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An update on testosterone, HDL and cardiovascular risk in men

Arthi Thirumalai^{1,*}, Katya B Rubinow², and Stephanie T Page³

¹University of Washington, Division of Metabolism, Endocrinology & Nutrition, 1959 NE Pacific Street, Box 356426, Seattle, WA 98195, USA

²University of Washington, Division of Metabolism, Endocrinology & Nutrition, South Lake Union Campus, 850 Republican Street, Box 358055, Seattle, WA 98109, USA

³University of Washington, Division of Metabolism, Endocrinology & Nutrition, 1959 NE Pacific Street, Box 357138, Seattle, WA 98195, USA

Abstract

Testosterone prescriptions have risen steadily and sharply in the USA despite a lack of clear understanding of the relationship between androgens and cardiovascular disease. In men with increasing age, testosterone levels decline and cardiovascular disease risk goes up. Ties between hypogonadism and cardiovascular disease are suggested by observational data, yet therapy with testosterone replacement has not been shown to mitigate that risk. To the contrary, recent literature has raised concern for increased cardiovascular disease in certain groups of men receiving testosterone therapy. In this article, we review current literature in an attempt to better understand what it suggests is the true relationship between testosterone and cardiovascular disease. We also take a closer look at effects of testosterone on lipids and HDL in particular, to see if this explains the cardiovascular effects seen in clinical studies.

Keywords

cardiovascular disease; HDL; male hypogonadism; testosterone; testosterone replacement therapy (TRT)

Cardiovascular risk increases in men with age in tandem with declining endogenous testosterone (T) production. Further, observational data suggest that men with low circulating T levels may be at greater risk for cardiovascular disease (CVD). Nonetheless, controversy remains regarding treatment of male hypogonadism, in part due to a lack of clear understanding of the risk/benefit profile of therapy. This controversy is mostly related to the treatment of late-onset hypogonadism, a clinical and biochemical state characterized by low T and typical symptoms [1]. Although cross-sectional studies have demonstrated higher prevalence of CVD among men with low endogenous androgens, limited clinical data

* Author for correspondence: Fax: 206 685 3781, arthidoc@uw.edu.

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have not shown that testosterone replacement therapy (TRT) reduces CVD risk. Moreover, appropriately powered randomized controlled trials of TRT, the gold standard for determining the risks and benefits of a clinical intervention, have not been performed. In lieu of such data, small randomized trials to date have been performed that evaluate CVD risk factors rather than events as study endpoints, and these demonstrate mixed effects of TRT. While meta-analyses of such trials [2] suggest that TRT does not increase CVD risk, a recent randomized trial suggested that TRT might increase risk in certain clinical populations [3]. In this article, we review newly published studies evaluating TRT in older men and explore alterations in circulating lipids as one possible mechanism whereby T might influence CVD risk.

Endogenous testosterone & CVD

Observational studies performed to investigate the association between circulating T concentrations and CVD risk have yielded inconsistent findings. Multiple cross-sectional studies have examined the association between endogenous T levels and the presence of coronary artery disease. Wu and von Eckardstein [4] performed an extensive review of these cross-sectional analyses and concluded that despite inconsistencies among the studies, overall, coronary disease appeared to be associated with low endogenous T concentrations in men. More recently, Malkin *et al.* [5] reported a 24% prevalence of biochemical T deficiency (using either total or bioavailable T concentrations) among men with coronary disease. The authors also found higher vascular and all-cause mortality among men with low plasma T levels when compared with men without androgen deficiency. However, while these types of analyses attempt to control for covariates, they do not allow clear discernment as to whether T levels are directly related to CVD risk or, alternatively, serve as a marker of ill health overall.

