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Hypogonadism Management and Cardiovascular Health

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Abstract

In the early days of its use, testosterone therapy faced skepticism regarding its safety and efficacy. After a converging consensus that testosterone therapy was safe and effective for the treatment of hypogonadism, several recent studies showed adverse cardiovascular outcomes associated with testosterone treatment, ultimately resulting in a mandated FDA label warning about the unknown safety of testosterone therapy. Given the clear efficacy of testosterone therapy in the treatment of hypogonadism, establishing the safety of this therapeutic tool is essential. This article summarizes the current evidence regarding the cardiovascular safety of testosterone therapy for the management of hypogonadism, as well as the proposed mechanisms that may explain testosterone's underlying effects.

Keywords: Hypogonadism; Testosterone; Cardiovascular Disease; Drug Safety

Introduction

Testosterone (T) is the dominant male sex hormone, secreted primarily by the testes. T is an essential hormone that influences the development of sex characteristics, sexual function, and lean body mass.[1,2] Male hypogonadism, a clinical syndrome characterized by a deficiency of T, is a congenital or acquired condition that presents with decreased libido, erectile dysfunction, fatigue, loss of lean muscle, and depression.[3–5] Testosterone therapy (TTh) is used for a variety of purposes and is the foundation of hypogonadism treatment. A general consensus that TTh was a safe and effective treatment for hypogonadism was questioned when some studies published between 2010 and 2014 suggested an increased risk of adverse cardiovascular events with TTh. Since then, there has been very little evidence to suggest that TTh increases cardiovascular risk, although an FDA label remains on all T products that warns about the inconclusive evidence

regarding the risk of myocardial infarction (MI) and stroke. In light of this recent controversy and reemergence of apprehension surrounding TTh, this review will explore the current evidence on the association between endogenous serum levels of T and cardiovascular disease, the association between TTh and cardiovascular disease, and the underlying physiological mechanisms with which T may confer benefits or harms.

History of TTh and the FDA Label Change

Since the early days of T utilization, various members of the medical community have rejected its efficacy or safety. The most influential claim that provoked long-standing fears about TTh came in 1941, when Charles Huggins reported that castration promoted the regression of prostate cancer and that TTh was presumed to promote cancer growth. This paper was founded on a single case of a man with known prostate cancer.[6] The fear of using TTh persisted until the late 1990s, when studies began to clearly demonstrate that high T was not associated with increased prostate cancer risk.[7,8]

By the early 2000s, TTh prescriptions began to rise as new formulations were synthesized and public interest grew. Although there were some preexisting concerns about T and its relationship with cardiovascular risk, most of these concerns were alleviated by various studies showing that low T levels were associated with an increased risk of cardiovascular events and that higher T levels were cardioprotective.[9] In 2010, however, a study suggested an increase in the cardiovascular risks of TTh, with three subsequent studies supporting those claims, ultimately spurring a reemergence of fear surrounding TTh. The 2010 study, a 6-month placebo-controlled T gel study, noted more cardiovascular events in men given T than in men given a placebo. However, these events included nonspecific changes that were not associated with heart failure and some suggest that these events were caused by higher doses of T than were approved,

resulting in unusually high serum concentrations.[10,11] The authors of the study even suggested that the differences among the two arms may be due to chance,[11] and the FDA seemingly dismissed the concerns raised by the study due to such a low total number of major adverse cardiovascular events (MACE).[12]

The three subsequent studies came in the following four years. In 2013, Vigen et al. published a retrospective report of 8,507 men in the Veterans Administration system who had low T and showed a greater risk of MI, stroke, and death in men given TTh.[13] The authors later issued an official correction for misconstruing their results, which actually showed a lower percentage of MACE in the group treated with TTh. The authors also admitted that over 1000 individuals were incorrectly categorized and that nearly 10% of the population was discovered to be women. Numerous medical experts and societies have requested a retraction of the study.[14] The following year, Finkle et al. reported higher rates of nonfatal myocardial infarctions in the 90 days after prescribing T compared with the 12 months prior to prescription. This study lacked a control group of hypogonadal men who were not given a T prescription, making it difficult to interpret the rates of MI.[15] Additionally, serum T levels were not reported, and TTh was defined as men who were prescribed T. It is not known whether these men filled and utilized the prescriptions.[14–16] A fourth study, a meta-analysis of placebo-controlled T trials, reported higher MACE in men given TTh,[17] although the FDA suggested that these results utilized incorrect data and that their definition of cardiovascular events that was too broad. The FDA itself analyzed the data and did not find a difference in MACE between the TTh and placebo groups.[12] Notably, an extensive analysis of papers published between 1940 and 2014 found that these four studies were the only reports that indicated increased cardiovascular risk with TTh.[10]

