Clinical Literature

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Testosterone and the Cardiovascular System: A Comprehensive Review of the Clinical Literature

coronary disease diabetes mellitus heart failure mortality testosterone

Introduction

Recent data from the Massachusetts Male Aging Study (MMAS) have revealed an increasing incidence of hypogonadism within the aging US population. The Massachusetts Male Aging Study estimates indicate that ≈2.4 million men aged 40 to 69 suffer from hypogonadism in the United States.[1] The Massachusetts Male Aging Study also projects ≈481 000 new cases of hypogonadism annually in US men within the same age group.[1] The true incidence of hypogonadism among US men may be in excess of the Massachusetts Male Aging Study estimates, given the stringent criteria that were used by the authors to define hypogonadism. Testosterone in men reaches maximum levels at approximately age 30, after which levels steadily decline at a rate of 1% to 2% annually.[1] Controversy exists regarding whether the decline in testosterone with increasing age is a normal physiologic process or whether it is a result of chronic comorbidities and lifestyle choices. Testosterone levels are lower in patients with chronic illnesses such as end-stage renal disease, human immunodeficiency virus, chronic obstructive pulmonary disease, type 2 diabetes mellitus (T2DM), obesity, and several genetic conditions such as Klinefelter syndrome.[2–3] Trauma, castration, radiation or chemotherapy, acute illness, and pituitary tumors are also known causes of hypotestosteronemia.[2,4] It is unknown whether low testosterone in patients who are ill is the cause of their illness or whether it is caused by their disease. The exact mechanism of action that leads to lower testosterone levels with age has not been discovered. New evidence from rat models suggests that the synthesis of testosterone by testicular Leydig cells in response to luteinizing hormone may decrease with age. Reactive oxygen species (ROS), which are generated by the mitochondria of Leydig cells, are a normal byproduct of testosterone synthesis. The accumulation of ROS over time may cause damage to the Leydig cell DNA and thereby render it incapable of producing testosterone.[5]

The past 2 decades have witnessed a significant increase in the number of prescriptions for testosterone replacement therapy. Estimates suggest that since 1993 prescriptions for testosterone, regardless of the formulation, have increased nearly 500%.[6] Reasons behind this dramatic increase in testosterone use include increased prevalence of physiologic testosterone deficiency secondary to the aging population, increased media attention to testosterone replacement therapy aimed at men and women, and the development and consequent wide marketing of new testosterone formulations, including transdermal testosterone. The recent flurry of direct consumer advertising of testosterone products on television and in print is difficult to ignore. On the other hand, the relationship between circulating testosterone and various aspects of cardiovascular health is not clearly understood. Furthermore, the effects of testosterone replacement therapy on risk factors of cardiovascular disease and major adverse cardiovascular outcomes are a point of contention.

The goal of this article is to provide a comprehensive review of the clinical literature that has examined the associations between testosterone and cardiovascular disease including incidence of coronary artery disease, severity of coronary artery disease, mortality secondary to cardiovascular disease, angina pectoris, vasomotor regulation of coronary arteries, congestive heart failure, and QT interval prolongation. We also summarize findings from the clinical literature on the association of testosterone with risk factors of atherosclerosis including T2DM, dyslipidemia, obesity, and biomarkers of inflammation. Finally, we summarize the effects of testosterone replacement therapy on cardiovascular disease and its risk factors and major adverse cardiovascular events. When analyzing the content of this review article, it is important to note that a certain degree of between-study heterogeneity is unavoidable because of the very large number of available studies. For instance, obesity is an important factor that must be considered when analyzing testosterone studies. Although most studies account for obesity in their analysis, others do not. Similar consideration should be given to the effects of obesity and insulin resistance on sex hormone–binding globulin (SHBG).

Levels of Endogenous Testosterone in Men With Coronary Artery Disease

Hypogonadism is not considered a traditional risk factor for coronary artery disease (CAD). However, it is widely accepted that men experience a gradual decline in their testosterone levels with increasing age,[7–12] and male sex has long been considered a strong risk factor for CAD. Together, these 2 facts have prompted numerous investigators to search for a possible relationship between endogenous testosterone levels and CAD. The volume of evidence that links low testosterone levels with CAD has been steadily growing during the past decade. This section is a comprehensive review

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of clinical literature that examines this relationship.

A growing body of evidence suggests that men with lower levels of endogenous testosterone are more prone to develop CAD during their lifetimes.[13–18] However, this is in direct contrast to findings from earlier studies that failed to find any significant association between baseline testosterone levels and the development of CAD.[19–22] There are 2 major potential confounding factors that the older studies generally failed to account for. These factors are the subfraction of testosterone used to perform the analysis and the method used to account for subclinical CAD.

Normally, testosterone exists in 2 different subfractions in human serum.[23–24] The biologically inactive form of testosterone is tightly bound to SHBG and is therefore unable to bind to androgen receptors. The biologically inactive fraction of testosterone comprises nearly 68% of the total testosterone in human serum.[23–24] The biologically active subfraction of testosterone, also referred to as bioavailable testosterone, is either loosely bound to albumin or circulates freely in the blood, the latter referred to as free testosterone.[23–24] It is estimated that ≈30% of total serum testosterone is bound to albumin, whereas the remaining 1% to 3% circulates as free testosterone.[23] Total testosterone is the sum of all testosterone subfractions. Therefore, it can be argued that using the biologically active form of testosterone to evaluate the association with CAD will produce the most reliable results. However, more research is required to definitively determine whether bioavailable testosterone is superior to free testosterone as a marker of hormone activity.

Accounting for both bioavailable testosterone and subclinical CAD, English et al[14] found statistically significant lower levels of bioavailable testosterone, free testosterone, and free androgen index in patients with catheterization-proven CAD compared with controls with normal coronary arteries. These results were confirmed by Rosano et al,[17] who showed once again that patients with catheterization-proven CAD had statistically significant lower levels of bioavailable testosterone. Four additional studies have confirmed these results, although it should be noted that none has accounted for both bioavailable testosterone and subclinical CAD simultaneously (Table 1).[13,15–16,18]

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Table 1.

Association Between Testosterone Level and Incidence of Coronary Artery Disease

On the other hand, some investigators have found no association between endogenous testosterone levels and the incidence of CAD. Although Kabakci et al[21] controlled for subclinical CAD by assessing cardiac catheterization results of both cases and controls, they performed their analysis using total and free testosterone levels. This represents a limitation of this study because the authors did not fully account for biologically active testosterone, which includes both free testosterone and testosterone bound to albumin.

In conclusion, existing evidence suggests that men with CAD have lower levels of endogenous testosterone,[13–18] and more specifically lower levels of bioavailable testosterone.[14,17] This finding is consistent with evidence that low testosterone levels are associated with risk factors for CAD such as T2DM[25–26] and obesity.[27–28] Currently, it is unknown whether low testosterone levels cause CAD or if they are a consequence of CAD. Caution should be taken in interpreting these results because of the relatively small number of subjects who have been included in the studies. Further prospective epidemiological studies are required to solidify the association between incident CAD and endogenous bioavailable testosterone.