Similar to these cross-sectional analyses, longitudinal data have shown mixed findings, although most studies have not demonstrated a relationship between circulating T levels and incident CVD. This type of study design generally entails measurement of a single, or possibly two, serum T levels in participants, whose health trajectories are then followed over the ensuing years. These longitudinal analyses, therefore, relate endogenous T levels to the development of disease over time. Multiple longitudinal studies [6–9] and a meta-analysis of these [10] have found that low T levels are associated with higher all-cause mortality but whether or not these results were attributable to increased CVD remains unclear. Additional studies have focused specifically on cardiovascular events and mortality. The Rancho Bernardo study followed 1000 men aged 40–79 years over a 12-year period and found no association between plasma T levels and either extant CVD or subsequent cardiovascular morbidity and mortality [11]. In contrast, men in the highest quartile of serum T in the MrOS study had the lowest incidence of CVD events over 5 years of follow-up [12]. Yeap *et al.* found that high concentrations of T and its potent metabolite dihydrotestosterone were associated with a lower risk of stroke over 6.5 years of follow-up but androgen levels were not associated with a differential risk of incident myocardial infarction [13]. Additional longitudinal studies have similarly found that neither high nor low T levels predict incident myocardial infarction [14–16]. An alternative approach, employed to examine the association between T levels over time and CVD, was a nested case–control study within the

Baltimore Longitudinal Study of Aging [17] and the Multiple Risk Factors Intervention Trial [18]. Subjects enrolled in these studies were followed over a long period of time and then divided into cases or controls, based on development of coronary events. T levels were then measured in stored blood samples from initial study visits and analyzed for differences between the two groups. Investigators found no differences in baseline circulating T levels, between the controls and those men who developed incident coronary events, over a decade of follow-up. In aggregate, though there have been mixed results regarding the relationship between low endogenous T levels and incident CVD, these studies suggest that, if anything, higher T levels may be protective.

The inconsistency among the longitudinal data may in part be due to the design of such studies and the reliance on single, or even duplicate measures of serum T. Since day-to-day variation of T concentrations in a given individual can be large [19], these single low measurements may not be as meaningful as multiple measurements over time. An alternative interpretation of these longitudinal data, like those from cross-sectional studies, is that low T levels are a marker of ill health. Ruigi *et al.* drew a similar inference from their systematic review and meta-analysis of 19 studies and, interestingly, also noted that an association between low endogenous T concentrations and higher risk of CVD and mortality was only seen in men older than 70 years of age [20]. Studies of very healthy older men do not show significant declines in serum T over time [21]. Overall, these types of longitudinal analyses also fail to provide evidence of a direct, causal relationship between androgen exposure and CVD. Given the absence of a clear, causal relationship, clinical use of TRT is predicated on the presence of hypogonadal symptoms rather than cardiometabolic disease.

Testosterone replacement therapy & CVD

Rather than observational findings, interventional data are required to infer causality between androgen exposure and CVD risk in men. Accordingly, clinical intervention studies have been performed to investigate whether TRT can mitigate CVD risk factors among men with low endogenous T concentrations; however, none of these have been powered to examine CVD event rates. Three meta-analyses of randomized controlled trials to date did not indicate an association between TRT and CVD [2,22–23], but a more recent meta-analysis [24] came to the opposite conclusion. However, these authors did not restrict their data to randomized controlled trials that limited enrollment to older men with low baseline T, making their conclusions more difficult to interpret regarding TRT and CVD in men treated according to clinical guidelines [1]. In contrast, another recent meta-analysis [25] that included the largest number of studies so far did not find any association between TRT and CVD risk. The authors further suggested that the Xu meta-analysis may have noted an association because their definition of cardiovascular events was more inclusive than typical restriction to major adverse cardiovascular events. Furthermore, another meta-analysis found that TRT appeared to confer mortality benefit specifically in hypogonadal men with Type 2 diabetes [26]. However, it is important to remember that all of these studies, regardless of findings, have methodological weaknesses that limit their interpretive value.