Despite the poor quality of the small number of studies that demonstrated an increased cardiovascular risk with TTh, the FDA moved in 2015 to change the labeling of T products, restricting the indicated population and warning about the inconclusive safety about the cardiovascular risk associated with T formulations.[18] However, the rise in TTh in recent years is believed to be a result of decades of suppression of hypogonadism diagnosis due to previous fears of prostate cancer risk associated with TTh.[9] As of 2018, the American Urological Association and the Endocrine Society indicate in their public guidelines that recent data is not suggestive of an increased cardiovascular risk associated with T use, but both acknowledge a lack of clear conclusions regarding its safety. Both organizations recommend against providing TTh to patients with a recent history of cardiovascular events. The American Urological Association recommends waiting 3-6 months before prescribing T, while the Endocrine Society recommends waiting at least 6 months. There is no contraindication to continue prescribing T if patients are using T prior to a CV event[19,20] Interestingly, the European Medicine's Agency did not mandate a label change regarding cardiovascular risks of T formulations.[21]

Endogenous T and Cardiovascular Health

Investigations of hypogonadism can illuminate cardiovascular health as it relates to either endogenous serum levels of T or exogenous TTh provision. Studies have consistently demonstrated an association between lower endogenous serum T levels and increased risk of cardiovascular disease, cardiovascular mortality and all-cause mortality in men. Some studies even display a protective effect of higher T levels. A study of 2,416 Swedish men found that those with a serum total T level > 550 ng/dl had a 30% reduced risk of a cardiovascular event.[22] In a cohort of 1,251 men in the Framingham Heart Study, men ages 55-69 years with lower T levels had a higher risk of atrial fibrillation during follow up.[23] A meta-analysis that included

more than 22,000 total individuals further indicated that lower T levels were associated with increased mortality and with cardiovascular mortality.[24] Men in the highest quartile of T have been shown to have a lower risk of abdominal aortic atherosclerosis and men with coronary artery disease have been shown to have lower T levels than controls.[25,26] More recent studies corroborate these earlier findings. A 2018 meta-analysis that included a group of 10,479 total subjects and a mean follow-up time of over 6 years showed that lower T levels were predictive of a higher risk of cardiovascular events, cardiovascular mortality and all-cause mortality.[27] A 2019 cohort study that followed 18,238 Danish men between 2000 and 2015 found that individuals with lower T levels had higher 1-year and 5-year risks of stroke, MI, venous thromboembolism and all-cause mortality. After adjusting for age and co-morbidity, the association between low T and all-cause mortality remained significant. Overall, the results suggest that men with lower T levels have a higher absolute risk of death and a higher absolute risk of cardiovascular events than men with normal T levels.[28] One study even shows that men with lower T levels and coronary artery disease had higher rates of all-cause and cardiovascular mortality than men with normal T levels and coronary artery disease.[29]

A small number of studies simply show no relationship between T levels and cardiovascular risk, while others show more complexity in the relationship. A 2019 investigation of 7,671 subjects from the FINRISK97 study included a median follow-up of 13.8 years and found that low T was not predictive of future cardiovascular risk or mortality. It should be noted that about half of these subjects were female.[30] Interestingly, two prior reports of the FINRISK97 study linked low T levels in men to diabetes, atrial fibrillation, and stroke.[31,32] Other studies show more subtlety in the association between T and cardiovascular outcomes, suggesting a U-shaped relationship in which T levels within a certain range may confer cardiovascular

protection compared with T concentrations at the extremes. For example, a 2013 study of 495 men found that those in the lowest and highest quintiles of serum T concentrations had a higher risk of ischemic arterial disease than men in the second quintile.[23] Another study found that men in the highest and lowest quartiles of serum T concentrations had a higher risk of all-cause mortality.[33]