Association Between Levels of Endogenous Testosterone and Severity of Coronary Artery Disease

There is growing evidence supporting an inverse relationship between the degree of testosterone deficiency and the severity of coronary artery disease. Four investigators have independently demonstrated that in men with CAD, lower levels of endogenous testosterone are associated with more severe CAD (Table 2).[15,17,29–30] These results must be interpreted with caution because of the relatively small sample size included in each study and differing study designs. The exact mechanism of action through which testosterone deficiency results in the worsening of CAD is unknown. Testosterone deficiency may cause the worsening of CAD by negatively affecting the components of the metabolic syndrome, such as insulin resistance, hypertension, dyslipidemia, and visceral obesity. The correlation between low testosterone levels and worsening T2DM[27] and obesity[27] has been well established. The evidence for the association between testosterone and different lipoprotein subfractions is less convincing.[31] Testosterone deficiency is also shown to negatively affect carotid intima-media thickness,[32] and therefore it would be reasonable to assume it would have the same deleterious effect on the coronary arteries. To the best of our knowledge, there are no published studies that have investigated the association between testosterone levels and coronary artery intima-media thickness. Finally, low testosterone may influence the severity of CAD by adversely affecting the mediators of the inflammatory response such as high-sensitivity C-reactive protein, interleukin-6, and tumor necrosis factor–α. Additional investigation using biologically active levels of testosterone is required to further elucidate the association between low testosterone levels and severity of CAD.

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Table 2.

Association Between Testosterone Level and Severity of Coronary Artery Disease

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Testosterone and Cardiovascular Disease

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Association Between Endogenous Testosterone Levels and Mortality

Data from the Massachusetts Male Aging Study have established that testosterone in healthy men reaches its highest levels at approximately age 30,[33] after which it starts to gradually decline at a rate of 1% to 2% annually.[34] It has also been shown that lower levels of endogenous testosterone are associated with conditions known to increase mortality, such as T2DM and obesity.[27] This has prompted numerous investigators to study the association between testosterone level and mortality.

A total of 7 population-based studies analyzed the association between mortality secondary to cardiovascular disease and levels of total testosterone. Although 3 of these studies found statistically significant greater cardiovascular mortality associated with lower levels of total testosterone,[35–37] the remaining 4 studies did not confirm these results.[20,38–40] In a meta-analysis of these 7 population-based studies, Araujo et al[41] showed a trend toward increased cardiovascular mortality associated with lower levels of total testosterone, but statistical significance was not achieved (RR, 1.25; 95% CI, 0.97 to 1.60; *P*=0.06). However, the authors showed that a decrease of 2.1 standard deviations in levels of total testosterone was associated with a 25% increase in the risk of cardiovascular mortality. When interpreting the results of this meta-analysis, the authors correctly pointed out the significant amount of between-study heterogeneity in the age of the cohorts, baseline testosterone levels, assays used to obtain testosterone levels, length of follow-up, and finally the time of day when blood samples were obtained.[41]

Ohlsson et al[27] performed an analysis of 2416 community-dwelling Swedish men (MrOS Study) in which they investigated cardiovascular events and event-free survival. The investigators demonstrated that levels of endogenous total testosterone were significantly inversely associated with the risk of major adverse cardiovascular events. The risk of major adverse cardiovascular events for subjects in the fourth quartile of total testosterone was significantly lower compared with those in the second quartile. Ohlsson et al[27] were also able to show that patients in the fourth quartile of total testosterone had significantly improved event-free survival for both major adverse cardiovascular events and coronary heart disease events.

On the other hand, combined results from 11 studies investigating the association between endogenous total testosterone levels and all-cause mortality showed statistically significant higher rates of all-cause mortality in those men with lower levels of endogenous total testosterone.[35–40,42–46] These findings were reported in a meta-analysis by Araujo et al, in which the relative risk of all-cause mortality in men with lower levels of total testosterone was calculated to be 1.35.[41]

Three studies analyzed the association between bioavailable testosterone and cardiovascular mortality, all of which indicated that higher risk of cardiovascular mortality is associated with lower levels of bioavailable testosterone.[39,46–47] Laughlin et al demonstrated that men with lower levels of bioavailable testosterone are at increased risk of mortality secondary to cardiovascular disease, regardless of age, body mass index (BMI), waist-to-hip ratio, smoking status, level of exercise, and alcohol intake.[20] The authors attained similar results when deaths within the first 5 years of follow-up were excluded from the analysis. Similarly, Laughlin et al[46] demonstrated that decreasing levels of endogenous bioavailable and total testosterone were associated with an increasing risk of death from all causes. Menke et al[39] reported that a reduction in levels of either endogenous bioavailable testosterone or free testosterone from the 90th to the 10th percentile correlated with a statistically significant increase in the rate of cardiovascular mortality. Menke et al[39] also discovered that reductions in free or bioavailable testosterone were significantly associated with an increasing risk of all-cause mortality. Finally, in a study of 930 men with coronary artery disease who were referred for coronary angiography, Malkin et al[47] reported improved survival from all-cause mortality in subjects with higher levels of endogenous bioavailable testosterone. Malkin et al also described improved survival from vascular mortality (defined by the authors as death from atherosclerosis, heart failure, or cardiac arrest) in men with levels of endogenous bioavailable testosterone of >2.6 nmol/L.[47]

Existing evidence seems to suggest that lower levels of endogenous testosterone are associated with higher rates of all-cause mortality and cardiovascular mortality.[41] Although results may seem contradictory when total testosterone is used to perform the analysis, results have been consistent when either free or bioavailable testosterone have been used in the analyses.[39,46–47] In other words, studies have shown that lower levels of endogenous bioavailable testosterone are associated with higher rates of all-cause and cardiovascular mortality.[39,46–47] It may be possible that using bioavailable testosterone to perform mortality analysis will yield more accurate results because it prevents the biologically inactive subfraction of testosterone from playing a potential confounding role in the analysis.

The exact mechanism of action through which low testosterone increases mortality is currently unknown. Testosterone may be acting directly on the cardiovascular system by a mechanism that is as yet undiscovered. On the other hand, testosterone could be functioning as a marker for an underlying disease entity that results in increased mortality risk. A list of studies that analyzed the association between testosterone level and mortality is presented in Table 3.

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Table 3.

Association Between Levels of Endogenous Testosterone and Mortality

Testosterone, Angina Threshold, and Coronary Artery Vasomotor Regulation

Testosterone replacement therapy for the treatment of angina pectoris is not a new concept. The

earliest published material on this matter dates to the late 1930s. In 1942 Lesser reported the results of his experiments performed on 92 men and 8 women, all of whom suffered from exertional angina.[48] Lesser treated all subjects with varying dosages of intramuscular testosterone propionate over a period of 4 to 5 months. At the completion of the study protocol, 51 subjects reported "marked improvement" in their symptoms, 40 subjects reported "moderate improvement," and 9 subjects reported no improvement in symptoms. Lesser defined marked improvement as an angina-free period of 2 months after the completion of the study, whereas moderate improvement was defined as a 50% reduction in the number of angina attacks compared with the period prior to initiation of testosterone replacement. Lesser did not provide statistical analysis of his data, and therefore the significance of his findings cannot be validated.[48] Other studies from this era also produced similar findings.[49] Although most of the earlier studies lacked statistical analysis and their study designs would be considered subpar compared with current standards, the concept that testosterone replacement therapy improves angina has yet to be proven wrong. In more recent studies, 3 randomized, placebo-controlled trials demonstrated that administration of testosterone improves myocardial ischemia in men with CAD. English et al,[50] Rosano et al,[51] and Webb et al[52] all showed that in men with CAD, testosterone prolongs the time to exercise-induced ST-segment depression, as measured on treadmill stress testing. The improvement in myocardial ischemia was shown to occur in response to both acute and chronic testosterone therapy and seemed to be independent of whether an intravenous or transdermal formulation of testosterone was used. One of the studies that also gathered data on quality-of-life measures reported statistically significant improvement in pain perception as well as role limitation due to physical problems in the testosterone therapy group.[50] In 2 of the studies that correlated baseline testosterone levels with the amount of change in time to 1-mm ST-segment depression, both studies showed that men with lower levels of baseline endogenous testosterone had greater improvement in time to exercise-induced 1-mm ST-segment depression.[50–51] Specifically, English et al, who randomized nonhypogonadal men with chronic stable angina to either 5 mg of testosterone daily by transdermal patch or control for a duration of 2 weeks, showed that administration of testosterone increased the time to 1-mm ST-segment depression on exercise stress testing by 69 seconds.[50] Rosano et al, who administered 2.5 mg of testosterone intravenously 30 minutes prior to exercise stress testing to nonhypogonadal men with coronary artery disease, showed that testosterone increased the time to 1-mm ST-segment depression by 108 seconds and total exercise time by 90 seconds.[51] Moreover, Rosano et al also discovered that the amount of change in time to 1-mm ST-segment depression was independent of the peak testosterone level that was achieved.[51]