Nevertheless, of potential concern are results from the TOM trial [3]. This randomized controlled trial of elderly, frail men was halted early by the data safety monitoring board due

to an excess of cardiovascular events noted among older men randomized to testosterone as compared with placebo. It is notable, however, that these community-dwelling participants had very significantly reduced mobility, a high prevalence of chronic disease, and that they received rather high doses of T in this study. Thus, broad extension of these findings to less frail and less chronically ill populations of hypogonadal men may not be appropriate. In fact, a similar study of comparable size and design did not observe such an increase in CVD events among men randomized to the T arm [27]. An additional noteworthy difference between these two studies was the baseline mean T concentration among study subjects; while baseline T concentrations in the TOM trial were in the hypogonadal range, those in the European study were in the low-normal range, perhaps reflecting differences in overall health status between the participants. Further, subjects in the TOM trial had higher baseline BMI, higher triglycerides, and lower HDL than individuals included in the second study. Therefore, the higher rate of cardiovascular events noted in the TOM trial might be attributable to a poorer baseline cardiometabolic profile among the participants. Importantly, the interpretive value of these randomized controlled trials remains limited, as these studies were not powered to look at CVD events as an outcome. Nonetheless, the results of the TOM trial provide important cautionary information regarding the potential for TRT to be harmful in at least some populations of older men and points to the need for larger studies.

Recently, larger cross-sectional studies have been undertaken to better define the cardiovascular effects of TRT. In contrast to the cross-sectional studies mentioned above, these studies have attempted to analyze large populations of men who received exogenous T, presumably as TRT. Two of these large analyses have concluded that TRT is associated with an increase in cardiovascular events and these studies have received significant attention in the media [28,29]. However, interpretation of these data is complicated by nature of their retrospective design and complexities in determining subject behavior within a population, and hence, do not allow for conclusions regarding causality. Vigen *et al.* reported an association between TRT and the incidence of myocardial infarction, stroke or death in approximately 8000 male veterans [30]. All patients included in this retrospective analysis had low serum T concentrations and had undergone coronary angiography. After adjustment for over 50 variables, those individuals who had received a prescription for T following coronary angiography had a higher incidence of CVD events compared with the group who had not received a T prescription over an average of 27.5 months of follow-up. However, the absolute number of events in each group, prior to adjusting for these multitude of factors, indicated the converse association, with a total event rate of 10% in the TRT group and >20% in the untreated men. Furthermore, the actual exposure to T among the subjects is not clear, as the treatment group was categorized on the basis of a single-filled prescription, and post-treatment T levels were not measured nor was long-term use confirmed. Notably, this study generated substantial controversy on the basis of these and other criticisms [31]. In a second study, Finkle *et al.* used a large healthcare database and also reported an association between T prescriptions and myocardial infarction in older men in the immediate 90-day postprescription period [32]. However, data on prescription fulfillment were lacking, and whether the men prescribed TRT truly were hypogonadal, by both symptoms and T concentrations prior to receiving the prescription for T, was not determined. Contrary to the results of the population-based studies reviewed above, Shores

et al. found that hypogonadal male veterans who were treated with T, including those with pre-existing cardiac disease, had a decreased rate of mortality compared with untreated men, even after adjustment for co-morbidities [33]. Overall, these types of retrospective analyses do not substantiate conclusions assigning a causal role for TRT in the development of cardiovascular morbidity but they clearly underscore the need for larger, randomized trials of TRT and CVD.

A randomized clinical trial powered to assess disease risk associated with TRT, including prostate cancer and cardiovascular events, has been estimated to require 7000–8000 subjects followed for approximately 7 years. Such a trial would be similar in scope to the Women's Health Initiative, and as such would require a substantial resource investment. However, such an investment is likely to yield critical scientific and clinical information as well as economic benefits. It has recently been shown that the Women's Health Initiative has saved \$140 for every dollar invested in the initial trial [34]. Of note, a preliminary study, the Testosterone trial (T trial) has just been completed [35]. In this randomized trial, investigators have examined the effects of TRT in approximately 800 older, hypogonadal men over a 1-year treatment period. The study endpoints include coronary artery plaque volume as measured by CT scan as well as serum lipids; thus, although resultant data merit interest, this study is underpowered to provide additional information regarding cardiovascular events.

