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Hypogonadism and Cardiovascular Disorders in Older Men

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Abstract

Late-Onset-Hypogonadism (LOH) has been well recognized for a long time by the medical community. LOH is associated with erectile dysfunction, depression, increased fat mass and decreased libido, vitality, and sexual function in addition to reduced muscle mass, muscle strength, bone mineral density, and erythropoiesis. Many individuals with LOH have been living a productive life and are very interested in further improvement of their physical and sexual functions and mental activities such as memory and vitality. Many studies had demonstrated that testosterone replacement therapy may improve various health issues in older men and may remediate some of theage-related problems. However, other studies had raised a red flag and had shown the "dark side" of testosterone therapy in this segment of the society who may be more prone to various adverse events of testosterone related treatment. The purpose of this work is to review the representative studies (for the sake of space) on the benefit or harmful effect of low testosterone and testosterone replacement therapy and to discuss the role of testosterone in various risk factors for cardiovascular disorders.

Keywords: Hypogonadism; Testosterone therapy; Cardiovascular events

Introduction

Waning function of hypothalamic- pituitary- testicular (HT-PIT-T) axis in aged men or Late-Onset-Hypogonadism (LOH) has been well recognized in the medical community. LOH is associated with erectile dysfunction, decreased libido, depression, and reduced vitality in addition to increased fat mass, reduced muscle mass, muscle strength, bone mineral density, and erythropoiesis [1]. LOH is diagnosed in many aged men, even in those who are living a considerably healthy life. Interestingly, the desire to enjoy an active life style in this segment of society was found very profitable by many entrepreneurs. Hence, testosterone has been advertised as a "fountain of youth". According to sales forecast by Global Industry Analysis in 2012, the sale of testosterone doubled since 2006 [2]. The use of Testosterone by men age>40 years increased by 3-fold during 2001-2011,as reported by Clinformatic Data Mart (CDM), one of the largest health insurance data bases in the United States [3]. There are two major, opposite trends emerging in the literature on testosterone replacement therapy. On one hand, some researchers found that there is a heightened concern and caution expressed by patients and clinicians, due to some published data linking increased risk of cardiovascular disorders (CVD) to testosterone therapy in older men. Others on the other hand, found no specific adverse effect of this therapy. On the contrary, they have demonstrated many positive effects of testosterone therapy on hypogonadal men, namely: decrease of CVD events, reduction in fat mass, enhancement of muscle mass, strength, and bone mass, as well as improvement of insulin resistance, quality of life and sexual function [1].

Cardiovascular disease remains the leading cause of mortality and morbidity affecting more men than women of the same age [4]. Consequently, testosterone became the topic of debate as a causative mediator of cardiovascular casualties for many years. None the less, the subject remains very controversial, partially due to differences in the design of the studies. Unquestionably, the relationship between testosterone level and CVD in older men is very complex. Thus far, clinicians and researchers haven't expressed an unequivocal opinion whether low testosterone level is a marker of poor cardiovascular health, the cause of cardiovascular events, or an adaptive mechanism as a response to the poor health conditions.

The association between testosterone level and/or testosterone therapy with CVD has been the subject of many studies. In this review, we will focus on several representative studies. First, we will, review the literature on the interrelationship between testosterone and CVD then, we will discuss the role of testosterone on main risk factors for CVD such as diabetes mellitus, hyperlipidemia, arteriosclerosis, and metabolic syndrome in older men.

Testosterone level and/or testosterone therapy and cardiovascular disorders

Historically, testosterone has been considered an important source of energy and wellbeing, otherwise known as "fountain of youth". However, in the mid and late 20th century, the reports of sudden death and highly abnormal lipids in athletes who had received pharmacological doses of testosterone to augment their physical performance, directed attention to the (potentially) harmful effect of testosterone therapy on cardiovascular health [5]. Despite numerous studies with various designs, differing in size of cohorts, and study types, a specific role of testosterone in CVD has not been confirmed. Consequently, the controversies around the clinical use of testosterone continue to rise. To address the issues around the interrelationship between testosterone and cardiovascular health, in our short review, we will present several representative studies from

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each design and allow the reader to decide whether his/her patient may benefit from testosterone replacement therapy.

