

Testosterone and the heart

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Abstract

Testosterone has generated a lot of interest and controversies lately. There are epidemiological studies showing the correlation of low testosterone level with poor health in men. Low testosterone predicts an increase in all-cause mortality. Testosterone replacement therapy (TRT) has been shown to improve mortality in men with testosterone deficiency. Normalization of testosterone levels has been shown to be beneficial to the heart. Besides the direct effect on the heart, TRT has also been shown to have a positive effect on the metabolic parameters (metabolic syndrome) that indirectly affect the heart. ■ *Heart Metab.* 2015;66:19-23

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Testosterone levels in men have been shown to decrease gradually with age. This decline is about 2% per year, but in healthier men, the decline is attenuated. The exact prevalence of testosterone deficiency is controversial. In a study involving more than 10 000 men, 80% were found to have symptoms of testosterone deficiency.¹ In another study done in the primary care setting, where a total of 2162 men >45 years old were sampled, the prevalence of testosterone levels of less than 300 ng/dL (8.4 nmol/L) was 38.7%.² In the US, less than 10% of men with low testosterone received testosterone replacement therapy (TRT). A total of 50% of older men with type 2 diabetes mellitus have testosterone deficiency. As a consequence, in the US where the prevalence of type 2 diabetes mellitus is expected to increase over the next 20 years, the health impact of testosterone deficiency syndrome will cost the US economy up to 500 billion US dollars.³

The rise in the usage of TRT has generated a lot of interests and controversies. Many studies have been done and the role of testosterone and its effect on the cardiovascular system is a hot issue at the moment. This review aims to address some of these issues.

Testosterone level and its association with the heart

There are some epidemiological studies that have shown the correlation between testosterone and cardiovascular disease. In over 40 epidemiological studies conducted so far, no one has found any association between high testosterone levels and cardiovascular disease. In contrast, many found an association between low testosterone levels and cardiovascular disease. These include studies on carotid artery atheroma and peripheral arterial disease.

Seventeen prospective cohort or nested case-controlled studies have also examined the relationship between testosterone levels and cardiovascular

Abbreviations

BMI: body mass index; **HDL:** high-density lipoprotein; **SHBG:** sex hormone-binding globulin; **TRT:** testosterone replacement therapy

morbidity and mortality. In ten of these studies, there was no correlation between baseline testosterone levels and subsequent development of fatal or non-fatal coronary heart disease, cerebrovascular disease, or heart failure after adjustment for confounders, during observation periods of 5 to 31 years. Weak correlations of high androgen levels with cardiovascular mortality were observed in two studies. Conversely, two studies reported significant correlations between low baseline testosterone levels and cardiovascular deaths, and two others between low baseline testosterone and progression of carotid artery intima-media thickness, or between low testosterone and an increased incidence of stroke or transient ischemic events. However, two other prospective studies were unable to confirm the correlations with intima-media thickness progression, and with an increased risk of stroke. Lastly, the Caerphilly study found a positive association of the cortisol/testosterone ratio with chronic heart disease incidence and mortality.⁴⁻⁷

Recent evidence has proven that men with lower levels of testosterone are more prone to developing coronary artery disease.⁸ This was shown after only taking into account bioavailable testosterone levels, as compared with older studies that did not do this. Bioavailable testosterone includes both free testosterone and testosterone bound loosely to albumin. Testosterone, which is bound to sex hormone-binding globulin (SHBG), is biologically inactive. There is also evidence that the lower the levels of testosterone, the more severe the degree of coronary artery disease.⁹ This could be due to its effect on the carotid intima-media thickness. Various studies have shown the inverse relationship between endogenous testosterone levels and intima-media thickness of the carotid arteries, abdominal aorta, and thoracic aorta.¹⁰ This suggests that those with low testosterone levels are more prone to developing atherosclerosis.

