Testosterone and cardiovascular disease

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Abstract
Low levels of endogenous circulating testosterone in men in community-based epidemiological studies are associated with an increased risk of mortality from all causes, with some studies identifying a link with cardiovascular (CV) disease. Testosterone deficiency is associated with several CV risk factors including central obesity, dyslipidemia, hypertension, and insulin resistance. Testosterone replacement therapy (TRT) in men with hypogonadism, when carefully replaced to the normal range, has been shown to improve some risk parameters including waist circumference, total and low-density lipoprotein cholesterol, lipoprotein(a), insulin resistance, and hyperglycemia. TRT does slightly lower high-density lipoprotein cholesterol in some trials; the clinical significance of this effect is not known. Beneficial effects of TRT have demonstrated reduced exercise-induced cardiac ischemia in men with chronic stable angina and improved functional exercise capacity, and $V_{O_2\text{max}}$ in men with moderate chronic cardiac failure. Evidence from well-conducted trials where TRT achieves normal testosterone values and meta-analysis of the studies have not identified any increased risk of major CV events. Some recent studies have shown increased CV risk, but have major flaws in design and either over- or under-treated patients. Clearly only a large, long-term, placebo-controlled randomized clinical trial may provide the definitive answer. The benefits of TRT on quality of life and sexual function are very important to the majority of men with hypogonadism. Furthermore, two retrospective studies have reported that TRT can reduce mortality in hypogonadal men with and without type 2 diabetes. Careful diagnosis, titration of testosterone dose to maintain levels within the mid-normal range, and long-term safety monitoring are key to the reduction in complications. ■ Heart Metab. 2015;66:7-12

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Sexual dysfunction has been identified as a biomarker for the presence of cardiovascular (CV) disease, which may predate the onset of a future CV event. Erectile dysfunction (ED) may be the first symptom of CV disease. It is well recognized that CV risk reduction by improvement in lifestyle (diet, exercise, and cessation of smoking) and control of hypertension, cholesterol, and diabetes can reduce CV events. ED is one of a triad of sexual symptoms found in male hypogonadism with reduced, or loss of, libido and morning erections accounting for the other two. Between 20% to 30% of men with ED have
Abbreviations

ADT: androgen deprivation therapy; BMI: body mass index; CHF: chronic heart failure; CV: cardiovascular; ED: erectile dysfunction; FDA: Food and Drug Administration; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LP(a): lipoprotein(a); MACE: major adverse cardiovascular events; PDE5: phosphodiesterase type 5; TRT: testosterone replacement therapy

Hypogonadism. There is good evidence that low levels of circulating testosterone have a high prevalence in men with CV disease, metabolic syndrome, and type 2 diabetes.4,5

Low testosterone may merely be a biomarker of illness secondary to the chronic inflammatory state of atherosclerosis. Accumulating evidence has demonstrated that low testosterone levels are associated with an increased risk of death and that higher endogenous testosterone may protect against major CV events.6-10 There is evidence, mainly from animal studies, that testosterone deficiency may promote atherogenesis, whereas replacement can ameliorate the disease.11 Testosterone replacement therapy (TRT) has been shown to improve exercise-induced cardiac ischemia, cardiac failure, and may improve mortality. However, some recent retrospective studies have raised concerns over testosterone therapy increasing CV events, although these are heavily flawed, whereas the majority of studies and meta-analyses have not supported this. This short review will discuss current clinical aspects of testosterone deficiency and replacement therapy.

Epidemiology

The majority of community-based population studies have reported that low testosterone levels (in particular <12 nmol/L) are associated with an increased all-cause mortality risk.6 Several of these studies have shown that the most common cause of mortality is CV disease.6 In disease-specific populations, which include men with proven CV disease by coronary angiography (Figure 1), and in type 2 diabetes, low testosterone increases mortality risk two-fold.12,13 Two studies support an effect of low testosterone on an increased risk of CV events. The MrOS study from Sweden has demonstrated that men in the upper quartile of testosterone levels have lower CV events than those in the lower three quartiles combined.8 Another study found that there was a “J-shaped” curve with a reduced frequency of CV events in the mid-normal range.10 The Health in Men (HIM) study from Australia reported that there was a reduced risk of all-cause mortality in the mid-to-higher normal range compared with low and high levels representing a “U” shaped curve.8 Additionally, this study found that CV mortality was decreased in men with dihydrotestosterone levels in the high-normal range. This knowledge that testosterone deficiency is associated with an increased risk of CV mortality is supported by the findings that men receiving androgen deprivation therapy (ADT) for prostate cancer have increased frequency of CV events and death.14

The reasons as to why testosterone deficiency is associated with CV disease and mortality have not been fully established. Low testosterone may be a biomarker as a consequence of ill health. Chronic inflammatory disorders, which include atherosclerosis, may suppress the hypothalamic-pituitary-testicular axis, thus lowering testosterone levels. However, there is evidence that testosterone deficiency is associated with major CV risk factors.5 These include central adiposity, dyslipidemia, insulin resistance, hyperglycemia, and a proatherogenic cytokine profile. Hypogonadism has an increased prevalence in men with type 2 diabetes and hypertension as well as CV disease.5,5

Carotid intima-media thickness (CIMT) is increased in men with low testosterone. One study showed that after a 4-year follow-up, progression of CIMT was greatest in men with testosterone levels in the lower tertile. Animal studies have demonstrated that testosterone deficiency leads to an increased risk of lipid streak formation within aortic and coronary arteries. Testosterone supplementation ameliorates the deposition of lipid. This raises the question as to whether or not TRT may have an atheroprotective effect.