Evidence suggests that testosterone increases angina threshold in men with CAD by causing vasodilation of coronary arteries. Webb et al[53] demonstrated vasodilation of the coronary arteries in response to intracoronary infusion of testosterone in men with CAD. Three other investigators documented vasodilation of the brachial artery in response to testosterone infusion,[54–56] whereas others have shown coronary artery dilation in response to testosterone in rabbit,[57] canine,[58] and swine[59] models. However, the exact mechanism of action through which testosterone exerts its effect on coronary vasculature is unknown.

Webb et al demonstrated that a stepwise administration of increasing doses of intracoronary testosterone (10^{-10} to 10^{-7} mol/L) in nonhypogonadal men induced up to 4.5% coronary vasodilatation versus baseline in addition to up to a 17.4% increase in coronary artery blood flow compared with baseline, as measured by intracoronary Doppler.[53] Interestingly, the authors also noted that testosterone had no effect on increases in either coronary artery blood flow or vessel diameter, caused by intracoronary acetylcholine infusion. This finding is significant because it suggests that the effect of testosterone on coronary arteries is independent of vessel endothelium. This observation is in agreement with the in vitro findings reported by Yue et al,[57] who demonstrated that testosterone had no effect on endothelial nitric oxide activity. There is growing evidence from in vivo animal models and in vitro models that testosterone induces coronary vasodilation by modulating the activity of ion channels, such as potassium and calcium channels, on the surface of vascular smooth muscle cells. Experimental studies suggest that the most likely mechanism of action for testosterone on vascular smooth muscle cells is via modulation of action of non-ATP-sensitive potassium ion channels, calcium-activated potassium ion channels, voltage-sensitive potassium ion channels, and finally L-type calcium ion channels.[53,57–61] Given that there is evidence for action of testosterone on both ion channels, it is possible that testosterone causes vasodilation by affecting both L-type calcium channels and various potassium channels simultaneously. Further research is required to completely clarify this matter.

Association Between Testosterone and Type 2 Diabetes Mellitus

It has been well established that men with T2DM have lower levels of testosterone compared with nondiabetic men. This association was first reported by 2 investigators in 1978[62–63] and since then has been confirmed by >20 additional studies. Recently, Ding et al[25] and Corona et al[26] performed 2 meta-analyses that combined the results of the above-mentioned studies and have produced similar results. Ding et al showed that men with T2DM have statistically significant lower levels of total testosterone compared with those in nondiabetics.[25] Corona et al confirmed those results by demonstrating that not only total testosterone levels are lower among diabetics, but also the levels of free testosterone and SHBG are lower in diabetic patients.[26] By showing that diabetics have reduced levels of free testosterone, Corona et al correctly concluded that the observed reduction in total testosterone in diabetics is not entirely caused by the reduction in SHBG levels.[26]

Other authors have investigated the association between endogenous testosterone levels and the risk of developing T2DM. Colangelo et al[64] discovered that with increasing quartiles of total testosterone, the risk of developing T2DM decreased significantly. However, no statistically significant association was noted between the levels of bioavailable testosterone and the development of T2DM in this study. Laaksonen et al[65] followed 702 Finnish men for 11 years and demonstrated that men in the lowest quartile of total testosterone, free testosterone, and SHBG were more likely to develop T2DM and metabolic syndrome. Similarly, Vikan et al followed 1454 Swedish men for 11 years and discovered that men in the highest quartile of total testosterone were

significantly less likely to develop T2DM. In addition, Vikan et al showed that the risk of developing T2DM decreased significantly with increasing levels of total testosterone. Vikan et al reported similar findings for the association between free testosterone levels and the development of T2DM. The authors also noted that their analyses for total and free testosterone lost statistical significance after adjusting for waist circumference.[66]

Still, other authors have investigated the risk of developing T2DM in the setting of low testosterone levels from a different perspective. For instance, Keating et al investigated the relationship between incident T2DM and cardiovascular disease in 14 597 male veterans with prostate cancer who had undergone androgen deprivation therapy.[67] These authors demonstrated a statistically significant increase in the incidence of T2DM in subjects receiving gonadotropin-releasing hormone antagonist therapy. In addition, a significant increase in the rate of myocardial infarction, stroke, sudden cardiac death, and development of cardiovascular disease was noted in patients receiving antiandrogen therapy.[67]

Testosterone replacement therapy has been shown to improve indices of glycemic control. Several authors have demonstrated that the administration of testosterone in diabetic men improves the homeostatic model of insulin resistance, hemoglobin A1c, and fasting plasma glucose.[26,68–72] The results of these studies are summarized in Table 4.

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Table 4.

Effects of Testosterone Replacement Therapy on Indices of Glycemic Control

Existing evidence strongly suggests that the levels of total and free testosterone are lower among diabetic patients compared with those in nondiabetics.[25–26] Epidemiologic data have demonstrated that low testosterone levels increase the future risk of developing T2DM,[25,64] whereas other studies have shown that having T2DM at baseline is a risk factor for hypogonadism.[73] A meta-analysis demonstrated that testosterone replacement therapy significantly improves hemoglobin A1c in addition to fasting plasma glucose.[26] This finding has been confirmed in animal models as well.[74] Other studies have provided strong evidence that testosterone replacement therapy significantly improves the homeostatic model of insulin resistance.[68–69] However, the relationship between testosterone and T2DM is very complex and needs further clarification. Whether T2DM causes hypogonadism or vice versa and the mechanism through which T2DM and hypogonadism interact with one another in the human body remain to be fully elucidated. In our opinion, the association between testosterone and T2DM is bidirectional and involves several organs. Testosterone partially influences this interrelationship by its effects on visceral adiposity. These effects have been shown in vitro and include increased lipolysis and decreased fat accumulation in visceral adipose tissue.[25,27,64,73–76] It is reasonable to assume that testosterone causes improvement in glycemic control at least in part because of its positive effects on visceral adiposity. In addition, insulin seems to be acting as a stimulant for the hypothalamus to secret gonadotropin-releasing hormone, which consequently results in increased testosterone production. It can be argued that decreased stimulation of the hypothalamus in diabetics secondary to insulin deficiency could result in hypogonadotropic hypogonadism.[28,77–79]