Besides coronary artery disease, testosterone levels have also been studied in congestive heart failure. Studies have shown that men with congestive heart

failure have significantly reduced total and free testosterone levels. As the severity of congestive heart failure worsens, the levels of both total testosterone and estimated free testosterone lower correspondingly. In fact, it was shown that reduced levels of total and estimated free testosterone were both predictors of increased mortality in men with congestive heart failure.¹¹

Metabolic syndrome, which is comprised of insulin resistance, hypertension, dyslipidemia, and visceral obesity, is associated with an increased risk of cardiovascular disease (relative risk, 2.35).¹² Testosterone levels are also known to affect metabolic syndrome. Low testosterone levels have been shown to correlate with worsening type 2 diabetes and obesity. In fact, not only are the total testosterone levels lower in diabetics, the free testosterone and the testosterone bound to SHBG are also lower. This means that total testosterone in diabetics is not entirely caused by the reduction in levels.¹³

At the moment, the evidence for testosterone levels and dyslipidemia is poor. Most of the studies done were cross-sectional studies based on small sample size.^{14,15} Therefore, the results are inconclusive. However, the relationship between testosterone levels and obesity is quite established. It has been shown that the odds ratio for having hypogonadism was significantly higher in obese men, and there was a statistically significant negative correlation between total testosterone level and body mass index (BMI).² In terms of mortality, studies have consistently shown that lower levels of endogenous bioavailable testosterone are associated with higher rates of all-cause and cardiovascular mortality.^{5,16}

Testosterone replacement therapy: a new approach for the heart

TRT may be beneficial to the heart. There are a few ways that testosterone, through its effect on other parameters (components of metabolic syndrome), may improve cardiovascular health.

Testosterone replacement therapy in obesity

As discussed earlier, low testosterone levels are associated with obesity. This could be because adipose tissue is rich with the aromatase enzyme, which converts testosterone to estrogen. Studies have shown

that TRT decreases fat mass and BMI.¹³ Testosterone is believed to cause a reduction in abdominal adiposity by inducing lipolysis. Besides that, testosterone also activates the enzyme 11-hydroxysteroid dehydrogenase in adipose tissue, which transforms glucocorticoids into their inactive form.¹⁷

Long-term testosterone therapy for up to 6 years has been shown to result in significant and sustained improvements in weight. In a study by Haider et al, TRT caused a decrease of waist circumference by 11.56 cm and weight decline by 17.49 kg (15.04%).¹⁸ What is more interesting to note is that the reduction in waist circumference with testosterone undecanoate in more than 500 hypogonadal men appears to be superior when compared with data published for other drugs, in combination with lifestyle and behavioral interventions.¹⁹

Testosterone replacement therapy in diabetes mellitus and glycemic control

There is also strong evidence that TRT in diabetic men improves the homeostatic model of insulin resistance, hemoglobin A_{1c}, and fasting plasma glucose.²⁰ How it does this is still controversial, although it is believed to be mediated partly by its effect on visceral fat. Besides that, testosterone is also believed to be involved in promoting glucose utilization by stimulating glucose uptake, glycolysis, and mitochondrial oxidative phosphorylation. Testosterone also increases Glut4 in cultured skeletal muscle cells. Glut4, in turn, facilitates glucose transportation into the cell.²¹

The effects of TRT on diabetic men with hypogonadism go beyond glycemic control. In a study by Muraleedharan et al,²² mortality was increased in the low testosterone group (17.2%) compared with the normal testosterone group (9%; $P=0.003$). TRT (mean duration 41.6±20.7 months; n=64) was associated with an 8.4% reduced mortality compared with 19.2% ($P=0.002$) in the untreated group (n=174).

Testosterone replacement therapy and hyperlipidemia

TRT has beneficial effects on lipids as well. In a 5-year study on the effects of TRT, an improvement in lipid profile (total/high-density lipoprotein (HDL) cholesterol ratio, -2.9 ± 1.5 ; $P<0.0001$) was shown.²³ However, a meta-analysis and systemic review on randomized

controlled trials showed that triglyceride values improved in those given TRT, but no specific difference was found in cholesterol levels between the TRT and control groups.²⁴

