

Testosterone and Cardiovascular Disease in Men

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Key words

Testosterone; Cardiovascular Disease; Coronary; Hormonal Therapy; Review Aging

Abstract

In this Century Cardiovascular Disease (CVD) is the most common isolated cause of death in developed countries. Many studies have suggested that men with low testosterone levels present higher incidence of components of metabolic syndrome and are at a greater risk of developing CVD.

Testosterone can affect the development of atherosclerosis in the coronary arteries. While this androgen seems to have a cardioprotective effect by benefiting endothelial function, inducing vasodilation, and reducing fat mass, insulin resistance and chronic inflammation, it also appears to increase endothelin, thromboxane A2 and reactive oxygen species and renal smooth muscle cells.

The relation between testosterone and coronary disease in men has been the focus of study of many authors. Most studies point to a neutral and/or protective effect of endogenous testosterone in male cardiovascular health. Unfortunately, many intervention studies have not been able to confirm this effect with testosterone therapy.

More studies are needed to elucidate the pathogenic mechanisms of testosterone in cardiovascular health and to evaluate androgen receptor polymorphisms and their physiological responses to testosterone.

Introduction

In the beginning of the 20th Century Cardiovascular Disease (CVD) was responsible for less than 10% of all deaths worldwide. In this century CVD has become the isolated leading cause of death in industrialized nations [1]. The male gender has traditionally been associated with a higher risk of CVD [2]. One explanation for this was elevated serum levels of testosterone known to be atherogenic.

Except for some indirect evidence, many studies have suggested that men with low levels of testosterone have higher incidence of the components of metabolic syndrome as well as a higher risk of developing CVD in their lifetime [2,3].

It is estimated ten percent of Myocardial Infarction (MI) patients do not have classic cardiovascular risk factors [4] and as a result new investigations for non-classic risk factors have emerged. Thus there has been a sharp increase in studies on the role of testosterone in the pathogenesis of ischemic cardiovascular disease.

This review summarizes the current evidence on the association between endogenous testosterone and CVD in men.

Testosterone and Aging

In men the most important serum androgen is testosterone, which is almost exclusively secreted by the testes. There it is produced more

specifically by Leydig cells in response to the stimulus of a gonadotropin called Luteinizing Hormone (LH) [6].

In plasma, approximately 2% of testosterone travels freely, 44% are bound to Sex Hormone Binding Globulin (SHBG) and the remaining 54% are bound to albumin and other proteins. The portions that are free or bound to albumin are readily available to tissues and are called Bioavailable Testosterone (BT).

In men testosterone levels are highest after 30 years of age and start declining thereafter at about 1-2% every year [6]. There are different aspects to the changes in testosterone levels in age men: there are reduced testicular response to the gonadotropic stimuli associated with an unsatisfactory compensation by the hypothalamus-pituitary axis [7] and there is an aged-associated increase of SHBG levels by about 1.2% per year, so that the decrease Free Testosterone (FT) and BT serum levels is larger than that of Total Testosterone (TT) [8,9].

As men age, this fall in the serum levels of testosterone intensifies: about one in every five men over the age of 60 and half of men over 80 have levels of testosterone below the lowest levels considered physiological in young men [8]. This relative deficiency is most commonly manifested with an increase in body fat and a reduction in both bone mass and muscle strength [8] contributing to the fat redistribution and to reduce in lean body mass [11,12]. Such loss in muscle mass at this age could explain the higher risk of falling, balance problems, obstructive sleep apnea, obesity, Diabetes Mellitus 2 (DM2),

depression, chronic obstructive pulmonary disease, kidney and liver diseases and other functional limitations [13-15].

Testosterone and Endothelial Dysfunction

Endothelial dysfunction refers to an imbalance in the endothelial production of mediators that regulate vascular tonus, platelet aggregation, coagulation and fibrinolysis. It is frequently referred to as a worsening of the endothelium dependent relaxation caused by the bioavailability of nitric oxide (NO) and other vasodilating substances. Thus it can be found in many metabolic and/or cardiovascular diseases.