Association Between Testosterone and Obesity

BMI has been shown to be inversely associated with testosterone levels. The Swedish MrOS study, which included an analysis of 2416 men, showed a statistically significant decrease in BMI with increasing quartiles of total testosterone.[27] The average BMI of the subjects in the fourth quartile of total testosterone was 24.9, compared with 28.1 for those subjects in the first quartile of total testosterone.[27] A similar inverse association between total testosterone levels and BMI was observed in the large population-based Hypogonadism In Males study as well.[28] The Hypogonadism In Males study compared 836 hypogonadal men with 1326 eugonadal men. The mean BMI for hypogonadal men was found to be 31.5 compared with 28.5 for eugonadal men. The authors also demonstrated 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 BMI.[28]

The effects of testosterone replacement therapy on BMI were investigated by Kalinchenko et al in 113 men with metabolic syndrome, who received a total of 3 intramuscular injections of testosterone —at baseline and after 6 and 18 weeks.[71] Patients receiving testosterone replacement therapy were shown to have statistically significant improvement in their BMI, which had decreased by 1.3 at 30 weeks.[71] Testosterone replacement therapy has also been shown to decrease fat mass. Corona et al demonstrated in their meta-analysis that testosterone replacement therapy resulted in a decrease of 2.19% in fat mass.[26] This discovery was confirmed in animal models as well.[74]

The exact mechanism of action through which testosterone and obesity interact is unknown. This interaction may be a result of the promotion of lipolysis in abdominal adipose tissue by testosterone, which may in turn cause reduced abdominal adiposity. On the other hand, given that adipose tissue has a higher concentration of the enzyme aromatase, it could be that increased adipose tissue results in more testosterone being converted to estrogen, thereby causing hypogonadism. Third, increased abdominal obesity may cause reduced testosterone secretion by negatively affecting the hypothalamus-pituitary-testicular axis. Finally, testosterone may be the key factor in activating the enzyme 11-hydroxysteroid dehydrogenase in adipose tissue, which transforms glucocorticoids into their inactive form.

Association Between Testosterone and Dyslipidemia

Elevated cholesterol levels have been consistently shown to be one of the most important risk

factors for the development of atherosclerosis. Moreover, epidemiologic studies have shown that men are at higher risk of having unfavorable lipid profiles[80] and suffer from cardiovascular disease mortality more frequently when compared with women.[81–82] These observations have prompted some investigators to hypothesize that the difference in incident dyslipidemia and cardiovascular disease between the 2 sexes is related to the different levels of circulating sex hormones. As a result, multiple studies have tried to correlate levels of sex hormones, including testosterone, with lipoprotein subfractions. Unfortunately, large, prospective population-based studies that investigate the association between testosterone levels and lipid subfractions are not currently available. The available data on this matter are almost entirely from cross-sectional studies, which often suffer from small sample sizes. Further adding to the uncertainty is the lack of consistent results reported by the available studies.[83–87]

Effects of testosterone replacement therapy on cholesterol levels have been investigated by several authors, results of which have been summarized in 3 meta-analyses. We have summarized these findings in Table 5.

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Table 5.

Effects of Testosterone Replacement Therapy on Cholesterol Levels

The evidence regarding the association between baseline testosterone levels and different lipid subfractions is conflicting, and therefore a clear consensus has not been achieved by the numerous authors who have investigated this association. Large, prospective, population-based studies are required to further elucidate this matter. The evidence on the effect of testosterone replacement on levels of lipid subfractions is similarly conflicting. Whitsel et al demonstrated that intramuscular testosterone replacement therapy caused a small reduction in the levels of total cholesterol.[88] The meta-analysis performed by Isidori et al revealed that testosterone replacement therapy improves total cholesterol levels in the setting of low baseline testosterone levels, whereas it has no effect if baseline testosterone levels are normal.[89] On the other hand, Haddad et al demonstrated the exact opposite association between testosterone replacement therapy and its effect on total cholesterol levels based on baseline testosterone levels.[31] As a result, no definitive statement can be made regarding the effect of testosterone replacement therapy on total cholesterol levels. Whitsel et al demonstrated that intramuscular testosterone replacement therapy caused a reduction in the levels of both HDL and LDL cholesterol and did not affect triglyceride levels.[88] On the contrary, Isidori and Haddad both revealed that testosterone replacement therapy has no effect on levels of either LDL cholesterol or HDL cholesterol.[31,89] Therefore, no definitive statement can be made regarding the effects of testosterone replacement therapy on the levels of either LDL or HDL cholesterol. Finally, Whitsel et al demonstrated that intramuscular testosterone replacement therapy has no effect on triglyceride levels.[88] This finding was confirmed by Haddad et al, who demonstrated that testosterone replacement therapy has no effect on triglyceride levels, regardless of baseline total testosterone levels.[31]

Association Between Testosterone and Markers of Inflammation

Because of increasing evidence that chronic, low-grade inflammation is a risk factor for atherosclerosis,[90–91] several investigators have hypothesized that testosterone may exert its protective effects against cardiovascular events by suppressing the inflammatory response. These authors have investigated a possible association between levels of testosterone and markers of inflammation. The majority of the research on this subject involves the association between testosterone and high-sensitivity C-reactive protein (hsCRP), but a few authors have also included tumor necrosis factor–α and interleukin-6 (IL-6) in their analysis.

The data regarding the association between levels of endogenous testosterone and levels of hsCRP from epidemiologic studies has revealed conflicting results. Although several authors have discovered statistically significant negative associations between levels of endogenous testosterone and CRP,[46,92–96] others have failed to demonstrate any association between testosterone and CRP levels.[84,97–99]

Results of the effects of testosterone replacement therapy on markers of inflammation are similarly conflicting. Although 4 authors found no change in serum levels of CRP in men receiving supplemental testosterone, 3 other authors documented statistically significant reduction in levels of CRP in men receiving testosterone replacement therapy. These studies are presented in Table 6.

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Table 6.

Effects of Testosterone Replacement Therapy on Markers of Inflammation

Given the conflicting evidence regarding the association between levels of endogenous testosterone and hsCRP, no conclusion can be made on this matter. However, it seems that age may be an important and defining factor in the relation between testosterone and CRP. The studies that have documented a statistically significant negative association between testosterone levels and CRP have all analyzed a relatively younger subset of patients. On the other hand, the studies that failed to find an association between testosterone and CRP used an older population group. Moreover, Nakhai Pour et al initially discovered a negative association between testosterone and CRP, but statistical significance was lost after adjusting the raw data for age.[98] Whether this observation is significant remains to be fully validated. No investigator has been able to offer a clear explanation for the mechanism by which increasing age may alter the association between testosterone and CRP.

Another possible explanation for the association between testosterone level and CRP is central obesity and waist circumference. Zhang et al proposed that obesity, with its proven proinflammatory properties as well as its association with reduced levels of testosterone, may be the factor that influences the association between testosterone and CRP levels.[95] In their analysis, Zhang et al also highlighted that the statistical strength for the association between testosterone and CRP decreased substantially once the data were adjusted for waist circumference or when only the subgroup of patients with obesity was analyzed.[95] However, larger prospective studies are required to fully validate the hypothesis that obesity may alter the association between testosterone and markers of inflammation. In regard to the association between testosterone and other proinflammatory markers such as IL-6 and tumor necrosis factor–α, no conclusive statement can be made at this time because of the scarcity of the existing data. Likewise, no conclusion can be made regarding the association between testosterone replacement therapy and its effect on CRP levels.