Pathogenesis

The European Male Aging Study (EMAS) has demonstrated that obesity and comorbidities are the major promoters for the suppression of testosterone deficiency, with aging accounting for a lesser effect. Evidence supports a bidirectional mechanism between obesity and testosterone status. Hypogonadism is well known to increase body fat and reduce muscle mass. This is evident in men with Klinefelter's syndrome who may present with a female distribution of body fat (eunuchoid habitus). Furthermore, men with low testosterone in epidemiological studies have an increased risk of developing the metabolic syndrome and type 2 diabetes, independent of obesity at baseline.

Obesity is considered to be a proinflammatory state as adipocytes secrete adipocytokines, which include tumor necrosis factor-α (TNFα), interleukin-1β (IL-1β), interleukin-6 (IL-6), and leptin. These adipocytokines act upon the hypothalamus to inhibit pulsatile gonadotropin-releasing hormone (GnRH) release leading to the suppression of luteinizing hormone and then testosterone secretion from the testes. In addition, the aromatase activity correlates positively with the degree of visceral fat, leading to more rapid breakdown of testosterone to estradiol, lowering circulating testosterone levels further. The testosterone-deficient state enhances the uptake of triglycerides into adipocytes and promotes the relative increase in fat cells derived from stem cells compared with muscle cells. This bidirectional relationship between fat and testosterone metabolism is known as the hypogonadal-obesity-adipocytokine hypothesis (Figure 2). The greater the fat deposition, the greater the breakdown of testosterone. Adipocyte aromatase activity increases further, eventually leading to a hypogonadal state. Weight reduction and exercise may break the cycle, but hypogonadism can be associated with lack of motivation and therefore a poor response to lifestyle changes.

Angina

Testosterone therapy was first shown to relieve symptoms of angina in 1939 with several case report studies finding that the majority of men and also women responded. More recently, these observations have been confirmed in placebo-controlled studies over periods between 1 and 12 months. Testosterone therapy improves time to 1 mm ST depression on exercise testing in men with chronic stable angina, either when administered acutely or over several months. Importantly, the lower the baseline testosterone level the greater the reduction in ischemia. Evidence strongly supports a role of testosterone as a rapid-acting arterial vasodilator in the coronary arteries as well as in other systemic vessels, including mesenteric and pulmonary vascular beds. In particular, one study in which testosterone was given directly into coronary arteries in men undergoing routine angiography showed testosterone significantly increased coronary artery diameter and coronary blood flow within a period of 2 to 5 minutes. In vitro experi-

![Fig. 2: Hypogonadal-obesity-adipocytokine hypothesis.](image)

Abbreviation: IL, interleukin; TNF, tumor necrosis factor.

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ments have shown that testosterone may promote vessel dilation by blocking L-calcium channels at the nifedipine binding site. Other sites of action include inhibiting potassium channels and intracellular, store-operated calcium release, increasing the expression of β1-adrenergic receptors as well as upregulating the response to noradrenaline and acetylcholine. Conversion of testosterone to estradiol may also lead to a vasodilatory response, but there is a direct effect of testosterone and its metabolite dihydrotestosterone (DHT) that is endothelium independent.

Chronic heart failure

Chronic heart failure (CHF) is commonly caused by coronary artery disease. CHF significantly impacts quality of life, causes cachexia, and has a high mortality rate that is worse than several forms of cancer. Low testosterone is common in men with CHF and is likely to occur as a consequence of chronic inflammation resulting from atherosclerosis, heart failure, and/or the cachectic state. Supraphysiological levels of testosterone promote the retention of extracellular water and if patients with hypogonadism are overtreated, then this can lead to an exacerbation of cardiac failure. Unlike older formulations, transdermal administration of testosterone replacement can be carefully titrated and replace testosterone to within the mid-normal range.

There have been a small number of trials of up to 12 months that have reported a beneficial effect of TRT in men with moderate CHF. Testosterone improved functional exercise capacity, VO2max, and, in one-third of men, improvement in New York Heart Association class in the 12-month study. Furthermore, in the 12-month study blood pressure and left ventricular length did not deteriorate, whereas there was worsening of these parameters in the placebo population. This suggests that testosterone may possibly retard progression of left ventricular dysfunction.