Testosterone is a vasoactive hormone with a predominantly vasodilating role in many vascular beds [16]. This androgen can exert its effects over the cardiovascular system through genomic models, by activating the androgen receptor (AR), and through non-genomic models, by activating the steroid receptors in the plasma membrane, which can also lead to blockage of the calcium L channels and opening of the calcium activated potassium channels [17]. The acute and chronic administration of testosterone has shown beneficial effects in ischemic myocardium induced by exercise in men with coronary arterial disease (CAD) [18,19].

The immunosuppressant effect of androgens has been well understood and greater levels of auto-immune diseases in women and hypogonadic men are thought to be due to a down regulation of pro-inflammatory cytokines caused by testosterone [20]. Testosterone is capable of stimulating the production of an anti-inflammatory cytokine called interleukin 10 (IL-10) [21] and reducing other pro-inflammatory cytokines such as tumor necrosis factor α (TNF α), interleukin 1(IL-1) and interleukin 6 β [22,23] commonly elevated in elderly patients in subclinical inflammatory states [25].

A recent study of orchidectomized mice by Freeman et al. observed that androgenic supplementation was associated with a decline in inflammatory markers; while sub physiological testosterone levels were associated with an elevation of these markers, suggesting that the modulation of these hormonally responsive pathways could contribute to the development of the vascular pathogenesis [34].

In the last few years chronic inflammation has emerged as an important independent predictor of CAD. C-reactive Protein (CRP) is the most well studied inflammatory biomarker and today it is the most important among all the available ones, functioning as an independent risk factor for MI, stroke, peripheral vascular disease and sudden death [26]. Kupelian et al. [27], in a population based observational study of a sectional cohort with 1559 men with urologic symptoms, found an inverse association between testosterone and CRP, providing evidence to support testosterone's role in the inflammatory process. Finally, Wickramatilake et al. [28] demonstrated, in a case-control study of 206 men with CAD submitted to coronary angiography, that CVD patients had lower levels of testosterone and higher levels of CRP compared to the control group's. While CRP did show a positive association with the degree of atherosclerosis, testosterone did not. Inversely, in a similar study of 400 healthy men by Nakhai-Pour et al. [29], levels of TT and BT were not statistically associated to CRP in spite adjusting for age.

Testosterone also affects endothelial function by modulating the release of NO. This promotes vasodilation, inhibits platelet aggregation and adhesion of leukocytes to the endothelium, migration and growth of smooth muscle cells and oxidation of LDL-cholesterol

(LDL-c). In a study using endothelial cell culture, Campelo et al. [30] demonstrated that testosterone increases the production of NO via AR.

Finally, testosterone also has vasoconstrictor effects. The administration of 200mg of testosterone cypionate to healthy men in a double-blind, randomised, placebo-controlled trial revealed increased platelet aggregation by modulating the expression of thromboxane A2 receptors [31]. In another study, testosterone was implicated for impairing coronary vasodilation in response to adenosine in isolated mice heart models [32]. Such effect was attributed to and acutely mediated by the release of thromboxane, which is a potent vasoconstrictor and platelet aggregate.

Endothelins are potent endogenous vasoconstricting peptides. The relation between testosterone and endothelin 1 (ET-1) is complex with some studies suggesting that testosterone increases levels of ET-, mediating vasoconstriction, while others suggest that the levels of these peptides are higher in hypogonadism situations [33].

Recently Chignalia et al. [34] proposed that testosterone induces the generation of Reactive Oxygen Species (ROS) in renal smooth muscle cells. Since ROS in the kidneys reduce the bioavailability of NO and increases vasoconstriction [35], it is possible that this androgen can contribute to the loss in renal function and vascular dysfunction via ROS production.

As discussed so far, testosterone modulates the mechanisms associated with endothelial dysfunction that occurs during old age. Although testosterone levels are associated with endothelial dysfunction and increased CVD, this relation of cause and effect still remains controversial. Some authors advocate that reduced levels of testosterone could function as a old age marker, and such reduction corresponding only to an epiphenomenon [36]. In reality, elevated levels of this androgen in the elderly reflect good health and a reduced risk for cardiovascular events [37].