Association Between Testosterone and QT Interval

There is growing evidence suggesting that testosterone may play an important role in the regulation of ventricular repolarization. Heart-rate-corrected QT (QTc) interval has long been accepted as an accurate measure of ventricular repolarization, and prolongation of the QTc interval is associated with increased incidence of ventricular arrhythmias, including Torsade de Pointe.[106] Moreover, sex- and age-related differences in ventricular repolarization have also been well established.[107–110] It is known that there is no difference in ventricular repolarization patterns between the 2 sexes prior to the onset of puberty.[111–113] However, men experience a gradual shortening of their QTc interval from approximately age 9 until around age 50, which is the period corresponding to the highest levels of circulating androgens in normal men.[111–113] Afterward, the male QTc interval starts to prolong gradually, until approximately age 60, at which point it becomes quite similar to the QTc interval of women of the same age.[111–113] In addition, castrated men have been shown to have QTc intervals that are longer than the QTc interval in normal men, and virilized women have been shown to have shorter QTc intervals compared with those in normal women.[114]

Given these findings, investigators have hypothesized that testosterone may play an important role in the regulation of QTc interval. Charbit et al evaluated electrocardiograms in 11 men with hypogonadism and revealed that men with the highest levels of endogenous total testosterone had shorter QTc intervals compared with those with the lowest levels of the hormone (maximum difference, 13.6 ms).[115] Charbit et al also discovered a statistically significant negative correlation between QTc length and total testosterone concentrations (r=−0.23, P<0.0001).[115] Van Noord et al used data from 2 large population-based studies, the Rotterdam Study (n=445 men) and the Study of Health in Pomerania Study (n=1428), to evaluate the association between testosterone and QTc interval length.[116] Van Noord et al demonstrated that increasing levels of endogenous testosterone were significantly associated with shorter QTc interval. When combining data from both studies, van Noord et al showed a reduction of 3.4 ms in patients with total testosterone levels in the third tertile, compared with that of those in the first tertile. Moreover, the change in QTc interval after logarithmic transformation of total testosterone values was calculated to be −8.1 ms. However, it should be noted that although the same trend was observed by van Noord et al, statistical significance was not achieved when analyzing each population-based study separately. The authors have attributed this issue to lack of power when analyzing each study separately.[116] Finally, in 3 separate studies, Pecori Giraldi et al demonstrated that lower testosterone levels are associated with longer QTc intervals.[117–119] In a study of 26 men with either primary or secondary hypogonadism, Pecori Giraldi et al demonstrated that men with low testosterone levels were significantly more likely to have a prolonged QTc interval.[117] In a separate study of 136 obese men, Pecori Giraldi et al showed that obese hypogonadal men have longer QTc intervals compared with those in obese, nonhypogonadal men (419 versus 408 ms, P<0.05).[118] The authors also demonstrated that the prevalence of prolonged QTc was significantly higher among hypogonadal obese men compared with obese men with normal testosterone levels (23% versus 10%, P<0.05).[118] Finally, Pecori Giraldi et al evaluated 19 men and 35 women with Cushing's disease, a condition known to cause reduced testosterone levels.[119] The authors discovered that age-matched men with Cushing's disease have a higher prevalence of prolonged QTc interval compared with men without Cushing's disease. Pecori Giraldi et al did not find a significant prolongation of QTc in women with Cushing's disease.[119] Although consideration of glucocorticoid levels is important when analyzing data in patients with Cushing's disease, this information was not provided by Pecori Giraldi et al.

Testosterone replacement therapy has been shown to decrease QTc interval length. In a study of 11 nonobese men with hypogonadism, Charbit et al evaluated the effects of a single intramuscular injection of testosterone enanthate 250 mg on heart rate–independent QT interval length.[115] The authors measured QT length at 3 points after the administration of testosterone. The median for corrected QT length was 352 ms 2 days after the administration of testosterone, what the authors referred to as high testosterone level. The median QT interval was measured as 357 and 363 ms 10 days (medium testosterone level) and 4 to 6 weeks (low testosterone level), respectively, after the administration of testosterone. All these findings were statistically significant. Higher testosterone level was associated with a shorter corrected QT interval when compared with lower testosterone levels (maximum change in QT, 13.6 ms). Charbit et al provided neither baseline testosterone levels nor QTc length.[115] Pecori Giraldi et al in their analysis of 26 men with hypogonadism demonstrated that testosterone replacement therapy caused normalization of the QTc interval in all the subjects who were found to have prolonged QTc.[117] The average QTc interval shortening in Pecori Giraldi's study was 66 ms. All patients received intramuscular testosterone except 1, who was on a testosterone transdermal patch. Pecori Giraldi did not provide the administered dose of testosterone.[117]

Existing evidence strongly suggests that testosterone plays an important role in the regulation of ventricular repolarization by shortening the length of the QTc interval. Epidemiologic studies have long established that states associated with higher endogenous testosterone levels, such as men between 10 and 65 years old or virilized women, are associated with shorter QTc intervals.[111–114] Furthermore, a negative correlation has been shown between testosterone level and QTc interval [115–119]

length in hypogonadal men. Although the mechanism by which testosterone affects ventricular repolarization has not been fully understood, Bai et al have provided convincing evidence that testosterone might be able to shorten the QTc interval by augmenting the activity of slowly activating delayed rectifier potassium channels while simultaneously slowing the activity of L-type calcium channels.[120] Finally, the results of testosterone replacement therapy on ventricular repolarization have provided consistent evidence that supplemental testosterone shortens the QTc interval.[115,117] Larger studies are required to completely validate these results. Moreover, outcome studies are required to confirm the clinical relevance of these findings.

Testosterone and Intima-Media Thickness

Intima-media thickness (IMT) of the carotid artery is considered a marker for preclinical atherosclerosis.[121–122] Increasing carotid IMT has been associated with generalized atherosclerosis[123] and increased incidence of myocardial infarction[124–125] and stroke[125] and is generally considered a poor prognostic factor for future adverse cardiovascular events. As mentioned earlier in this article, low endogenous testosterone has also been associated with worsening cardiovascular mortality, T2DM, and obesity. A number of studies have examined the association between testosterone levels and carotid IMT, with all the studies showing an inverse correlation between these 2 variables.[32,126–132] The results of these studies are summarized in Table 7.

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Table 7.

Association Between Endogenous Testosterone Level and Carotid Intima-Media Thickness

Although some authors have focused on the association between testosterone levels and IMT of the carotid artery, other authors have evaluated the association between endogenous testosterone levels and IMT of the aorta. In a large population-based study of 504 nonsmoking men and 528 nonsmoking women (the Rotterdam Study), Hak and colleagues demonstrated an inverse correlation between endogenous testosterone levels and atherosclerosis of the abdominal aorta in men.[133] Hak et al reported decreasing relative risk for severe atherosclerosis of the abdominal aorta with increasing levels of endogenous total testosterone as well as increasing levels of endogenous bioavailable testosterone after adjustment for cardiovascular disease risk factors in men only. No significant association was found between testosterone levels and the presence of severe abdominal aortic atherosclerosis in women by Hak et al. These authors also discovered that men with higher levels of total or bioavailable testosterone experienced a significantly slower rate of progression of abdominal aortic atherosclerosis. Again, Hak et al did not find a significant association between testosterone levels and progression of atherosclerosis in the female abdominal aorta.[133] Demirbag et al performed similar analysis on 42 men, but instead investigated the association between testosterone and thoracic aorta IMT.[134] Demirbag et al discovered an inverse association between total testosterone and thoracic aorta IMT.[134]

It is not clear whether the inverse correlation between endogenous testosterone levels and IMT is cause or effect. Reduced levels of testosterone might cause increased thickness of the intima-media of the vasculature. On the other hand, it can be argued that widespread atherosclerosis may impair adequate blood flow to the testes or to the pituitary gland, which would in turn result in decreased production of testosterone and luteinizing hormone, respectively. Van den Beld et al have shed some light on this question. These authors demonstrated that the association between testosterone levels and IMT was independent of cardiovascular disease. Moreover, van den Beld et al demonstrated that the inverse correlation between endogenous testosterone levels and carotid IMT had similar statistical robustness in patients with and without cardiovascular disease.[126] This finding may suggest that low levels of endogenous testosterone cause increased IMT. However, further follow-up studies are required to confirm these earlier results. Furthermore, the exact mechanism by which testosterone may cause increased IMT of the carotid artery or the aorta is currently unknown. Testosterone may cause decreased IMT by downregulating the inflammatory response, regulating apoptosis, or enhancing vascular smooth muscle cell stability.