T deficiency has consistently been linked to metabolic syndrome (MetS), which is characterized by abdominal obesity, high blood sugar, high serum triglycerides, and low serum high-density lipoprotein (HDL).[34] It is important to note that rates of obesity have nearly doubled since the 1980s[35] in many countries and that more than one-third of United States men are obese,[36] with some citing obesity as the most common cause of idiopathic hypogonadism in the developed world.[21] Obesity is a well-established predictor of cardiovascular disease.[36] Men in the lowest quartile of serum T concentrations have been observed to have twice the risk of developing type 2 diabetes and MetS than men with normal serum T concentrations.[10] Recent studies support these findings. Two investigations from 2019 demonstrate that low T contributes to type 2 diabetes and is a marker for both insulin resistance and cardiovascular disease.[37,38] In a large randomized controlled trial (RCT), TTh was shown to improve insulin resistance in hypogonadal men with type 2 diabetes and/or MetS.[39] The relationship between low T and serum lipid and HDL levels is less clear, with some studies indicating that higher T levels are associated with lower total cholesterol and LDL cholesterol as well as triglycerides,[40,41] while others indicate that low T is also associated with lower levels of HDL cholesterol.[42] Given the interplay between total cholesterol, LDL cholesterol, triglycerides, and the established positive impact of HDL cholesterol, it remains difficult to assess the ultimate effects of low serum T levels on lipoprotein profiles and their contributions to cardiovascular disease.

The vast majority of studies show that endogenous T levels are a risk factor for cardiovascular disease, cardiovascular mortality and all-cause mortality. Although a small number of studies may show that serum T levels are not useful predictors of cardiovascular or mortality outcomes, there has been virtually no evidence published since the FDA label changes that show higher serum T concentrations leading to higher risks of cardiovascular events and mortality. Nevertheless, it is important to remember that population studies cannot demonstrate causality.

TTh and Cardiovascular Health

A number of observational and retrospective studies that evaluated cardiovascular risks associated with exogenous T have been published since the FDA Advisory Committee meeting. A large case-control study utilizing 934,283 men from an insurance claims database found that current use of TTh was not associated with an increased risk of MI. There was a slightly increased risk of MI with first time exposure.[43] Interestingly, a study evaluating cumulative exposure to T in 10,311 men also found that men with short-term exposure to TTh had an increased risk of cardiovascular events compared with controls. However, this study also showed that TTh was associated with decreased mortality and major cardiovascular events, especially among men with longer total exposure.[44] This suggests that a slightly higher risk of cardiovascular events associated with early exposure is mitigated with longer treatment durations. Most retrospective studies do not indicate serum T concentrations for men on TTh. Notably, a 2015 report from Sharma et al. examine varied cardiovascular outcomes among men who reached therapeutic serum T concentrations compared to men who had perpetually low serum T levels. Men receiving TTh but with consistently low T levels had higher risks of mortality, MI and stroke compared to men who attained therapeutic serum T levels. The risk of

stroke and MI in men with low on-treatment T was similar to that in men who did not receive any TTh.[45]

A follow-up to the previously mentioned study, also from Sharma et al., showed reduced risk of atrial fibrillation in men with normal serum T levels after TTh compared to men not treated with TTh. The study included 40,856 men with normal T levels and 11,853 untreated men.[46] Three more 2017 studies showed better cardiovascular outcomes in men receiving TTh compared with untreated men. One of these studies found improved cardiometabolic function and reduced cardiovascular risk in hypogonadal men receiving long-term TTh,[47] while another found that men receiving TTh had a lower risk of cardiovascular events than untreated men.[48] The third study evaluated on-treatment T levels of over 12,000 men in the VA system and demonstrated that non-smokers with therapeutic serum on-treatment T levels had a lower risk of all-cause mortality and MI than those with non-normalized T levels.[49] Later, a 2019 report examined cardiovascular outcomes in 165 patients exposed to TTh and found no difference in the risk of cardiovascular events between the treatment group and control group.[50] Finally, a report published in 2020 analyzed 805 hypogonadal men and showed that long-term TTh of up to 12 years improved metabolic and cardiometabolic risk factors, such as markers of obesity, lipid profiles, glycemic control, and hypertension.[51]

Randomized Controlled Trials

There have been a number of RCTs in recent decades evaluating the cardiovascular risk associated with TTh, mostly evaluating the effect of TTh on exercise tolerance and capacity. Some of these previous trials investigated the effect of TTh in patients with chronic stable angina using ECG changes during exercise in treated and untreated men.[52–57] Others evaluated the effect of TTh on patients with heart failure.[58–61] Overall, these trials showed improvements in ECG

signs of ischemia as well as an increase in exercise capacity. Most of these studies were relatively underpowered and used a sample size ranging from 13 to 87 total individuals.

