

Research Article

Testosterone and Arterial Thrombosis

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Abstract

Epidemiologic studies suggest that cardiovascular disease affects men at an earlier age and may contribute to greater mortality. Cross sectional and prospective studies have considered the role of endogenous testosterone levels in cardiovascular disease and mortality but few prospective or randomized trials have looked at supplemental testosterone therapy and long term cardiovascular outcomes. Recent retrospective studies suggest that testosterone therapy increases the risk of cardiovascular disease and associated mortality, however it is still unclear by what mechanism. In this review we begin with a case report and attempt to summarize the mechanisms by which testosterone may promote arterial thrombosis and hemostasis. Overall testosterone plays a complex role in the thrombotic pathway, and may have different effects when given acutely or long term, especially in those with other modifiable and non-modifiable risk factors for cardiovascular disease.

INTRODUCTION

A 71 year old gentleman with hypertension, hyperlipidemia, coronary heart disease, type II diabetes and hypogonadism presents to clinic with concerns regarding use of testosterone therapy. He was diagnosed with central hypogonadism over 15 years ago in the setting of chronic illness and has been maintained on testosterone therapy since then. Most recently he has been using androgel 1.62% at 60 mg daily. Despite testosterone therapy he notes libido is variable and he continues to have erectile dysfunction. He also has mild urinary hesitancy and frequency and was diagnosed with benign prostatic hypertrophy, with a negative prostatic biopsy performed due to a rising PSA. He has no prior history of elevated hematocrit, no prior history of falls or fractures, and no prior history of sleep apnea.

His cardiac history began in 2000 when he developed worsening dyspnea with mild exertion and intermittent 'tingling' in his chest which occurred at rest. In 2003 a stress echocardiogram noted mild inferior and posterior hypokinesis of the left ventricle with 1 mm ST segment depression on electrocardiogram and increased dyspnea associated with exercise. Left heart catheterization noted significant mid LAD stenosis and 90% stenosis of the LAD diagonal which prompted angioplasty and placement of two drug eluting stents. Over the next five years he required angioplasty and three more drug eluting stents to LAD, circumflex coronary artery and right coronary artery. His last procedure was five years ago and his most recent catheterization showed no stenosis or ischemia. He continues to endorse intermittent episodes of sharp chest

pain which occur at rest, lasting minutes without associated symptoms. He also notes dyspnea with climbing stairs, bending over and minimal exertion despite negative serial cardiac and pulmonary workup. He continues to try to be active, plays golf regularly and does exercise videos. He denies current tobacco use and is attempting weight loss through dietary changes and exercise.

His examination is remarkable for an obese male weighing 101 kg with a blood pressure of 140/86 and pulse of 60. Heart exam is notable for holosystolic murmur at the apex with normal S1 and S2, good peripheral pulses and no elevation in JVP. His lungs are clear with no evidence of gynecomastia.

With intermittent therapy his total testosterone is 232 ng/dL by liquid chromatography mass spectrophotometry (LCMS), free testosterone is 44 pg/mL with low sex hormone binding globulins of 19 nmol/L, normal liver function, hematocrit and stable PSA 2.9 ng/mL.

Should this man continue with testosterone therapy?

TESTOSTERONE AND CARDIOVASCULAR DISEASE

Cardiovascular disease continues to be a leading cause of death, with cross-sectional statistics showing earlier onset and greater mortality in males than females [1]. Testosterone, the predominant sex hormone produced from leydig cells within the testes, has often been implicated. Cross-sectional and prospective studies have looked at the risk of cardiovascular

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Low T or True Male Hypogonadism

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disease and mortality related to endogenous testosterone levels and after supplemental testosterone therapy, with few randomized trials of long term data. With regards to endogenous testosterone, meta-analyses of prior prospective studies show that low testosterone levels are modestly associated with increased all-cause and cardiovascular disease mortality [2], as well as incident cardiovascular disease [3] after controlling for other cardiovascular risk factors. This may partly be explained by the excess association of low testosterone with obesity, diabetes and other chronic morbidities [4]. Recent studies also implicate high endogenous testosterone levels with all-cause mortality and ischemic cardiovascular mortality [5]. Possible explanations include that high endogenous testosterone levels raise hemoglobin and hematocrit, cause fluid and salt retention, and alter the balance in lipoproteins, all which may contribute to cardiovascular disease, heart failure and ischemic stroke. There is heterogeneity in prospective trials of exogenous testosterone supplementation, with limited focus on cardiovascular events as a primary outcome. In 2010 a randomized trial of testosterone supplementation in elderly men with hypogonadism and limited mobility was discontinued due to excess cardiovascular events in the treatment group [4]. This risk was further emphasized by an observational study using a national health-care database which suggested increased mortality particularly in the elderly and in younger men with prior coronary heart disease and within the first 90 days of filling a testosterone prescription [6].

