



OPINION ARTICLE

The putative mechanisms underlying testosterone and cardiovascular risk [v1; ref status: indexed, <http://f1000r.es/374>]

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Abstract

The use of testosterone supplementation therapy (TST) is increasing primarily in men with symptomatic hypogonadism. While TST has been shown to have numerous benefits, as its use increases, the role on cardiovascular health must be explored. Previous evidence showed no adverse cardiovascular risks associated with TST use; however, more recent studies suggest that there may be an associated risk. The exact mechanism by which TST may contribute to cardiovascular risk has not been elucidated. Numerous mechanisms have been proposed which include testosterone's effect on thromboxane A2 receptors, vascular adhesion molecule 1 receptors, erythropoiesis, and obstructive sleep apnea, all of which can ultimately lead to atherogenesis and increased cardiovascular risk.

Article Status Summary

Referee Responses

Referees	1	2	3
v1 published 04 Apr 2014	 report	 report	 report

- 1 **M. Emre Bakırcıoğlu**, Bahçeci Health Group Turkey
- 2 **Matthew S. Wosnitzer**, New York Presbyterian Hospital USA
- 3 **Boback Berookhim**, Memorial Sloan Kettering Cancer Center USA

Latest Comments

No Comments Yet

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Testosterone supplementation therapy (TST) is used to treat patients who suffer from symptomatic hypogonadism. The benefits of TST are numerous and include improved sexual function, bone mineral density, muscle mass and strength¹. Currently, there is no direct evidence linking TST with cardiovascular risk factors; however, several small studies have theorized potential mechanisms (Figure 1) by which TST contributes to cardiovascular risk and these are summarized in this article.

One proposed mechanism by which cardiovascular risk could be affected is in the regulation of platelet thromboxane A2 (TXA2) receptor expression by testosterone². TXA2, by acting on membrane receptors, helps in platelet aggregation and vascular smooth muscle contraction³. TXA2 synthesis is increased in numerous thrombotic cardiovascular events⁴. Ajayi *et al.*² examined the relationship between testosterone and TXA2 by measuring platelet TXA2 receptor density in response to TST in healthy men². Men were given testosterone cypionate 200 mg IM or placebo at day 1 and day 14 of the 10-week study period. Platelet TXA2 receptor density and dissociation constant then were measured. Testosterone supplementation was associated with increased TXA2 receptor density compared with placebo, suggesting that testosterone regulates the expression of platelet TXA2 receptors. The mechanism by which this occurs is not completely understood. However, it has been shown that inhibition of both transcription and translation of TXA2 attenuates testosterone's effects on TXA2 receptor density in multiple cell lines⁵. This finding suggests that testosterone may increase TXA2 receptor density by acting at the genomic level to stimulate its synthesis.

Testosterone has also been shown to contribute to atherosclerotic lesions by promoting monocyte adhesion⁶. Atherosclerotic lesions are due to low density lipoprotein (LDL) infiltration into the arterial intima layer that subsequently results in endothelial cell activation and monocyte recruitment⁷. The endothelial cells express vascular cell adhesion molecule 1 (VCAM1) which allows for monocyte

adhesion before transmigration through endothelial junctions⁷. These monocytes then release local inflammatory cytokines and metalloproteinases. The inflammatory cytokines promote smooth muscle proliferation that contributes to local plaque formation. Several studies have explored the role of dihydrotestosterone (DHT), a potent testosterone metabolite, in the various aspects of atherosclerotic plaque development⁸. McCrohon *et al.* studied the effect of DHT in male umbilical vein endothelial cells⁹. They demonstrated increased VCAM1 expression with increased monocyte adhesion. Similar findings have been observed using arterial endothelial cells⁹.