Although more research is required, there are signals in existing data that suggest testosterone deficiency may play some role in the creation and progression of atherosclerosis. Studies have shown that levels of endogenous testosterone are inversely associated with IMT of the carotid artery,[32,126–130] as well as both the thoracic[134] and the abdominal aorta.[133] In addition, 1 study has demonstrated that lower levels of free testosterone are associated with accelerated progression of carotid artery IMT,[132] whereas another study has reported that decreased levels of total and bioavailable testosterone are associated with progression of atherosclerosis in the abdominal aorta.[133] These findings suggest that normal physiologic testosterone levels may help to protect men from the development of atherosclerosis. To the best of our knowledge, there are no published studies that evaluate the effects of testosterone replacement therapy on IMT.

Testosterone and Congestive Heart Failure

A key pathologic feature of congestive heart failure (CHF) is a metabolic shift toward catabolism, which results from the activation of neuroendocrine and inflammatory pathways.[135–136] This imbalance, in turn, causes progressively worsening exercise intolerance, as well as cardiac cachexia.[135–136] Emerging evidence indicates that there might be a significant association between testosterone deficiency, CHF, and exercise capacity. In a study of 208 men with CHF and a median left ventricular ejection fraction (LVEF) of 33%, Jankowska et al demonstrated a statistically significant prevalence of testosterone deficiency among men with CHF who were either ≤45 or ≥66 years old.[137] Levels of estimated free testosterone were also shown to be significantly reduced among CHF patients. Namely, 62% of men with CHF who were 45 years old or younger, 22%

between 46 and 55, and 36% ≥66 years old were shown to have significant reductions in their serum levels of estimated free testosterone by Jankowska et al. Not only did Jankowska et al demonstrate that men with CHF have significantly reduced levels of total and free testosterone, the authors were also able to demonstrate that with worsening severity of CHF, there was a significant stepwise decrease in the levels of both total testosterone and estimated free testosterone. Of note, neither total testosterone nor free testosterone showed any correlation with LVEF. Finally, Jankowska et al demonstrated that reduced levels of total and estimated free testosterone were both predictors of increased mortality in men with CHF.[137] Similar findings have been reported by other investigators as well. In a study of 2078 men who were referred for coronary angiography, Wehr et al discovered an independent association between low levels of free testosterone and CHF mortality.[138] Wehr reported the hazard ratio for CHF mortality in the fourth compared with the first quartile of free testosterone to be 0.38 (95% CI, 0.17 to 0.87). The hazard ratio for CHF mortality per 1 standard deviation increase in free testosterone was calculated to be 0.37 (95% CI, 0.15 to 0.89) in the same study. The LVEF in Wehr et al's study ranged from preserved to severely reduced.[138]

The association between testosterone levels and exercise capacity in patients with CHF has been investigated by several authors. Using peak oxygen consumption (peak VO_2), peak O_2 pulse, and ventilatory response to exercise (VE-VCO_2 slope) as objective measures of exercise capacity, Jankowska et al were able to show that testosterone was inversely and independently related to exercise tolerance.[139] Specifically, lower levels of endogenous total and free testosterone were associated with decreased peak VO_2. These findings were independent of CHF severity, plasma brain natriuretic peptide levels, and age. The association between testosterone levels and exercise capacity retained its statistical significance after adjustment for lean tissue mass in the leg. Interestingly, Jankowska et al also discovered that the only predictor of the extent of deterioration in exercise capacity, as measured by peak VO_2 and peak O_2 pulse, was the magnitude of reduction in circulating testosterone levels. Peak VO_2 and peak O_2 pulse, both of which offer an accurate reflection of aerobic exercise capacity, were shown to have a positive and statistically significant association with testosterone levels in multivariable-adjusted models.[139] This indicates that the association between circulating testosterone levels and aerobic exercise capacity in CHF patients is most likely independent of heart failure severity, beta-blocker use, and chronotropic response to exercise.

Four authors have investigated the effects of testosterone replacement therapy on exercise capacity in men with CHF.[140–143] Toma et al performed a meta-analysis of these studies and discovered that there was a net pooled improvement of 0.52 standard deviations in exercise capacity among those who were treated with testosterone.[144] The meta-analysis revealed that patients treated with testosterone replacement therapy experienced an increase of 16.7% (equivalent to ≈54 m) in the 6-minute walk test, an increase of 15.9% in the isometric walk test, and finally an increase of 22.7% in peak VO_2.[144] All 4 studies included in this meta-analysis evaluated the effects of testosterone replacement therapy on LVEF as well. Although testosterone was shown to significantly improve exercise capacity, none of the studies found a significant change in the LVEF.[140–143] New York Heart Association class was shown to improve in 2 of the studies included in the meta-analysis.[144] Thirty-five percent of the patients in the testosterone group (20 of 57) experienced an improvement of ≥1 New York Heart Association class in their functional capacity compared with only 9.8% of patients in the placebo group (5 of 51). The difference between testosterone and placebo groups in functional class improvement was statistically significant. Finally, Toma et al accumulated safety data from these 4 studies and found no statistically significant change in the prostate-specific antigen (PSA) levels with testosterone replacement therapy. In addition, major adverse cardiovascular events (MACE) were evenly distributed among the 2 groups, with the testosterone replacement group experiencing 7% of the total major adverse cardiovascular events compared with 6% for the placebo group.[144]

Anabolic hormones such as testosterone are determinants of exercise capacity, and an age-related decline in testosterone has been well associated with reduced exercise tolerance in the elderly.[139] Moreover, testosterone levels have been known to have a positive correlation with muscle mass and strength. Therefore, it is reasonable to assume that reduced levels of testosterone in CHF patients would result in decreased exercise capacity. There is evidence from basic science literature that supports this hypothesis as well. Czesla et al performed experiments on latissimus dorsi muscle of sheep by exposing the muscle fibers to metenolone, an analogue of testosterone.[145] Czesla et al successfully demonstrated that the muscle specimens that were exposed to metenolone had a significant shift in their composition toward type I muscle fibers. Type I muscle fibers, also known as slow-twitch or oxidative fibers, are associated with enhanced strength and physical capability, whereas type II, or fast-twitch, fibers are not. It has been shown that those with advanced CHF have a higher percentage of type II muscle fibers, based on muscle biopsy.[145] Given that no study has found LVEF to improve with testosterone replacement therapy,[140–143] it is reasonable to consider that testosterone may be positively affecting exercise capacity involving a peripheral mechanism such as the skeletal muscles. In other words, testosterone replacement therapy may be causing a shift toward more type I muscle fibers in patients with CHF, thereby improving their exercise capacity while their LVEF remains the same.

