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The Cardiovascular Benefits of Testosterone Treatment: A Comprehensive Review

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Abstract

Testosterone, which is an important hormone in both males and females, plays a crucial role in various physiological processes, including cardiovascular health. Testosterone deficiency (TD) is a well-established medical condition that negatively impacts male and female sexuality and general health. Many studies, mostly observational studies, have investigated testosterone's impact on cardiovascular outcomes, yielding intriguing findings. This paper aims to provide a brief review of TD-associated cardiovascular risks and suggested cardiovascular benefits associated with testosterone replacement therapy (TRT).

Testosterone's effect on cardiovascular risk factors, endothelial function, atherosclerosis, arterial stiffness, and myocardial function are analyzed. Additionally, I will discuss some of the potential mechanisms underlying these effects and highlight the clinical implications of testosterone therapy in cardiovascular disease management.

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide in both males and females. Established risk factors, such as hypertension, dyslipidemia, obesity, smoking, sedentary lifestyle, diabetes, and low testosterone, contribute to CVD development and progression. Testosterone, beyond its role as a sex hormone, has emerged as an important factor influencing cardiovascular health.

Testosterone deficiency (TD) and cardiovascular disease

In the 1970s and 1980s epidemiologic studies demonstrated that for every decade of life, males suffered higher myocardial infarction and cardiovascular death rates than females. The cause was speculated to be that higher total testosterone (TT) levels played a significant role in cardiovascular disease. It was noted that there is a clear difference between males, females, and their serum total testosterone concentrations.[1] Over time, this belief largely disappeared once epidemiologic studies investigating the relationship between testosterone and cardiovascular disease began to show that atherosclerosis in males was more prevalent in testosterone deficient males (TD-M) and that males with higher testosterone concentrations appeared to be protected.[2]

Several studies have been performed investigating the relationship between serum total testosterone and cardiovascular mortality. One such study was the European prospective investigation by Khaw et al. It studied the prospective relationship between endogenous serum total testosterone concentrations and mortality due to all causes including cardiovascular disease as well as cancer. The study population included 825 males without cancer or known cardiovascular disease at baseline who subsequently died. These were compared with a control group of 1489 alive males matched for both age and baseline visit date. Khaw found that there was a statistically significant inverse relationship between serum total testosterone concentrations and overall cardiovascular mortality.[3] The lowest quartile for serum TT was associated with the greatest cardiovascular and overall mortality risk, whereas males in the upper quartiles were at reduced risk of death. [3]

In another study, Haring et al. investigated overall mortality as well as cardiovascular mortality using data from the prospective population–based study of health in Pomerania. Among 1954 males that were evaluated with baseline serum TT concentrations and followed for a mean of 7.2 years there were 195 deaths. The investigators reported that males with a low serum TT concentration, defined as less than 250 ng/dL, demonstrated a significantly greater all-cause mortality than males with higher serum testosterone levels. This was also true for cardiovascular mortality (HR: 2.56: 95% CI: 1.15–6.52). In TD-M, there was an increased mortality seen in both the younger (20–59 years) and older (60-79 years) age groups, with the greatest risk noted in the older population. [4]

TD significantly contributes to cardiovascular risk factors

It has been shown that testosterone deficiency is associated with chronic medical conditions such as metabolic syndrome, diabetes, dyslipidemia, hypertension, sexual dysfunction, vascular stiffness, atherosclerosis, and inflammation, which are associated with cardiovascular disease. [5]

Elagizi et al. demonstrated that testosterone deficiency contributes to a reduction in lean body mass, bone density, energy, and physical/sexual function, and an increase in adiposity. Metabolically, TD impairs fasting glucose and increases diabetes mellitus risk and LDL cholesterol while lowering HDL cholesterol. It increases pro-inflammatory cytokines TNF-alpha and IL-1B and reduces anti-inflammatory cytokines. TD is associated with acute conditions including acute myocardial infarction (MI), sepsis, and trauma and chronic conditions such as renal failure, malignancy, hypertension, and hyperlipidemia. All these are associated with increased atherosclerosis, coronary artery disease (CAD), and cardiovascular (CV) events. [6]

Data suggests that TRT favorably impacts CVD outcomes

Diabetes is a major risk factor for CVD morbidity and mortality. Wittert et al., in a two-year randomized, double-blind, placebo-controlled trial, evaluated males with impaired fasting glucose/type 2 diabetes and testosterone deficiency. All participants were enrolled in a lifestyle modification program and half the group were randomized to testosterone therapy and the other half placebo. In the testosterone treated males there was improved glycemic control such that there was a reduced proportion with diabetes when compared to lifestyle alone. [7]

There was a significant improvement in the 2-hour oral glucose tolerance test. In males at high risk for developing diabetes, the progression to diabetes was less in the testosterone treated group (7.6%) versus the placebo group (14.9%). Diabetes was reversed in more newly diagnosed males after 2 years of testosterone treatment, with only 31.8% of the testosterone treated group remaining diabetic vs. 45.2% in the placebo group.[7]