Testosterone also plays a role in increasing hematocrit levels. Several studies have reported increased hematocrit levels following TST administration^{10,11}. This correlation is likely to be secondary to the stimulation of erythropoiesis by testosterone. Increased hematocrit levels, or polycythemia, can itself contribute to adverse cardiovascular events. For example, an increased number of red blood cells can result in increased blood viscosity and predispose to thrombosis. A recent study by Marchioloi *et al.* analyzed the cardiovascular risks in patients with polycythemia vera¹². Patients, whose mean age was 64 (62% males), were divided into either a less intensive treatment group in which the target hematocrit was 45–50% or an intensive treatment group in which the target hematocrit was 45–50%. The choice of therapeutic approach was left to the investigator. The primary endpoint studied was the time until death from a cardiovascular cause or a major thrombotic event. The authors found that those whose hematocrit was maintained below 45% had significantly lower rate of cardiovascular death and major thrombotic events compared to those who had a hematocrit between 45–50%¹². Additionally, Kunnas *et al.* evaluated the association between hematocrit and coronary heart disease (CHD) in men over 55¹³. This study's conclusions were similar to that previously discussed, in that men with a hematocrit greater than 50% were 1.8 times (1.1–2.7) more likely to die from CHD compared with men with a hematocrit of less than 50% after adjusting for coronary risk factors¹³.

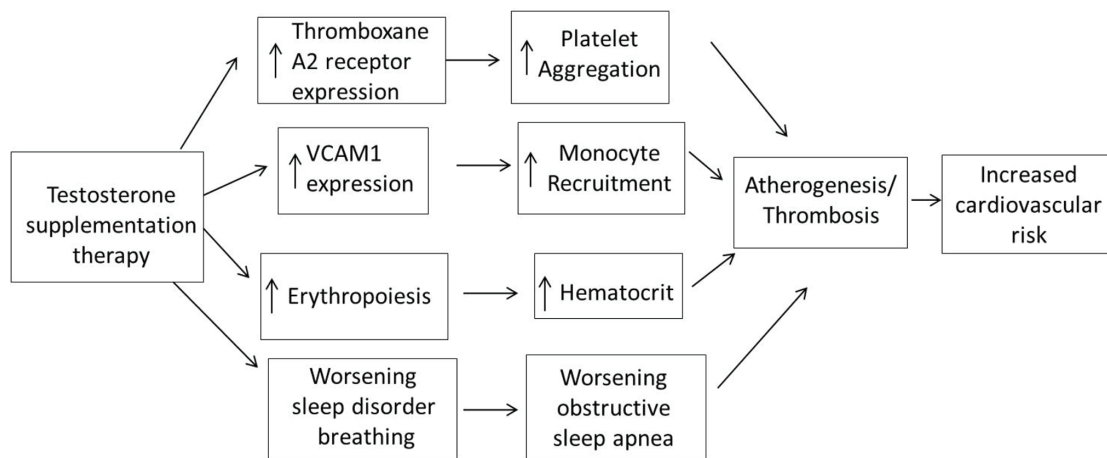


Figure 1. Proposed schematic by which TST may contribute to cardiovascular risk. TST increases TXA2 receptor expression, VCAM1 expression, erythropoiesis, and worsens sleep disorder breathing, all of which ultimately contribute to atherogenesis and worsening of cardiovascular health. VCAM1 - vascular cell adhesion molecule 1.

Testosterone may also contribute to cardiovascular disease by worsening pre-existing obstructive sleep apnea (OSA). Androgen deficiency is often observed in men who are obese or who have OSA^{14–16}. Obese men have lower serum testosterone compared to age-matched non-obese men¹⁷. This may be secondary to hypothalamic dysfunction or increased metabolic clearance as a result of central obesity¹⁷. Similarly, previous studies have shown that men with OSA have low systemic testosterone levels, independent of increasing age or obesity, that correlate with the severity of hypoxia during sleeping hours^{16,18,19}. Additionally, the low systemic testosterone levels in these men have been shown to be reversible with nasal continuous positive airways pressure therapy (CPAP)^{16,19}. The mechanism of reduced testosterone in men with OSA is likely to occur through OSA mediated dysfunction of the pituitary-gonadal axis^{17,20}. Although controversial, TST has been used in men with severe OSA, given that men may remain androgen deficient if they are unable to comply with continuous positive airway pressure (CPAP) or lose weight²¹. Hoyos *et al.* studied the effects of TST by conducting a randomized, double-blind, placebo controlled trial in 67 men with severe OSA. Testosterone treatment worsened the oxygen desaturation index and nocturnal hypoxemia compared to placebo, suggesting worsening of OSA¹⁴. OSA itself is an independent risk factor for cardiovascular disease, and is associated with myocardial infarction and stroke²². OSA likely contributes to disease by worsening atherosclerosis by affecting multiple atherogenic