Several RCTs were published in the few years following the FDA Advisory Committee meeting. Two of these trials had primary outcomes related to MetS. Dhindsa et al. randomized 44 hypogonadal men to receive either a placebo or intramuscular T injections every 2 weeks for 24 weeks and measured insulin sensitivity via glucose infusion rate (GIR) during hyperinsulinaemic-euglycaemic clamps. After 24 weeks, GIR significantly increased by 32% in treated men while the placebo group saw no change. The treated group ultimately had improvements in fat mass and lean body mass compared to placebo.[62] Another trial consisting of 334 Japanese men found that 1 year after initiation of TTh, treated men showed improvements in the short form-36 health survey (SF-36), reduced waist circumference, and reduced serum triglycerides. The study reported no significant difference in cardiovascular events between the groups (1m 37).[63] Two more trials utilized TTh but did not evaluate outcomes related to cardiovascular health as a primary endpoint. The trials evaluated the impact of TTh on ejaculatory dysfunction[64] as well as on pain perception in men with androgen deficiency secondary to opioid use.[65] In both trials, TTh resulted in favorable primary endpoints and neither study reported major cardiovascular events in either the treated or placebo group.

The Testosterone Trials consisted of seven multi-institution, double-blind, placebo-controlled trials that investigated the influence of TTh on sexual and physical functioning, anemia, bone mass, cognition, and coronary artery plaque volume. The results of these trials were published in 2016 and 2017. In the cardiovascular sub-study of the T Trials, 138 individuals were evaluated with CT angiography to scan for progression of both non-calcified and calcified coronary artery plaque volume as well as a coronary artery calcium score.[66] After 1

year of treatment, TTh was not associated with increased calcified plaque compared to placebo, although noncalcified plaque volume significantly progressed in the TTh group compared to placebo. Non-calcified plaque volume has not been associated with adverse cardiovascular outcomes,[67] whereas coronary calcium scores are shown to correlate with cardiovascular outcomes.[68] There was no difference in coronary calcium scores or in the number of adverse cardiovascular events between the groups. The precise ramifications of these outcomes remain unclear. Notably, another RCT investigated common carotid artery thickness as well as coronary artery calcium scores. Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM), a placebo-controlled, double-blind trial with 308 men, found no changes in common carotid artery intima-media thickness or in coronary artery calcium scores in men prescribed daily TTh for 3 years compared to men given placebo. Although this trial was not designed to evaluate adverse cardiac events, no major adverse cardiovascular events were reported.[69]

A 2018 meta-analysis of 31 RCTs found no increase in cardiovascular morbidity or mortality with TTh compared to placebo,[70] corroborating the findings of two prior meta-analyses that were published in the years following the FDA Advisory committee meeting.[71,72] Overall, RCTs in recent years do not indicate that TTh is associated with an increased risk of cardiovascular events or mortality.

Limitations of Current Studies and Looking Forward

RCTs provide more robust evidence than observational studies in illuminating the cardiovascular safety of TTh. However, most RCTs suffer from a number of limitations. First, some of these trials do not evaluate cardiovascular events as a primary endpoint. In addition, most of these RCTs are underpowered. Other potential reasons that could undermine the results of these trials are differences in duration, differences in T formulation, inclusion criteria, age,

weight, underlying cardiovascular risk, varied definitions of cardiovascular events, and lack of follow-up on serum T levels.[73,74] The Testosterone Trials improved significantly in terms of consistency and coordination, but the longest RCT to date remains a 3-year study.

Initiated in 2018, the TRAVERSE trial is a very large, randomized, controlled trial that will likely be sufficiently powered to show clear relationships between TTh and cardiovascular events.[75] The trial randomly assigned 6,000 hypogonadal men at high risk of cardiovascular disease who are ages 45-80 to receive either T gel or placebo. The treatment duration is currently set at 5 years. The primary endpoint for the trial is time to MACE, which includes nonfatal MI, nonfatal stroke or cardiovascular mortality. The TRAVERSE trial will give a more coherent picture of the outcomes associated with TTh.

Physiological Mechanisms of T

Men appear to have a higher risk of cardiovascular disease than women, and some suggest that sex-specific hormones are partially responsible for these differences.[76,77] Over the years, various in vitro and human epidemiological studies have highlighted the potential underlying mechanisms of testosterone's effect on cardiovascular physiology. Some of the proposed mechanisms could explain potentially adverse influences of T, while others might shed light on its potential cardiovascular protection.