Given the recent growth in the testosterone treatment options and controversy regarding cardiovascular risk associated with supplemental testosterone therapy, the timing is ideal to further investigate the mechanism by which testosterone could result in coronary heart disease. In this review we investigate mechanisms by which testosterone may promote arterial thrombosis, thus contributing to clinical cardiac events. A review of the literature was conducted using search terms 'low testosterone', 'platelets', 'testosterone replacement', 'blood coagulation', 'clotting', 'endothelium', 'inflammation', 'cardiovascular disease'.

T and endothelium

Vascular endothelium plays a crucial role in maintaining vessel growth dilation, tone, and mediating the inflammatory and coagulation pathways. Angiogenesis contributes to maintaining equilibrium. While one study showed that endothelial progenitor cells are more dependent on estradiol rather than androgens in vivo and in vitro [7], another study showed increased activity of endothelial progenitor cells in vitro after injection of physiologic doses of a synthetic androgen [8]. In studies of vascular plaque formation, testosterone administration in physiologic doses was shown to reduce neo-intimal plaque progression in animal models in vitro, which is felt to be secondary to up-regulation of the androgen receptor in the vessel wall [9]. Impaired coronary vasodilation and reactivity has also been shown to be a predictor of future cardiovascular events [10]. Testosterone infusion at physiologic and supra-physiologic doses has been shown to promote vasodilation both in vivo and in vitro [11], as well as promote coronary vasodilation and increased coronary diameter when infused short term in subjects with cardiovascular disease [12]. Brachial artery reactivity, a correlate of coronary artery function, as measured by flow mediated dilation at the brachial

artery, was negatively correlated with endogenous total and free testosterone in males [13]. Studies of supplemental testosterone in hypogonadal men have shown positive results on flow mediated dilation, with one study showing improvement in brachial artery reactivity in subjects with coronary heart disease after 12 weeks of therapy with oral testosterone [14]. These data suggest vasodilatory effects of testosterone both when given short and long term.

Testosterone and platelets

Platelets play a key role in thrombus formation through adhesion to the vascular wall, aggregation, and stimulation of coagulation through release of metabolites such as thromboxane A₂ which further promotes platelet activity and vascular muscle contraction. In vitro studies in animal models suggest that testosterone deficiency is associated with decreased platelet aggregation and thromboxane A₂ receptor density, with testosterone therapy improving platelet activity and thromboxane A₂ receptor density [15]. In a randomized blinded placebo controlled study of healthy young men, testosterone therapy by injection twice at physiologic doses two weeks apart was shown to increase platelet aggregation activity and thromboxane A₂ receptor density with a return to baseline within four weeks of therapy administration [16]. The G coupled protein receptor P2Y₁₂ on the platelet surface also plays an important role in platelet aggregation. In a study using a human megakaryocytic cell line, administration of testosterone in culture resulted in increased gene expression of P2Y₁₂, suggesting another pro-thrombotic mechanism [17]. In contrast nitric oxide has been shown to play an important role in vascular vasodilation and regulating hemostasis. In human umbilical vein endothelial cells, testosterone exposure at physiologic concentrations in cell culture resulted in increased nitric oxide production and nitric oxide synthase activity, which stopped with exposure to supraphysiologic concentrations of testosterone [18]. Similarly in animal studies with rat aortic endothelial cells, testosterone administration in vitro resulted in increased nitric oxide production and reduced platelet aggregation [19]. Thus, both animal and human data suggest a mixed effect of testosterone on platelet activity and function.