pathways such as hypertension, insulin resistance, dyslipidemia, endothelial dysfunction, and oxidative stress²².

While testosterone has not been definitively linked to cardiovascular risk, these proposed mechanisms provide some insights into TST's physiological effect on the cardiovascular system. Despite recent studies demonstrating an increased cardiovascular risk associated with TST²³, there is a large body of literature demonstrating the benefits of testosterone therapy. In fact testosterone replacement has demonstrated to decrease mortality^{24,25}. Until the results of randomized trials are available, appropriate patient counseling and an emphasis on the importance of compliance with follow-up are essential prior to initiating testosterone replacement.

Author contributions

All the authors contributed equally to the writing of the manuscript.

Competing interests

No competing interests were disclosed.

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Current Referee Status:

Referee Responses for Version 1



Boback Berookhim

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Maganty and colleagues provide a timely and interesting report on a rather controversial topic which has been the subject of a number of recent, large, population-based, retrospective studies that have received media attention. The role of testosterone replacement therapy in worsening cardiovascular disease remains unanswered, and will likely require extensive, well-matched, randomized, placebo-controlled trials to prove its effect - whether protective, or aggravating - in cardiovascular disease.

The authors, however, provide a well researched review of the putative mechanisms underlying this possible, though unproven, relationship. While the thromboxane A2, monocyte activation, polycythemia vera and obstructive sleep apnea pathways proposed are plausible, there is - to date - no clear evidence that any of these contribute to increased cardiovascular risk in men. Platelet activation and increasing atherosclerotic intimal plaque would be interesting topics for further research in testosterone replacement therapy, and will help to better elucidate this issue.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.



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This is a comprehensive summary of the potential mechanisms (i.e. platelet thromboxane A2 receptor, monocyte adhesion via endothelial cell vascular cell adhesion molecule 1, increased hematocrit level) underlying the possible association of testosterone supplementation therapy (TST) with cardiovascular outcomes. The discussion of possible mechanisms is important in light of recent questions about the cardiovascular side effects of TST, with studies showing both decreased and increased cardiovascular and mortality risk. An ideal study would be prospective and include additional measurements of hematocrit (or TXA2, VCAM1 for example) which could be related to cardiovascular outcomes and help to better select which men may derive the most benefit and least risk from TST.

Additionally, a recent by Yassin et al.¹ adds more data for the safety of TST (intramuscular testosterone

undecanoate) in older men with late-onset hypogonadism and erectile dysfunction (mean age 59 years with mean treatment duration of over 4 years). No cardiovascular side effects were noted during the study and there was improvement of metabolic syndrome-related characteristics including obesity, blood glucose, cholesterol, and BP. Subjects were mostly were overweight or obese, and a minority had baseline cardiovascular comorbidities (12%), DM2 (31%) or HTN (45%) issues (which are similar to - or increased compared with - the baseline characteristics of the Finkle et al. study² – reference 23 in the article). In the future, more studies are needed to confirm these findings, especially investigating the mechanisms by which TST may affect cardiovascular outcomes.

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I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.



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This manuscript - '*The putative mechanisms underlying testosterone and cardiovascular risk*' - gives valuable information about the mechanisms of cardiovascular effects of testosterone supplementation therapy in hypogonadal men. This opinion article is well written and deserving of indexation.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.