Erythrocytosis is the most commonly reported adverse effect of TTh in men and has been a documented effect of TTh for many years.[20,78] An increase in red blood cells may confer a higher oxygen carrying capacity, but erythrocytosis in excess can result in hindered blood flow and an increased risk for thrombosis.[79] Additionally, there is evidence that TTh increases platelet aggregation by upregulating thromboxane A2 receptor densities on platelets in humans.[80] Other reports indicate that T-induced erythrocytosis is explained by decreased expression of hepcidin, a

major regulator of iron. This results in enhanced iron absorption and iron transport, augmenting erythropoiesis.[81,82] These data regarding T-induced hematocrit increases conflict with the lack of clear evidence that TTh increases the risk of cardiovascular events. A very small study suggested that TTh changes erythrocyte flexibility by increasing the number of unsaturated fatty acids in red blood cell membranes, facilitating hemodynamics and ameliorating the increased blood viscosity.[83] The exact reason for the lack of increased thrombotic events in TTh-treated men remains unclear.

Animal studies indicate that T slows atherosclerosis progression. In rabbits, T provision reverses aortic atherosclerosis in castrated rabbits fed high-cholesterol diets.[84,85] Similarly, mice with low endogenous T that are fed high-cholesterol diets display progressive aortic lipid accumulation that is reversed by T administration.[86] In addition, mice with apolipoprotein-E deficiency and a knockout of the *Ar* gene, which is responsible for androgen receptor production, show increased atherosclerotic progression.[87] In humans, the evidence that T reverses atherosclerosis is less clear. As previously discussed, the Testosterone Trials had complex outcomes involving plaque formation, while the TEAAM trial demonstrated no changes in carotid intima-media thickness or coronary artery calcium scores in TTh-treated men.

T's effects on cardiomyocyte electrophysiology and cardiac contractility has been explored in both in vitro studies and in humans. Ventricular cardiomyocytes isolated from guinea pigs that are exposed to T have shorter ventricular repolarization action potentials, mediated by various interactions with potassium channels and L-type calcium channels.[88] In humans, lower endogenous T has been correlated with prolonged QT intervals,[89] with some theorizing that decline in T levels with age is partially responsible for the age-related increase in QT intervals.[90] Accordingly, one European study found that hypogonadal men had a higher risk of torsades de

pointes that was attenuated by TTh.[91] Together, these findings suggest that T could be protective against cardiac arrhythmias.

In vitro studies show that T enhances cardiomyocyte contractility. After prolonged T deficiency induced by orchiectomy, rat hearts showed decreased cardiac contractility that was reversed by T administration.[92] Isolated ventricular cardiomyocytes from rats exposed to T displayed increased rates of cardiomyocyte relaxation.[93] The enhanced contractility and relaxation rate after T exposure is theorized to be caused by alterations in calcium release from the ryanodine receptor and by enhanced calcium clearance from the cytosol.[94] In humans, TTh has been shown to improve cardiac output and improve aerobic capacity in men with congestive heart failure.[59,60,95]

As previously discussed, T's effect on lipid profiles in humans is unclear, as it is shown to reduce total cholesterol, LDL cholesterol, and triglycerides while simultaneously reducing HDL cholesterol. In vitro studies in cell lines and in mice confirm that T increases hepatic cholesterol reuptake and decreases serum cholesterol and LDL.[96,97] In vitro studies are less clear with regard to the effect of T on serum HDL, with some finding no significant change in HDL after T exposure.[98]

Conclusion

Testosterone is clearly a major player in cardiovascular and metabolic health and physiology. Although some epidemiological data show an increase in adverse cardiovascular events with provision of T, most studies do not support this suggestion. Most RCTs to date are underpowered and do not provide clear, conclusive evidence to repudiate the small numbers of studies that indicate an increased risk. To bolster the evidence regarding the safety of TTh, larger clinical trials such as the TRAVERSE trial will provide key insights. Until then, clinicians should be

aware of the overall health impacts of hypogonadism and TTh and advise patients with honest communication about the current evidence.

Disclosures

The contents of the paper and the opinions expressed within are those of the authors, and it was the decision of the authors to submit the manuscript for publication.

Dr Mohit Khera has worked as a consultant for AbbVie, Boston Scientific, Clarus and Metuchew

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