Testosterone & lipids

In parallel to these clinical investigations, ongoing research efforts have been invested in better understanding the mechanisms by which T may influence cardiovascular health. Specifically, the effects of T on plasma lipids have been a focus of attention. Lower endogenous T levels are associated with a proatherogenic lipid profile. A positive correlation exists between HDL-c and circulating T concentrations, as seen in multiple studies including the San Antonio Heart study [36], the Tromso study [37], the Turku Male Aging study [38], the Rancho Bernardo study [39], MRFIT [40] and a study from Ghent, Belgium [41]. Most of these studies have also demonstrated an inverse relationship between T levels and both plasma triglycerides [32–34,36] and total cholesterol [32,34]. Elevated levels of VLDL are associated with increased risk of atherosclerosis. The Rancho Bernardo study also showed an inverse relationship between circulating T levels and plasma VLDL [35]. Additionally, data from the MESA study demonstrated that T levels were positively associated with smaller or less atherogenic VLDL particles [42]. Ohlsson *et al.* showed that higher T concentrations were associated with a more favorable apoprotein profile, with a lower apoB/apoA-1 ratio [11]. These findings prompted a prospective look at the relationship between plasma T levels and dyslipidemia through longitudinal studies. In the Study of Health in Pomerania, Haring *et al.* [43] examined the relationship between T levels and lipids, both at baseline and prospectively over 5 years. They divided the men into quartiles of T levels and noted that the lowest quartile of men had higher total cholesterol and triglyceride levels in both cross-sectional and longitudinal analyses. The lowest quartile was also at higher risk for incident dyslipidemia, with a stronger effect noted in younger men (20–39 years age). However, the authors did not observe an association between T concentrations and HDL-c or LDL-c levels. While in another study by Canoy *et al.* [44]

again no association was noted between T concentrations and HDL-c in young men, they did, however, note a positive correlation between total T concentrations controlled for sex hormone binding globulin and total cholesterol, LDL-c and triglycerides. However, in an analysis in older men from the Framingham heart study [45], no association between plasma lipids and T concentrations was observed. Interestingly, these authors reported that when T concentrations were tracked over time, a greater decline was evident among men with multiple CVD risk factors than men without risk factors, with T levels in some subjects reaching the hypogonadal range. These findings again support the possibility that lower T concentrations may be a reflection rather than a cause of ill health.

Contrary to the positive association seen between endogenous T and HDL-c concentrations, meta-analyses of studies of TRT in hypogonadal men have generally demonstrated that exogenous T lowers HDL-c; however, this effect is commonly associated with a concomitant lowering of total cholesterol and LDL-c concentrations [46,47]. Nonetheless, this HDL-c lowering effect has raised concern regarding the cardiovascular safety of TRT. Notably, substantial decreases in HDL-c concentrations have mainly been demonstrated with supraphysiologic doses of androgens administered to young men [48] and the use of anabolic androgens among athletes [49]. The HDL-c lowering effect appears variable with age, dose, and route of T administration [43] and it is most striking with high-dose, oral therapy. In contrast, normalization of circulating T levels with transdermal TRT did not affect HDL-c levels in older, hypogonadal men [50]. Importantly too, HDL-c concentrations in isolation may not be a reliable marker of CVD risk, since no long-term clinical data have established a link between the lower HDL-c concentrations caused specifically by TRT and increased incidence of CVD. In fact, the utility of HDL-c as an index of CVD risk has broadly fallen into question. This stems from results of trials including the ILLUMINATE trial in which the cholesteryl ester transfer protein inhibitor torcetrapib raised HDL-c levels by 72% but was still associated with increased cardiovascular events [51]. Focus has shifted from measuring HDL cholesterol content alone to assessing HDL particle function, which may prove a better predictor of CVD risk.

HDL particles perform myriad functions, including immunomodulatory roles, the regulation of endothelial cell function and removal of cholesterol from the artery wall through reverse cholesterol transport [52]. HDL particles facilitate reverse cholesterol transport by accepting cholesterol from lipid-laden macrophages in peripheral tissues and transporting it to the liver for excretion in bile. This prevents the deposition of cholesterol in the arterial wall and thereby protects against atherogenesis. Interestingly, *in-vitro* findings suggest that T could accelerate reverse cholesterol transport [53], and it has been suggested that reductions in HDL-c caused by TRT actually could reflect this accelerated process [54]. This raises the possibility that these reductions in HDL-c do not confer increased CVD risk at all and conceivably could reflect a protective effect. As the predictive utility of changes in HDL cholesterol content appears limited, emergent metrics of HDL composition and function are increasingly used to gauge the relative cardioprotective capacity of HDL particles. These metrics include analysis of HDL protein composition as well as functional assays. The cholesterol efflux assay, for example, measures the capacity of serum HDL to efflux cholesterol from lipid-loaded macrophages and therefore is considered an index of HDL