Emerging evidence indicates that CHF is more than just a syndrome affecting a failing heart. It is becoming evident that the pathophysiology of CHF involves other pathways as well, including the skeletal muscles and the endocrine system. Studies have shown that men with CHF suffer from reduced levels of total and free testosterone.[137] It has also been shown that reduced testosterone levels in men with CHF portends a poor prognosis and is associated with increased CHF mortality.[138] Reduced testosterone has also been shown to correlate negatively with exercise capacity in CHF patients.[139] Those with more severe CHF, as indicated by higher New York Heart Association class, have been shown to have lower levels of testosterone, and the decline in testosterone levels has been shown to be the only predictor of the magnitude of deterioration in exercise capacity.[139] Testosterone replacement therapy has been shown to significantly improve exercise capacity, without affecting LVEF.[140–144] Given emerging evidence from basic science models,[145] it is reasonable to assume that testosterone replacement therapy positively affects the exercise capacity of CHF patients via a peripheral mechanism, such as promoting increased type I

muscle fiber proliferation.

Adverse Cardiovascular Events Associated With Testosterone Replacement Therapy

A number of publications have studied the adverse events associated with testosterone replacement therapy. Given the very large number of these studies, it is impractical to analyze each study separately. Instead, this section will focus mostly on results from 3 meta-analyses that have investigated the association between testosterone replacement therapy and adverse events. It should be noted that the majority of the studies have focused on such adverse events as cardiovascular events, prostate-related events, and changes in red blood cell indices. When analyzing the results from individual studies, it is important to consider baseline testosterone levels, the administered dose of testosterone, and finally the method of testosterone delivery.

Calof et al performed a meta-analysis of 19 randomized placebo-controlled trials that included 651 men who received testosterone replacement therapy and 433 men who received placebo.[146] Inclusion criteria for this meta-analysis were randomized controlled trials that recruited men aged ≥45 years, testosterone replacement duration of ≥90 days, and medically stable subjects who had low or low-normal testosterone levels. Calof et al discovered 2 major differences between the testosterone replacement group and the placebo group. The testosterone replacement group was shown to have a greater combined incidence of all prostate-related adverse events compared with that in the placebo group, with a pooled odds ratio of 1.78 (95% CI, 1.07 to 2.95); the odds ratio reported to be “significantly different from placebo.” Combined prostate events included all instances of prostate biopsies, prostate cancer, PSA >4 ng/mL or an increase in PSA of 1.5 ng/mL during the study period, increase in international prostate symptom score, and acute urinary frequency. It should be noted, however, that none of the individual prostate-related adverse events significantly differed from those in the placebo group. This included cases of prostate cancer, which showed no significant difference between the testosterone group and the placebo group. It was only the sum of all the above-mentioned prostate-related adverse events that significantly differed from the placebo group in Calof's meta-analysis. The second major difference between the testosterone replacement group and the placebo group that was uncovered by Calof et al was a significant rise in hematocrit >50% in the testosterone group. This was the most common adverse effect noted in the testosterone replacement group, with a pooled odds ratio of 3.69 (95% CI, 1.82 to 7.51); the odds ratio was reported to be “significantly different from placebo.” Among the subjects with a hematocrit of >50%, there was only 1 incident of serious complication (cerebral hemorrhage). Skin irritation at the site of testosterone application was the only other major adverse events that was reported by Calof et al. This adverse event was only witnessed in the studies that used topical testosterone preparations.[146]

Calof et al did not find a significant difference in the rate of cardiovascular events between the testosterone replacement group and the placebo group.[146] Specifically, the authors found no statistically significant differences between the 2 groups in the rates of atrial fibrillation, atrial arrhythmia, myocardial infarction, chest pain or ischemia, coronary procedures including coronary artery bypass grafting, vascular events, and cerebrovascular events. When all the above-mentioned cardiovascular events were pooled, Calof et al still did not find a statistically significant difference between the 2 groups. Calof et al reported no deaths in the testosterone group, but there were 2 deaths, of unspecified etiology, in the placebo group.[146]

Haddad et al performed a meta-analysis of 30 placebo-controlled randomized trials, which included 808 men in the testosterone replacement group and 834 men in the placebo group.[31] The authors found no changes in systolic or diastolic blood pressure with testosterone replacement. The effects of testosterone replacement on different lipoprotein subfractions have been reported in a previous section of this review article. Finally, Haddad et al used only 6 articles to perform their meta-analysis for adverse cardiovascular events, which included 161 men in the testosterone replacement group and 147 men in the placebo group. Haddad et al defined adverse cardiovascular events as cardiovascular death, fatal and nonfatal myocardial infarction, angina, arrhythmia, revascularization procedures, and stroke. The authors discovered a total of 14 adverse cardiovascular events in the testosterone replacement group and 7 total events in the placebo group. The pooled odds ratio for the cardiovascular events was 1.82 (95% CI, 0.78 to 4.23), and the difference in adverse cardiovascular events between the testosterone and placebo groups was not statistically significant in Haddad et al's meta-analysis.[31]

The most recent meta-analysis analyzing the adverse effects of testosterone replacement therapy was performed by Fernandez-Balsells et al in 2010.[147] This meta-analysis included 51 studies. The eligibility criteria for this meta-analysis included all placebo-controlled studies (randomized and nonrandomized) that enrolled men with low or low-normal testosterone levels and who received any testosterone formulation for ≥3 months. Similar to the previous reports, testosterone replacement therapy resulted in a significant increase in hemoglobin levels as well as hematocrit levels. Fernandez-Balsells et al did not find any statistically significant difference between the testosterone and placebo groups for rate of death, myocardial infarction, coronary revascularization procedures, or arrhythmias. Furthermore, the authors found no difference in the rates of prostate cancer, the need for prostate biopsy, international prostate symptom score, increase in PSA, or total number of prostate-related adverse events when comparing the testosterone group with the placebo group.[147]

In a recent study that was not included in the previously mentioned meta-analyses, Shores et al analyzed clinical data from 1031 male veterans in a retrospective observational study. The authors showed that treatment with testosterone in middle-aged men with low levels of endogenous testosterone was associated with decreased mortality compared with that in hypogonadal men who did not receive testosterone supplementation. Shores et al included all testosterone formulations (intramuscular, transdermal, or gel) in their analysis. The mortality rate in the testosterone-treated group was found to be 10.3% compared with 20.7% in the untreated group (P<0.0001). After multivariable adjustment, including obesity, the hazard ratio for all-cause mortality in men who were treated with testosterone was 0.61 (95% CI, 0.42 to 0.88; P=0.008).[148] In another recent study that

was not included in the meta-analyses, Glueck et al demonstrated that men with previously undiagnosed hypercoagulable conditions, such as factor V Leiden mutation or elevated homocysteine levels, may be at greater risk of developing deep venous thrombosis or pulmonary embolism within 3 months of initiating testosterone replacement therapy. However, the authors correctly pointed out that their study was limited by a very small sample size and was therefore meant to be a hypothesis-generating study. Given that some hypercoagulable conditions may be undiagnosed in asymptomatic patients, it is prudent to screen for these diseases prior to initiation of testosterone replacement therapy.[149]