Testosterone replacement therapy and hypertension

The positive effect of TRT on blood pressure has also been documented. A study by Francomano et al showed an improvement in both systolic and diastolic blood pressure (-23 ± 10 and -16 ± 8 mm Hg; $P<0.0001$) over 5 years.²³ However, a meta-analysis of randomized controlled trials did not show any significant difference in the blood pressure between TRT and the control.²⁴

Testosterone replacement therapy and lifestyle

It is widely known that lifestyle modifications, along with diet, exercise, and weight loss, are able to reduce insulin resistance, and therefore, prevent the progression to overt diabetes. However, the addition of TRT to lifestyle interventions has been shown to improve the glycemic control better and, in fact, is able to reverse the metabolic syndrome in 52 weeks.²⁰ The combination of TRT and lifestyle modifications is also able to increase insulin sensitivity, reduce fatty liver, and improve muscle mass, compared with placebo and lifestyle modifications alone.^{13,25}

Testosterone replacement therapy and myocardium

Besides its effects on metabolic syndrome, TRT has a direct effect on the heart as well. It has been found to improve myocardial ischemia in men with coronary artery disease. In fact, TRT has been shown to increase time to angina in stress tests.²⁶ Both acute and chronic testosterone therapy improved myocardial ischemia independent of the method of administration. It is hypothesized that testosterone promotes coronary vasodilation by its action on the calcium and potassium channels on the surface of vascular smooth muscle cells.

TRT has also been demonstrated to shorten the corrected QT (QTc) interval by augmenting the activity of slowly activating delayed rectifier potassium channels, while simultaneously slowing the activity of L-type calcium channels.²⁷ This stabilizes the heart.

Testosterone replacement therapy and mortality

TRT was associated with decreased risk of death (hazard ratio [HR], 0.61; 95% confidence interval [95% CI], 0.42-0.88; $P=0.008$). In fact, TRT is able to reduce mortality by 50% in men with low testosterone (testosterone <300 ng/dL) as compared with those not receiving TRT.²⁸ The key is to achieve optimal testosterone levels with TRT and not to go overboard with supra-normal testosterone levels. Yeap et al have also shown that the greatest benefits are seen with testosterone levels in the third quartile.²⁹ They concluded that optimal androgen levels are a biomarker for survival because older men with mid-range levels of testosterone and dihydrotestosterone had the lowest death rates from any cause.

Conclusion

Testosterone levels have been shown to be associated positively with metabolic syndrome and cardiovascular diseases (Figure 1). TRT, on the other hand, has also shown positive outcomes in terms of metabolic parameters and cardiovascular outcomes, but the long-term effects are not known. So far, all the studies published were small and short-term. The two controversial papers, which raised the alarm on TRT, showed that more needs to be done to allay our fears on TRT.^{30,31}

Despite the obvious benefits of TRT on the heart, caution needs to be heeded, especially in men with severe heart problems and those above 75 years of age. In frail elderly men, it is not advisable to use high-dose TRT. The administration of TRT requires

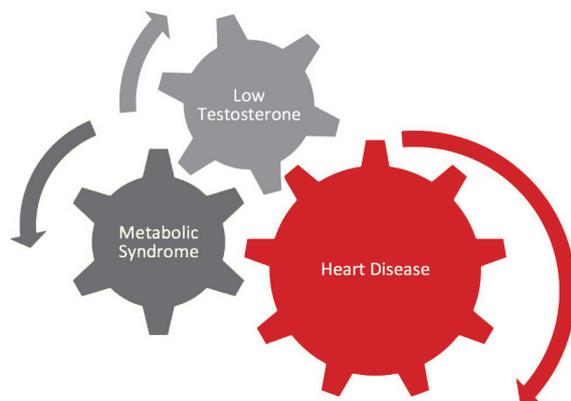


Fig. 1 An illustration of how testosterone deficiency may affect the heart directly, or indirectly through the metabolic syndrome.

close monitoring. Lifestyle changes are also needed to complement the benefit of TRT. When men are appropriately diagnosed, treated, and monitored, TRT is relatively safe and beneficial. Indeed, the ongoing Testosterone Trial in Older Men (NCT00799617) will provide important guidance to older men who meet current recommendations for TRT. ■

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