Observational studies on association between testosterone level and CVD: In this section, we present several observational studies that had examined the association between testosterone level and CVD events. In the Rancho Bernardo study, baseline testosterones levels in 1009 white community dwelling men age40-79 years, were not associated with cardiovascular disease at baseline and during the subsequent 12 years of follow up [6]. Likewise, Atherosclerosis Risk in Communities (ARIC study), a cross sectional study, which included 1558 subjects with established CVD, stroke, or heart failure, did not find any association between testosterone levels and mean carotid intima media thickness, coronary heart disease, and cardiac associated mortality [7]. Shores et al. reported data froma longitudinal, observational Cardiovascular Health Study (CHS) of a cohort of healthy community dwelling men age 66-79 years without CVD at baseline, where the subjects were followed for a median of 9 years. Similarly, to ARIC study during this study, no correlation was found between the baseline level of total testosterone and incidence of CVD and all-cause mortality [8]. However, there was a curvilinear association between baseline dihydrotestosterone (DHT) level (a powerful androgen and a metabolite of testosterone) and incidence of CVD, with more CVD incidence noted in those patients with the lowest and the highest DHT levels. It is worth noting, that crucial information, such as testosterone levels and information regarding testosterone therapy during the observation, was not included in this report [8]. In contrast, the Health in Men Study, a prospective observational study of 4230 community dwelling men age 70-89 years, showed that individuals with higher DHT had lower incidence of ischemic heart disease (IHD), IHD related mortality, and all-cause mortality [9]. Still, the cumulative mortality was highest in the sub-cohorts with the highest and the lowest total testosterone levels, while no information is available on the level of testosterone binding globulin. Of interest, men with mid-range levels of testosterone and DHT had the lowest mortality and there was no association between estradiol level and all-cause mortality and ischemic heart disease [9]. Although these last two studies were conducted on two slightly different cohorts, one more racially diverse than the other. These were retrospective studies, of interest, the cohort were not very selective and were more similar to the general population and if they were taking testosterone probably not on a very standardized fashion of a trial but in a relax mode [8,9], the end results of both indicated that those who were older and those with the highest levels or below normal levels of testosterone or DHT, were more prone to sustain CVD events. Unfortunately, to apply the end results to the community we would need the history of testosterone use of the participants.

Furthermore, the European Male Aging Study (EMAS), a prospective non-interventional study of 2599 community dwelling men age 40-79 years, showed that those with low testosterone (<8nmol/l, 230ng/dl) and 3 symptoms of hypogonadism had 5-fold higher risk of all-cause mortality while men with low testosterone levels without any symptoms had 3-fold higher risk of all-cause mortality, both compared to those of eugonadal men [10]. Moreover, in a cross sectional observational study of 3443 community dwelling men age>70 years, after adjusting for cofounders, lower testosterone level (<337ng/dl) was found to be a significant predictor of transient ischemic events (TIA) or stroke [11]. Based on this finding, a "normal" instead of "high" or "low" testosterone levels in community dwelling aged men, may have a protective role in maintaining healthy cardiovascular condition. On the other hand, lower or higher testosterone level may predict worse cardiovascular outcomes, especially in older men with history of CVD. However, whether the lower testosterone level is a marker of low grade CVD not yet clearly diagnosed, or is it the cause of CVD in otherwise healthy aged men, should be studied in the future.