Haider et al., using registry data, demonstrated that TD-M with type 2 diabetes had a significant reduction in fasting glucose, glycosylated hemoglobin (HGB A1c), insulin resistance, and fasting insulin levels when treated with testosterone over 11 years. Diabetes remission occurred in one third of the patients treated with testosterone vs none in the comparator group. In the testosterone group, this was associated with fewer deaths, myocardial infarctions, strokes, and diabetic complications.[8]

Testosterone and cardiovascular events

Ohlsson et al. evaluated 2416 males aged 69 to 81 years for 5 years and 485 cardiovascular events occurred. Total testosterone levels were inversely associated with cardiovascular event risks. Males in the highest testosterone quartile with TT levels greater than 550 ng/dL had a lower cardiovascular event risk when compared with males in the lower 3 quartiles. There were 95 major cardiovascular events in the highest quartile.[9]

Boden et al., in the AIM-HIGH-5 Study, evaluated 2118 male participants with metabolic syndrome and low HDL, randomized to niacin or placebo plus simvastatin. This sub study assessed the relationship between low baseline TT levels and subsequent CV outcomes during a mean 3-year follow-up.[10]

This study group consisted of 643 males with metabolic syndrome, low HDL, and low TT concentrations and 1475 males with normal TT concentrations. The primary endpoint was a comparison of the composite of coronary heart disease death, nonfatal myocardial infarction, hospitalization for acute coronary syndromes, ischemic stroke, or symptom-driven coronary or cerebral revascularization–time to first event in males with TT levels less than 300 ng/dL (low T group) versus those with TT levels greater than 300 ng/dL (normal T group).[10]

In the low T group 20.1% versus 15.2% in the normal T group had an event, consistent with a 24% increased primary composite outcome. The secondary endpoint, a composite of coronary heart disease (CHD), death, nonfatal MI, and ischemic stroke, was 31% higher in the low TT group (11.8% in the low T group and 8.2% in the normal T group). Cardiovascular death was 3.4% in the low T group versus 2.2% in the normal T group. In the low vs the normal T group, overall mortality was 6.4% versus 4.6% and coronary events were 17.7% versus 14.0%, respectively.[10]

The authors concluded that there was an association between low baseline TT concentrations and an increased risk of subsequent cardiovascular events in TD-M with metabolic syndrome, low HDL, and cardiovascular disease, particularly for the composite secondary endpoints of CHD, death, MI, and stroke.[10]

Testosterone and Endothelial Function
Endothelial dysfunction plays a pivotal role in atherosclerosis pathogenesis and cardiovascular events. Several studies have suggested that testosterone has a positive impact on endothelial function. Testosterone has been shown to enhance endothelial nitric oxide synthesis (eNOS), promote vasodilation, and improve vascular tone. [11,12] These effects have been observed in both healthy individuals and in those with endothelial dysfunction. [13,14]

Moreover, testosterone replacement has been associated with improvements in endothelial function markers such as increased flow-mediated dilation. Additionally, TRT has been associated with favorable blood pressure effects, with some studies reporting decreases in both systolic and diastolic blood pressure. [15,16]

Testosterone and Atherosclerosis
Atherosclerosis, characterized by the arterial wall plaque accumulation, is a major contributor to cardiovascular events in both males and females. Testosterone appears to exert favorable effects on atherosclerosis progression and plaque stability. Studies have shown that testosterone replacement therapy may be associated with improved lipid profiles by reducing total cholesterol, LDL cholesterol, and triglyceride levels, while increasing HDL cholesterol. [17,18] Testosterone supports lipid metabolism regulation, promoting cholesterol mobilization from arterial walls. [19,20]

Testosterone also exhibits anti-inflammatory effects, reducing pro-inflammatory cytokine and adhesion molecule expression, which are implicated in atherosclerosis development. [21,22] Furthermore, testosterone replacement therapy has been associated with reductions in carotid intima-media thickness, a surrogate atherosclerosis marker. [23,24]

Testosterone and Myocardial Function
The heart has testosterone receptors, and alterations in testosterone levels may affect myocardial structure and function. Testosterone has been associated with positive effects on myocardial function. Moreover, testosterone treatment has demonstrated potential benefits in heart failure management, including increased exercise capacity and improved quality of life. [25]

Testosterone replacement therapy is safe for the cardiovascular system in middle aged and older men
In males with testosterone deficiency and pre-existing or high cardiovascular disease risk, testosterone replacement therapy was noninferior to placebo with respect to the incidence of major adverse cardiac events. However, in the testosterone treated males, there was a statistically significant increase in atrial fibrillation, acute kidney injury, and nonfatal arrhythmias. To date, no subgroup analysis has been performed to evaluate these findings to better understand them.[26]

Venous thromboembolism (VTE) risk with testosterone therapy in middle aged and older males
A case control study involving 30,572 males, 40 years and older, demonstrated that TRT was not associated with an increased VTE. In addition, none of the specific routes of administration examined, topical, transdermal, or intramuscular, were associated with an increased VTE risk. [27]

Conclusion
This paper was written to demonstrate that testosterone deficiency may be associated with an increased incidence of cardiovascular risk factors as well an associated increased cardiovascular morbidity and possibly mortality. It also has been demonstrated that treating testosterone deficient males with testosterone may be associated with reduced CV risk and may be associated with decreased cardiovascular morbidity and mortality.

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