efficiency in the initial step in reverse cholesterol transport. Notably, HDL efflux capacity can differ markedly among individuals with identical HDL-c concentrations [55]. Furthermore, efflux capacity was a better predictor of extant coronary artery disease than was HDL-c concentration in a large clinical population. We have previously demonstrated that TRT in older, hypogonadal men confers changes to the protein composition of HDL without altering HDL-c concentrations or its cholesterol efflux capacity suggesting a neutral effect with regard to HDL-related cardiovascular risk. However, this was a small study and there is a need to verify the findings and better understand the functional implications of the observed changes in HDL constituent proteins [45]. In summary, the interaction between circulating androgens and HDL particles is likely quite complex and remains poorly understood. Continued research is critical to better elucidate both the effects of T on HDL composition and function and the utility of various HDL metrics in CVD risk prediction.

Conclusion

Thus, despite numerous research efforts to date, the role of hypogonadism in the pathogenesis of CVD remains unclear, as does the cardiovascular risk profile of TRT. The inconsistent findings to date and lack of standardized approach to TRT administration in these studies mandate a large-scale randomized controlled trial to better define the cardiovascular effects of TRT. This study must be powered for CVD outcomes and, ideally, should examine TRT among a broad spectrum of hypogonadal men to stratify treatment effects by age and baseline health status, among other clinical variables. In the absence of such data, caution and clear goals for treatment should be discussed with men with known CVD while prescribing TRT. In parallel, ongoing work is required to further elucidate the mechanisms by which T may influence CVD risk, including its effects on HDL and other plasma lipids. Thus, expanded research efforts are needed to adequately address both the clinical and biological complexity of the relationship between androgens and CVD.

Future perspective

We anticipate there will be a better understanding of the predictive value of the different metrics of HDL particles in relation to CVD. Hopefully, a randomized controlled trial, sufficiently powered to look at cardiovascular outcomes in a wide range of hypogonadal men receiving TRT, will be under way.

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Executive summary

Endogenous testosterone & cardiovascular disease

- Cross-sectional observational data suggest lower testosterone concentrations are associated with higher cardiovascular disease (CVD) risk.
- Longitudinal studies have either not borne out such an association or suggest higher testosterone levels may be protective from CVD.
- Low endogenous testosterone levels have not been shown to have a causal relationship CVD and could simply be a reflection of ill health.

Testosterone replacement therapy & CVD

- A single randomized controlled trial in frail, elderly men with multiple comorbidities noted higher cardiovascular events in men receiving testosterone and was stopped prematurely (TOM trial), raising concern for the safety of testosterone replacement therapy (TRT).
- A single meta-analysis of multiple trials, which used an atypical definition of CV events, showed a positive association between TRT and CVD. However, all other meta-analyses that have included more number of trials and used major adverse cardiovascular events as outcomes have not shows such an association.
- Two large cross-sectional studies further explored this question and also concluded that TRT is associated with an increase in cardiovascular events and these studies have received significant attention in the media. However, both had flaws in study design and the duration of androgen exposure was not clear.
- The Testosterone trial has recently been concluded and the results will merit interest, however, it is not powered to look at cardiovascular outcomes.

Testosterone & lipids

- Endogenous testosterone is associated with an antiatherogenic lipid profile with higher HDL-c and lower total cholesterol and triglycerides.
- TRT can lower HDL-c, however, it is usually accompanied with lowering of total cholesterol and LDL-c.
- Though HDL-c lowering has been considered a mechanism for increased CV risk with TRT, the true role of that metric has come into question.
- Other metrics such as HDL particle size, protein composition and functional assays may explain effects on CV risk better than cholesterol content of the particles.

Conclusion

- A large randomized controlled trial, similar to the Women's Health initiative, is needed to answer the question regarding TRT and CVD and is likely to yield critical scientific and clinical information as well as economic benefits.