Observational studies on association between testosterone therapy and CVD: The following information is based on several representative retrospective observation studies that assessed the role of testosterone therapy on CVD events. In a much-debated study using a healthcare database of over 55,000 men, the relative risk of myocardial infarction increased by two-fold during the first 90 days after the initiation of testosterone therapy in men who had prior history of heart disease. Men over age 65 exhibited greater risk of CVD events than those under 65 [12]. However, the study did not have a control group, the data were not adjusted for various cardiovascular risk factors, and most importantly, testosterone levels were not available, either at baseline or during the testosterone treatment period [12]. Another retrospective study used a cohort of 1223 from 8709 men who were treated with testosterone in the Veterans Health Care System data base 913. This study revealed that there was a higher incidence of death and cardiovascular events in men who were hypogonad (testosterone <300ng/dl) with documented coronary artery disease by coronary angiography prior to starting testosterone therapy. The estimated cumulative percentage of CVD events was higher in testosterone treated arm but the differences became significant only at 4th year of therapy [13]. There were no significant differences in the underlying comorbidity between the two groups. Of interest, the second testosterone level in this study was obtained in only 60% of cohort with mean level of testosterone rising from 175.5 to 332.2 ng/dl, not even to a mid-normal level. In addition, testosterone therapy was defined as filling the first prescription without any actual documentation whether patients had used the prescribed testosterone [13]. Furthermore, a more recent report comparing the safety of testosterone administration utilizing data from Medicare, a commercial insurance claims company in USA, and the UK cohort accessed from the Clinical Research Data link (CPRD) found, that more cardiovascular events, hospitalizations, and death in group of individuals who were on testosterone, as well as the incidence of adverse events, were higher in older individuals [14]. Nevertheless, the study is limited by several shortcomings. For example, the doses and the frequency of testosterone administration were not stated, testosterone levels from baseline or during the study were not available on many study participants, and finally, there was no data correlating the CVD outcomes with testosterone levels during the study [14].

The studies cited above, although with limitations, suggest the possibility, that testosterone treatment may be associated with increased CV events. However, other studies suggest the opposite. For example, Shores et al. reported decreased risk of death in testosterone treated group versus untreated group, 10.3% versus 20.7%, respectively. This was an observational study consisting of a total of 1031 men, age>40, with low testosterone (<250ng/dl) of which 398

had received testosterone replacement [15]. In another study, a cohort of over 83,010 male veterans with confirmed low testosterone level without prior MI or stroke received either testosterone replacement therapy to achieve and maintain mid normal testosterone level (supported by follow up testosterone level) or no treatment for nearly 14 years. In this study, Sharma et al. found significantly lower all-cause mortality, fewer MIs and ischemic strokes in the testosterone group as compared to the group who was either not treated or treated but did not achieve normal testosterone levels [16]. The results were adjusted with potential acceptable confounders.

Bearing in mind the findings from the studies presented thus far, while taking in consideration their shortcomings, we may conclude, that testosterone therapy may decrease CV outcomes if recipients are younger men without previous CVD. Older age and previous history of CVD, both remain two main factors that may contribute to the ill effect of testosterone therapy. However, such conclusions must be made with caution because the studies cited so far are observational rather than prospective interventional trials.

Interventional studies on testosterone therapy and CVD: We next examined the interventional studies on the effect of testosterone therapy on cardiovascular events in elderly men. In 1946, Lesser was the first to demonstrate that testosterone therapy in individuals with angina pectoris caused moderate to marked improvement in physical function without precipitating angina pectoris [17]. In a more recent pilot study, English et al. treated 50 men with low normal testosterone and history of angina pectoris with daily transdermal administration of 2.5mg of testosterone for 12 weeks and showed a significant improvement on the exercise induced myocardial ischemia demonstrated by increasing mean time to develop 1mm ST suppression in testosterone treated arm. They also found an improvement in quality of life scores; however, there was no significant change in frequency of angina in either of the study arms [18].

