TRT due to the belief that these treatments increase the risk of cardiovascular (CV) events. However, the data supporting this belief are conflicting. A systematic review and meta-analysis of 30 randomized trials assessed the effect of TRT on CV events and risk factors in 1642 men with different degrees of androgen deficiency – 808 were on TRT.[30] The results were inconsistent across trials, but did not support an association between testosterone use and important CV effects. In another systematic review and meta-analysis of 51 randomized trials, the relative risks of myocardial infarction, arrhythmia, coronary bypass surgery and all-cause mortality were not significantly increased with TRT use.[10]

The Testosterone in Older Men with Mobility Limitations (TOM) trial randomly assigned 209 men with mobility issues and low testosterone to 6 months' treatment with testosterone gel to improve lower extremity strength and physical function.[31] In this population of older men with limitations in mobility and a high prevalence of chronic disease, testosterone gel was associated with an increased risk of CV events. However, these results should be interpreted with caution, as the study was not designed to assess CV disease, and more patients in the testosterone arm had hypertension or dyslipidemia at baseline. Moreover, the prescribed dose of testosterone was two times the standard starting dose and the criteria for CV events were relatively subjective and non-specific, including for example the complaint of shortness of breath, tachycardia or leg edema. The small size of the trial and the unique population should limit physicians from making broader assumptions about the safety of TRT for other patient populations.

More recently, a retrospective study of 8709 hypogonadal men who underwent coronary angiography in the Veterans Affairs system between 2005 and 2011 assessed the association between testosterone therapy and all-cause mortality, myocardial infarction (MI) or stroke.[32] Overall, the unadjusted data demonstrated a protective effect of TRT use on CV risk; however, the adjusted data showed an adverse impact. Puzzling, however, is that the testosterone levels among the men on TRT versus men not on TRT were unknown. The testosterone levels among the men experiencing a CV event versus men without an event were unknown. Also concerning is that about 100 of the "men" in this study were later reported to be women.

## Conclusions

Concerns regarding the risk of TRT on CV events need to be balanced with the evidence showing a positive impact of testosterone on heart health. Further studies are needed. Until then, we should be cautious of increasing testosterone levels too high, particularly in older men with significant risk factors for CV disease.

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**Correspondence:** Dr. Ethan Grober, Murray Koffler Urologic Wellness Centre, 60 Murray St., 6th Floor, Box 19, Toronto, ON M5T 3L9; fax: 416-586-8354; egrober@mtsinai.on.ca