T and coagulation

Coagulation follows platelet stimulation with tissue factor initiating the pathway leading to thrombin formation. Prior studies have shown increased cardiovascular risk associated with greater levels of pro-thrombotic proteins factor VII and fibrinogen [20]. Low testosterone has also been associated with higher levels of factor VII and fibrinogen cross-sectionally after controlling for age, obesity and other metabolic parameters [21]. Case control studies from Norway in elderly males have shown those with low testosterone have lower ex vivo plasma levels of the inhibitor protein of tissue factor called tissue factor pathway inhibitor (TFPI) as well as a more rapid initiation of coagulation [22]. A follow up placebo controlled interventional study in elderly men with low testosterone given replacement therapy with multiple injections over one year showed no difference in levels of TFPI, activated factor VII or in coagulation time despite normalization in testosterone levels [23]. Further analysis suggests that this may have been due to inappropriate timing of

lab assays with testosterone administration, due to endothelial changes with aging or differences between short term and long term effects of testosterone [24].

Testosterone has also been seen to promote coagulation by affecting proteins involved in the fibrinolytic pathway, which is initiated by plasmin, stimulated by tissue plasminogen activator (tPA), and inhibited by plasminogen activator inhibitor-1 (PAI-1) and plasminogen activator inhibitor-2 (PAI-2). First discovered in 1962 [25], cross sectional studies have shown an association between lower endogenous testosterone and greater levels of (PAI-1) in subjects with coronary artery disease, suggesting increased cardiovascular risk from reduced fibrinolysis [26]. This inverse association between endogenous testosterone levels and PAI-1 was also seen in obese patients and those with greater central obesity compared with healthy controls [21], and in men with newly diagnosed hyperlipidemia [27]. In cell culture studies using human umbilical vein endothelial cells, physiologic dosing of testosterone stimulated tissue plasminogen activator (tPA) and decreased PAI-1 production [28]. Prospective interventional studies in healthy men have shown a reduction in fibrinolytic proteins with administration of testosterone metabolite DHEA or with other anabolic androgens [24]. In healthy men attempting to increase fertility, testosterone administered by injection over 52 weeks was associated with an initial fall in PAI-1, protein C protein S with return to baseline over the course of treatment, with no changes in tPA over the course of therapy [29]. In a randomized, double blinded, placebo controlled study of men with stable coronary heart disease; testosterone therapy administered in the form of transdermal patch resulted in no changes in plasma levels of fibrinogen, tPA or PAI-1 over greater than three months of therapy [30]. Overall the discrepancies observed in testosterone studies may reflect differences in the age of subjects, different formulations of testosterone with physiologic and supra-physiologic dosing, and differences in duration of therapy.

T and inflammation

Chronic inflammation is felt to play a role in the development and progression of atherosclerosis with inflammatory markers such as CRP and ESR implicated as predictors of coronary heart disease [31]. Inflammatory cytokines such as IL-1, IL-6, TNF-alpha also help propagate the development of atherosclerosis and are associated with increased cardiovascular risk [32,33]. In vivo animal studies have shown that inflammatory interleukin cytokines are elevated in androgen deficiency [34]. Cell culture studies also show that incubation with testosterone reduced inflammatory cytokine TNF α production in vascular endothelium and other cell lines [35] and stimulated anti-inflammatory cytokine IL-10 production [36].

Human studies have shown elevated inflammatory cytokines in young hypogonadal untreated males without metabolic disease or cardiovascular disease, suggesting a mechanism for future atherosclerosis [37]. In males with stable coronary artery disease and without myocardial infarction, pro-inflammatory IL-1 β levels were elevated in hypogonadal versus eugonadal subjects [38]. A randomized placebo controlled cross-over intervention based trial in hypogonadal men showed a reduction in TNF α and IL-1 after one month of injectable testosterone therapy compared to

placebo, with subgroup analysis showing significant reduction only in TNF α among subjects with coronary heart disease [39].