Furthermore, among the studies where CVD events were the secondary outcomes, there is a recently published study consisting of 790 men, age >65 years with history of CVD (myocardial infarction in 15% and other CVD in 4%) and with serum testosterone less than 275mg/dl. The subjects were treated with testosterone gel/placebo for 12 months and serum testosterone level was kept in mid normal level for young men. The authors found no significant increase in CVD outcomes in testosterone treated arm, however there was a relative improvement of some aspects of the trial's objectives in terms of well-being and physical function improvements [19]. In contrast, in the Testosterone in Older Men with Sarcopenia study (TOM Study), a prospective, double blind placebo control study, a cohort of 209 community–dwelling males, age>65 years, with testosterone level of <350ng/dl with some motility limitation, was treated with either testosterone or placebo. The trial was stopped early due to higher frequency of cardiovascular–related event in men assigned to the testosterone arm [20].

Although, there are several less robust, prospective and interventional studies in literature, their outcomes could not be generalized to a larger, longer and more diverse cohorts due to the size and diversity in the design of these studies.

Meta-analysis studies on testosterone and CVD outcomes: There are several meta-analysis studies on this subject. In one study, the authors chose 27 trials out of 1882, comprising 2994 subjects who were followed for 4.3 years. In general, they report edno conclusive association between testosterone therapy and cardiovascular-related events; however, they noted, that several studies had shown that testosterone therapy was probably associated with an increased risk of CVD-related events [21]. In another meta-analysis, out of 984 studies (both randomized and non-randomized), encompassing older men undergoing testosterone therapy for 3-36 months, only 51 studies were selected, due to large variation in the design of the studies. In this analysis, no significant association between cardiovascular outcomes and testosterone therapy was found [22]. Similarly, Corona et al., after examining more than 2800 studies with various designs and cohorts, did not find any significant association between either testosterone therapy or lack of testosterone with CVD events [23]. Finally, Haddad et al. from Mayo Clinic had analyzed 30 randomized studies from 659 trials; out of 1642 men, 808subjects had received testosterone therapy. The pooled fatal and non-fatal myocardial infarction had odds ratio of 2.24, favoring placebo, but a wide confidence interval (95%CI, 0.50-10.02) suggests that the association between myocardial infarction and testosterone therapy was not very strong. In fact, the authors determined that no valuable conclusion regarding testosterone therapy and CVD outcomes could be reached due to variability of methodology and/or lack of many important data in most studies [24].

In Summary, The assessment of several studies, some reported above, leads to two plausible conclusions. First, despite numerous controversies, low testosterone levels in healthy aged men may be considered a "contributing factor" in more CVD events. Second, testosterone replacement therapy in healthy aged men (age less than 65-70) without major CVD may improve future cardiovascular outcomes. However, many controversies still exist.

Testosterone and cardiovascular risk factors

To understand the influence of testosterone on CVD we will examine the effect of testosterone on various CVD risk factors.

Testosterone level and testosterone therapy and hyperlipidemia: Hyperlipidemia is a major but modifiable risk factor for CVD. Prepubertal boys and girls have identical lipid panels such as HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), and triglycerides (TG). However, HDL-C level decreases while LDL-C and TG levels increase after the onset of puberty in boys but not in girls [5]. This observation, coupled with the reported higher incidence of CAD in men, triggered an idea of testosterone being a contributing factor in CAD in men. The interrelation between testosterone levels and/or testosterone therapy and lipid parameters, a major risk factor for CAD, continues to be the subject of many studies. For example, Barrett-Conner et al. found decreased free and total testosterone, DHT, and dehydroepiandrosterone sulfateb (DHEA-S) in older men with diabetes. Furthermore, total testosterone level had a positive association with HDL-C level and negative correlation with TG levels [25]. The same correlation was found in Turku Male Aging study assessing 2513 out of 15, 496 men aged 40-69 which reported testosterone has a significant positive relationship with HDL-C level and inverse association between with levels of TG [26]. Finally, the Rancho Bernardo and San Antonio Heart Studies had also shown the

presence of positive association between HDL-C and testosterone levels [27,28]. It's worth noting that these correlations were reported on subjects without very high testosterone levels.