Testosterone and Cardiovascular Risk Factors

Low levels of endogenous testosterone have been associated with the presence of many components of metabolic syndrome, including dyslipidemia, visceral obesity, Systemic Arterial Hypertension (SAH), DM2, hepatic steatosis, and others [18,38-40].

Important meta-analysis and prospective studies have demonstrated a negative association between testosterone and the incidence of Diabetes Mellitus in men [41-43]. However the temporal nature of this association is still controversial, with some arguments in each direction. Some have suggested that diabetes mellitus in mice cause a reduction in the number of Leydig cells [44] resulting in lower levels of testosterone, while other authors have put forth that elevated levels of this androgen increase lean mass and reduce the levels of TNF- α and insulin resistance [41-43].

Morbidly obese patients with peripheral insulin resistance frequently have low levels of TT, which increase with weight loss. The mechanisms responsible for the reduction in the levels of testosterone in obese men are not fully understood. The reduction in FT in severe obesity is not associated to an increase in LH suggesting a form of hypogonadotropic hypogonadism. One postulated hypothesis would be a dysfunction in the testicular hypothalamic-pituitary axis characterized by the reduction of peaks of LH [45]. Another suggested mechanism would be an increase in the peripheral conversion of androgens into estrogens by the enzyme aromatase, which is present in

elevated concentrations in adipose tissue [45]. Furthermore, obesity is one of many conditions that can result in low levels of SHBG, with insulin being an important inhibitor of the production of this globulin in the liver [45]. This way, individuals with insulin resistance tend to present with lower values of TT.

Through the activation of β -adrenergic AR expressed in adipose cells, androgens stimulate hormone sensitive lipase and inhibit the activity of lipoprotein lipase, the main enzyme that regulates the intake of glucose in adipose tissues [46]. As a result testosterone is able to reduce the fat reserves in adipose tissue by stimulating lipolysis. This explains the increase in body fat mass associated with low levels of testosterone observed in hypogonadism patients.

Some interventionist prospective studies have revealed beneficiary effects of testosterone therapy in the parameters for metabolic syndrome. Kalinchenko et al. [47], in a study with 184 men with metabolic syndrome and low levels of testosterone, demonstrated that treatment for 30 weeks with Intramuscular (IM) testosterone undecanoate reduced Body Mass Index (BMI), Waist Circumference (WC), insulin levels, CRP, IL-1 β and TNF- α in comparison with placebo but there was no significant change in levels of glucose, IL-6 and IL-10 and in lipid profile. In another prospective, longitudinal study by Yassin et al. [48] of 261 men, treatment with IM testosterone undecanoate during five years reduced WC, BMI, cholesterol, LDL-c, triglycerides, fasting glucose, glycated hemoglobin and arterial pressure (AP) but did not produce an increase in HDL-cholesterol (HDL-c).

Haddad et al. [49] in a meta-analysis of 30 randomised placebo-controlled studies, with 1642 men, 808 of which treated with testosterone in the commercially available forms (IM, transdermal, oral and buccal) showed negligible effects of testosterone on the levels of lipids, AP, glycaemic control and cardiovascular events.

Finally, Kelly et al. [50] in a study with orchidectomized mice, with androgen receptor deficiency and with a cholesterol rich diet, observed the effect of testosterone therapy over regulatory enzymes in the synthesis of fatty acids. In the testosterone supplementation group there were smaller fat deposits in hepatocytes when compared to placebo. Such result suggests a different mechanism of action of testosterone, independent of AR, over the regulation of the main lipogenic enzymes and protection against hepatic steatosis.

Testosterone and Cardiovascular Disease

Atherosclerosis is a complex pathology characterized by endothelial dysfunction, vascular inflammation and lipid buildup in the intima layer of blood vessels. The development of atherosclerosis is promoted not only by systemic factors, but also metabolic, vascular and inflammatory dysfunctions of the vessels' walls.

Testosterone can affect the development of atherosclerosis in coronary arteries. While it seems to have cardioprotective effects by benefiting endothelial function, inducing vasodilation and reducing insulin resistance and chronic inflammation [40,51,52], it also appears to increase endothelin, thromboxane A2 and ROS in renal smooth muscle cells [31,32,34,35].