Testosterone replacement therapy and cardiovascular risk factors

The major clinical indication for TRT is to improve the symptoms of hypogonadism, which primarily include sexual dysfunction. However, there have been several studies that have reported beneficial effects on certain CV risk factors, which include central adiposity, total and low-density lipoprotein (LDL) cholesterol, lipoprotein(a) (Lp[a]), and insulin resistance, as well as suppressing serum levels of proinflammatory cytokines.

Visceral adiposity, as assessed by waist circumference, waist:hip ratio, and computed tomography (CT)/magnetic resonance imaging (MRI) scanning, in hypogonadal men is significantly decreased by TRT. Furthermore, several trials have reported a reduction in fat mass and an increase in lean mass supported by a fall in serum leptin when this has been measured. The corresponding rise in muscle bulk may explain why most studies have not shown changes in body mass index (BMI). A longer-term observational study has shown a gradual improvement in waist circumference and BMI over a period of 3 years.

TRT consistently lowers total cholesterol by 0.25 to 0.5 mmol/L. Some studies have demonstrated falls in LDL cholesterol and/or triglycerides, whereas some have not. The effect of TRT on high-density lipoprotein (HDL) cholesterol is less clear, with small decreases, no change, or increases. The explanation for these alterations in HDL are not clear, however commentators have suggested that as a result of reverse cholesterol transport, increased shuttling of cholesterol from lipid laden tissues back to the liver may lead to the fall in concentration. Further work needs to examine and exactly determine the biological and indeed clinical relevance, if any, of these phenomena. Lp(a) correlates positively with CV risk and research has shown that TRT significantly lowers levels of this lipoprotein. No studies, however, have been performed to determine if suppression of Lp(a) improves CV outcomes.

TRT does decrease insulin resistance in hypogonadal men with metabolic syndrome and/or type 2 diabetes. Insulin resistance is considered to be an intermediate CV risk factor as it does lead to hyperglycemia, hypertension, dyslipidemia, as well as endothelial dysfunction and a proinflammatory serum cytokine profile. TRT suppresses TNFα, IL-1β, and IL-6, and raises IL-10, an antiatherogenic cytokine.

Whether or not there is an overall benefit of TRT on CV risk in men when replaced to the normal physiological range is unknown.

Testosterone replacement therapy and cardiovascular safety

There has been some recent controversy over whether or not TRT increases the risk of adverse CV events.
as a result of two retrospective studies and one trial that used high doses of testosterone in elderly men. Many clinical trials (including several randomized controlled trials), clinical use of TRT over more than 70 years, and other meta-analyses have not unmasked any increased risk. Indeed a meta-analysis of studies in men with metabolic syndrome and type 2 diabetes has shown reduced risk.

Both retrospective trials have received heavy criticism due to flawed study design and analysis. The Vigen et al study compared two groups; those receiving TRT and those who did not. There was a complicated statistical analysis using over 50 variables, which changed a positive effect of TRT with lower CV events to an adverse result. Furthermore, there was no evidence that all patients were carefully diagnosed with hypogonadism and, once on treatment, 17.6% received only one prescription. The mean testosterone level on treatment in those who continued was subtherapeutic. Later, the authors also admitted that they had included a significant number of females in their analysis. Comments and responses to the Vigen et al paper are discussed in the Journal of the American Medical Association.

The Finkle et al study using data on 55,000 testosterone prescriptions in California compared reporting of myocardial infarction in the first 3 months with either the same patients in the 12 months prior to the prescription or a cohort of men receiving phosphodiesterase type 5 (PDE5) inhibitors. They reported an increased risk of myocardial infarction on TRT compared with the other group. No data were given on whether hypogonadism was diagnosed before initiation of therapy or if testosterone levels had been performed, nor testosterone levels on treatment. The comparator groups were not appropriate. Use of nitrates associated with more severe CV disease are contraindicated with PDE5 inhibitors, so the latter group would potentially have been a healthier cohort in respect to preexisting disease.

A recent systematic review and meta-analysis of randomized placebo-controlled clinical trials (testosterone treated, n=3016; placebo, n=2747) did not detect any increased risk of major adverse CV events (MACE) in those men on TRT. Other meta-analyses have been limited by not having a defined end point of MACE and have used a wide definition of CV-related episodes. The US Food and Drug Administration (FDA) have stated that “these studies do not provide conclusive evidence of increased risk associated with the use of testosterone therapy.” Recently a large study of 6355 testosterone treated men did not show an increased risk of myocardial infarction.

Many experts in the field have called for a large, well-powered clinical trial to determine whether or not TRT has adverse or beneficial effects on CV outcomes. This has now been recognized by the FDA.

Conclusion

Erectile dysfunction and testosterone deficiency are independent biomarkers for the presence and severity of CV disease, metabolic syndrome, and type 2 diabetes. Each biomarker could potentially raise awareness as an early marker of atherosclerosis. Hypogonadism requires careful diagnosis preferably by an experienced clinician in this area. Quality of life is very important to many people and TRT may achieve an improvement. The decision to treat with TRT should be discussed with patients with regards to benefit and risks. Only a longer-term trial will provide answers to whether or not there is an effect, positive or negative, on patients.

REFERENCES