Although the results of the 3 meta-analyses seem to indicate that testosterone replacement therapy does not cause an increase in the rate of adverse cardiovascular events,[31,146–147] a study published by Basaria et al in 2010 reported contradictory results. Basaria et al evaluated the safety and efficacy of daily application of transdermal testosterone gel in 209 men.[150] Given the increased rate of adverse cardiovascular events in the testosterone group, the study was stopped prematurely. The decision to stop the trial was based on the observation that 23 subjects in the testosterone group suffered ≥1 adverse cardiovascular events compared with 5 subjects in the placebo group, a statistically significant difference. The adverse cardiovascular events that Basaria et al reported in the testosterone group included 1 incident of acute coronary syndrome, 1 incident of chest pain, 2 self-reported cases of syncope, 2 cases of myocardial infarction, 1 subject requiring angioplasty and coronary artery bypass grafting, 5 cases of peripheral edema, 1 case of ectopy on electrocardiogram (defined by authors as premature ventricular contraction or couplets), 1 incident of left ventricular strain pattern on exercise stress testing, 1 incident of ST-segment depression on exercise stress testing, 3 cases of elevated blood pressure, 1 incident of atrial fibrillation with rapid ventricular response requiring hospitalization, 1 incident of stroke, 1 case of self-reported tachycardia and fatigue, 1 incident of CHF exacerbation, and 1 incident of death.[150]

Extreme caution should be taken when assessing the generalizability of the results obtained by Basaria et al. According to the authors themselves, 3 major factors may have compromised the generalizability of this trial's results.[150] First, it should be noted that the population under study by Basaria et al had a mean age of 74 years (all patients <65 were excluded from this study). A very high percentage of the patient population in this study also suffered from various serious chronic illnesses including long-standing diabetes, dyslipidemia, obesity, hypertension, and most importantly preexisting heart disease. Moreover, given that the primary purpose of this study was to measure improvements in physical strength, the patient population that was selected by Basaria et al had significant limitations in mobility at baseline. Second, the sample size included in Basaria et al's trial was relatively small. The number of adverse cardiovascular events in the testosterone group was relatively small as well, and the trial was stopped early. Third, Basaria et al's trial was not originally designed to analyze either primary or secondary cardiovascular outcomes. Basaria et al had intended to analyze the effects of testosterone replacement therapy on lower extremity strength and functional status in older men with limitations in mobility. Therefore, the authors were unable to perform a structured analysis of adverse cardiovascular events. In addition, a number of the adverse cardiovascular events that were reported by Basaria et al may be minor phenomena and not significant adverse cardiac events. For instance, the 2 cases of syncope may not have been secondary to cardiovascular disease and could have just been a vasovagal phenomenon. Premature ventricular contractions are very common in the general population and alone are generally not considered a major adverse cardiovascular event. Left ventricular strain pattern on exercise stress testing may have been caused by a variety of causes including underlying ventricular hypertrophy or hypertension. Thus, some of these adverse events are consistent with the baseline characteristics of Basaria et al's patient population, which was suffering from prevalent underlying chronic diseases. Finally, the cases of peripheral edema that were witnessed by Basaria et al could have been a result of the vasodilating effects of testosterone and not of CHF exacerbation. The authors did not made this distinction in their analysis.

Existing evidence seems to suggest that the most commonly encountered adverse event associated with testosterone replacement therapy is an increase in hematocrit, which is considered a known physiologic function of testosterone.[146–147] The clinical implications of increased hematocrit secondary to testosterone replacement therapy remain to be fully investigated. If a transdermal preparation of testosterone is used, a skin reaction at the site of testosterone application is common.[146] The clinical implications of this finding remain unknown at this time. Data from 3 meta-analyses seem to contradict the commonly held belief that testosterone administration may increase the risk of developing prostate cancer. One meta-analysis reported an increase in all prostate-related adverse events with testosterone administration.[146] However, when each prostate-related event, including prostate cancer and a rise in PSA, was analyzed separately, no differences were observed between the testosterone group and the placebo group.[146] Finally, the existing data from the 3 meta-analyses seem to indicate that testosterone replacement therapy does not increase the risk of adverse cardiovascular events.[31,146–147] Evidence to the contrary has been reported by Basaria et al, however.[150] The 3 major factors that should be noted when interpreting the results of Basaria et al were thoroughly discussed above. Most recently, Vigen et al reported a higher rate of adverse cardiovascular events with testosterone replacement therapy in a retrospective cohort study of male veterans with hypogonadism who underwent coronary angiography.[151] Vigen et al showed a 5.8% absolute risk increase for the composite of all-cause mortality, MI and ischemic stroke in male veterans who were treated with exogenous testosterone. Although these results are statistically significant, the authors correctly point out the weaknesses of their study which include retrospective study design and lack of randomization, small sample size at extremes of follow-up, lack of outcome validation by chart review and poor generalizability of the results given that only male veterans with CAD were included in this study. The controversy over the safety of testosterone replacement therapy will require large, prospective, randomized, placebo-controlled trials in which cardiovascular events are the primary outcomes. Results from the Effects of Testosterone Replacement on Atherosclerosis Progressions in Older Men with Low Testosterone Levels (TEAAM) study are eagerly awaited to clarify any possible long-term adverse consequences from testosterone replacement therapy. The Effects of Testosterone Replacement on Atherosclerosis Progressions in Older Men with Low Testosterone Levels study will be a new trial assessing the effects of exogenous

testosterone on adverse events related to atherosclerosis in elderly men. Until the results of such large-scale studies become available, we recommend caution when administering testosterone to elderly men.

Concluding Remarks

Given the very large population of patients in the United States who suffer from hypogonadism coupled with a projection of ≈481 000 new cases of hypogonadism annually,[1] an extensive amount of attention has been dedicated to the interplay between testosterone and various aspects of cardiovascular health and well-being. Low endogenous bioavailable testosterone levels have been shown to be associated with higher rates of all-cause and cardiovascular-related mortality.[39,41,46–47] Patients suffering from CAD,[13–18] CHF,[137] T2DM,[25–26] and obesity[27–28] have all been shown to have lower levels of endogenous testosterone compared with those in healthy controls. In addition, the severity of CAD[15,17,29–30] and CHF[137] correlates with the degree of testosterone deficiency. Testosterone replacement therapy in men who suffer from hypogonadism and CAD has proven effective in increasing time to 1-mm ST-segment depression with exercise stress testing[50–52] and causing coronary artery vasodilation.[53] In patients with CHF, testosterone replacement therapy has been shown to significantly improve exercise tolerance while having no effect on LVEF.[140–144] It is highly likely that testosterone therapy causes a shift in the skeletal muscle of CHF patients toward a higher concentration of type I muscle fibers.[145] Testosterone replacement therapy has also been shown to improve the homeostatic model of insulin resistance and hemoglobin A1c in diabetics[26,68–69] and to lower the BMI in obese patients.[71] There is growing evidence that suggests that testosterone may be able to control ventricular repolarization by modulating the length of the QTc interval. Lower levels of endogenous testosterone have been associated with longer duration of the QTc interval.[115–119] Interestingly, testosterone replacement has been shown to shorten the QTc interval.[115,117] Finally, a negative correlation has been demonstrated between endogenous testosterone levels and IMT of the carotid arteries, abdominal aorta, and thoracic aorta.[32,126–130] These findings suggest that men with lower levels of endogenous testosterone may be at a higher risk of developing atherosclerosis. This review article has demonstrated that normal testosterone levels play an important role in maintaining cardiovascular health, and testosterone replacement therapy in men with hypogonadism improves obesity, T2DM, myocardial ischemia, exercise capacity, and QTc length. Current guidelines from the Endocrine Society make no recommendations on whether patients with heart disease should be screened for hypogonadism and do not recommend supplementing patients with heart disease to improve survival.[152] Longitudinal, placebo-controlled, randomized trials of testosterone replacement therapy in men with low testosterone levels are required to completely clarify the role of testosterone in survival of patients with heart disease.

Disclosures

None.

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