The relationship between testosterone and CAD in men has been the focus of study of many authors. Most of the studies point to a neutral and/or protective effect of endogenous testosterone in cardiovascular health.

In this line of research, Callou de Sá *et al.*[53], in a case-control study of 144 patients who underwent elective coronary angiography found a neutral effect of TT, BT, FT and free androgen index in the prevalence of CAD. Similarly, Vikari et al. [52] in a study with 1318 men followed for 9.1 years, did not find an association between TT and FT and the incidence of MI. Araujo et al. [55] in a meta-analysis with 11831 participants did not find a statistically significant correlation between reduced levels of testosterone and cardiovascular mortality either.

On the other hand, Hyde *et al.*[56] in a population based prospective study of 3637 elderly men followed by 5.1 years, found that reduced FT levels were associated with higher mortality by CVD. Furthermore, Li Li *et al.*[56], in a study of 803 patients who underwent elective coronary angiography, demonstrated reduced levels of TT to be associated with CAD and with its severity determined by the Gensini score.

Despite the beneficial effects of endogenous testosterone in men's cardiovascular health well described in the literature, a number of studies were not able to replicate these beneficial effects with testosterone therapy. In fact, when observed studies involving interventions with testosterone therapy and CVD, results vary greatly between authors.

In the TOM study [57], elderly participants with limited mobility and low levels of testosterone were randomly assigned to either a placebo group or a therapy group receiving transdermic gel with 100 mg of testosterone during six months. It had to be discontinued prematurely due to a higher incidence of cardiovascular events in the testosterone group. Similarly, Xu *et al.*[58] in a meta-analysis of 27 randomised placebo-controlled trials, with 2994 participants, 1733 of which used testosterone, found RR 1.54 for cardiovascular events (95% CI, 1.09 to 2.18) for the testosterone group. In accordance with these results Vigen et al. [59] in a retrospective cohort study of 8709 men with low levels of testosterone who underwent coronary angiography, of which 1223 received testosterone therapy, showed increased mortality, MI and stroke rates in the testosterone group.

Haddad *et al.*[49] in a previously cited meta-analysis showed only negligible effects of testosterone in cardiovascular events OR 1.86 (95% CI, 0.78 to 4.23). Similarly Fernandez-Balsells et al. [60], in a meta-analysis of 51 studies with 2716 men who used testosterone did not find a significant difference in mortality by all causes, arrhythmias, coronary bypass surgery or MI between the testosterone group and the control group.

On the other hand, Toma *et al.*[61], in a meta-analysis of randomised controlled trials of 198 men with heart failure, found testosterone therapy was associated with a significant improvement in exercise capacity compared with placebo (New York Heart Association functional class improved by ≥ 1 grade, increase in the 6-minute walk test and the peak oxygen consumption in exercise).

Finally, many authors agree that low testosterone levels could be interpreted as a factor, which when associated with old age contributes to an increase in comorbidities [51], or could help reveal previously existing hidden pathologies [16,39,51] functioning as a biomarker for old age [16,51]. High levels of this androgen in the elderly reflect good health and a reduced risk of cardiovascular events [16,51].

Conclusion

Endogenous testosterone exerts a neutral and/or beneficial effect in the male cardiovascular system. This androgen favors vasodilation, has a pro and anti-aggregate role, and reduces the fat mass, inflammatory biomarkers, insulin resistance and the incidence of diabetes mellitus. Lending support to this line of thought, some observational studies point to a larger prevalence of cardiovascular disease and cardiovascular mortality in populations with reduced serum levels of this hormone. On the other hand, interventional studies in which testosterone replacement was used do not reach a uniform consensus with regards to the cardiovascular endpoints, with some suggesting higher risk, some neutral and others describing lower risk. It is important to keep in mind that this study describes the cardiovascular effects of testosterone replacement therapy and does not investigate improvements in the quality of life of the patients. Testosterone replacement therapy in men with hypogonadism by pituitary or testicular diseases deserves special consideration. More studies are needed to try to describe the pathogenic mechanisms of testosterone in cardiovascular health and to investigate polymorphisms of the androgen receptor in the physiological response to it.

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