DISCUSSION AND CONCLUSION

In the search for risk factors associated with cardiovascular disease incidence and mortality in men, recent studies have implicated both endogenous testosterone levels as well as supplemental testosterone therapy. Long term data is limited and few intervention based trials have focused on cardiovascular outcomes. In this review we investigated testosterone's effect on various mediators in the thrombotic pathway, and considered studies looking at endogenous testosterone and/or with supplemental testosterone. Despite heterogeneity among studies, it appears that testosterone plays a role at all levels in the thrombotic pathway, as summarized in Table 1. At the level of vascular endothelium, testosterone administration appears to be anti-thrombotic with in vitro studies showing increased activity of endothelial progenitor cells [8], and both in vitro and human studies showing vascular vasodilation after acute or long term treatment [11,12,14]. Testosterone therapy appears to have a mixed effect on platelets, with in vitro and human studies showing increased thromboxane A2 receptor density and gene expression of P2Y12 which promote platelet activity and aggregation [16,17], and in vitro studies also showing increased nitric oxide production which reduces platelet activity [18,19]. With regards to the coagulation cascade, androgen deficiency is associated with increased pro-thrombotic factors [21,22] and increased inhibitors of fibrinolysis [26], but testosterone therapy does not appear to change the balance in coagulation proteins [23] or the balance in factors involved in fibrinolysis when given for longer duration [30,31]. Studies in inflammation do show that androgen deficiency is associated with elevated inflammatory cytokines [34,38], suggesting a pro-thrombotic mechanism in those untreated, while a therapeutic trial over one month in men with symptomatic androgen deficiency showed a reduction in inflammatory cytokines [39]. Taken in sum these studies suggest the role of testosterone on the vasculature is mixed. It is difficult to specify the weight of each of these mediators in the pathogenesis of atherothrombotic events.

It is also possible that testosterone's effect on the vasculature may be confounded by other modifiable and non-modifiable factors including age, BMI, lifestyle, and other chronic comorbidities [4]. Despite attempts to adjust for such factors in experimental and prospective studies, it is hard to assess which factors are downstream effects of the testosterone level versus which are distinct mediators in the atherothrombotic pathway. One limitation in this analysis is that in vitro and in vivo analysis may not always translate into similar results in human studies. Another difficulty is the use of different reference values for testosterone and different assays in different studies. Prior immuno-assays are now replaced by liquid chromatography mass spectrophotometry (LCMS), which make comparison difficult. Another difficulty in assessing the effect of testosterone on thrombosis is that testosterone can be converted via 5 α -reductase to dihydrotestosterone or aromatized to estradiol. Both of these testosterone end products may have differential effects on various mediators associated with thrombosis. Lastly many of these studies included here are non-randomized, with

Table 1: Testosterone's impact on various mediators of thrombosis.

	Pro-thrombotic mechanisms	Anti-thrombotic mechanisms
Endothelium		-May increase activity of endothelial progenitor cells in vitro [8] -May reduce progression of plaque formation in animal models [9] -T therapy promotes coronary vasodilation, reduces brachial artery reactivity [14]
Coagulation	-Low T associated with increased factor VII, fibrinogen [21], lower TFPI [22]	
Fibrinolysis	-Low T associated with greater PAI-1 levels [26]	-T therapy stimulated tPA and reduced PAI-1 levels [28]
Platelets	- T therapy may increase aggregation and thromboxane A2 receptor density [16] -T therapy promotes P2Y12 receptor expression in vitro [17]	-T therapy promotes nitric oxide production in vitro [18,19]
Inflammation	-Low T associated with elevated interleukins in vivo in animal models [34] -Low T associated with elevated IL-1 β in hypogonadal men [38]	-T infusion reduced TNF α in endothelial cells in vitro [36] -T therapy reduced TNF α and IL-1 in hypogonadal males [39]

small numbers of subjects, and limited long term follow up.

In returning to our initial case, we presented a hypogonadal male on testosterone for many years who had progression of coronary heart disease while on therapy. Despite intensive interventional and medication based therapy he still experienced angina type symptoms. And despite chronic testosterone therapy our patient did not notice a difference in libido or well being. Review of the literature suggests that testosterone has a complex effect on the pathophysiology of thrombosis and does not clearly support continuing or stopping therapy. In such a situation, a discussion is required between the clinician and patient about the specific risks and benefits of continuing testosterone therapy. Testosterone therapy may be continued with close monitoring of symptoms. Patients should also know that further research is needed to assess the role that testosterone plays in promoting arterial thrombosis, especially in considering those who may require long term testosterone replacement therapy.

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