In addition, the falling testosterone level in aging men was found to influence oxidation of LDL-C and to cause more atherogenic lipid particles [29] while higher levels of lipoprotein (a) (Lp a), a very atherogenic lipid particle and an independent cardiovascular risk factor, were found to be inversely associated with testosterone level in aged men [30].

To learn about the effect of testosterone therapy on lipid levels, in their prospective and interventional study, Singh et al. treated a group of eugonadal men age18-35 years with weekly injections of various doses of testosterone (25-600 mg) for 20 weeks. They found no adverse effect of testosterone therapy on insulin sensitivity, plasma lipids, and Apolipoprotein A (Apo A is the main protein component in the HDL-Cand is associated with reverse cholesterol transport and decreases CVD risk) with various doses of testosterone, There was however, an inverse correlation between free and total testosterone levels (a reflection of testosterone dose) and HDL-C and Apo A, in group of individuals receiving testosterone 600mg (a pharmacological dose) [31]. Similarly, but in older men, Snyder et al. assessed the effect of testosterone replacement therapy (using transdermal testosterone) on cardiovascular events and lipid particles in hypogonadal men age >65 years. No significant differences on lipid and apoprotein parameters were noted between the two study arms after 3 years of treatment [32]. Of interest, Ohlsson found an inverse relationship between increasing testosterone levels and ApoB/ApoA, indicative of testosterone being involved in improving lipid metabolism and decreasing more atherogenic lipid particles [33].

In summary, a decreasing level of testosterone in men is associated with more atherogenic lipid particles, whereas testosterone replacement therapy in aged men reverses the lipid metabolism to a more favorable and less atherogenic lipid particle.

Association of testosterone level or testosterone therapy with diabetes mellitus or insulin resistance: Various studies utilizing various animal and human models have demonstrated the presence of a strong link between low testosterone and risk of obesity, greater incidence of insulin resistance and/or overt diabetes mellitus. In a study of rodents with orchiectomy-induced testosterone deficiency there was a significant decrease in insulin level, insulin receptor number, and insulin receptor mRNA. Furthermore, these changes were accompanied by decreased glucose oxidation in target tissues such as skeletal muscle, liver and fatty tissue, all these changes were reversed with testosterone therapy [34]. Other studies have demonstrated that testosterone therapy in sterptozotocin-induced diabetic and gonadectomized rats lowered the incidence of β cells apoptosis and enhanced tissue immune-reactivity to insulin, catalase, and superoxide dismutase, all very important factors in glucose metabolism [35]. These animal studies clearly showed a significant influence of testosterone on insulin functions in the target tissues.

In humans, a number of cross-sectional and population based studies have indicated the presence of a functional defect(s) in hypothalamic-pituitary- gonadal (HPG) axis, by pointing out either slightly elevated or inappropriately normal LH and FSH with low testosterone levels in obese individuals with or without DM [36-39]. Many epidemiologic and longitudinal studies have also shown a high prevalence of testosterone deficiency in men with obesity, metabolic syndrome and/or type 2 diabetes mellitus (T2DM), [40-44]. Further, the Third National Health and Nutrition Examination Survey (NHANESIII) reported a negative association between free testosterone level and incidence of DM even independent of adiposity [45]. This study also showed that individuals with lowest tertile of free or bio available testosterone had four times higher chance of developing DM, suggesting that low testosterone is a risk factor in development of diabetes in men [45]. These reports demonstrate presence of a complex relationship between possible defect in the hypothalamic and/or pituitary signaling and the production of testosterone in individuals with obesity, DM, or metabolic syndrome. Interestingly, men with DM with or without obesity may benefit from testosterone replacement therapy by showing some improvement in insulin sensitivity and blood sugar and lipid metabolism.

Still, men with prostate cancer on androgen deprivation therapy (ADT) or gonadectomy to reduce testosterone levels, served as a model to study the role of testosterone in various cardiovascular risk factors. A retrospective analysis of data in men with low grade prostate cancer on medical or surgical gonadectomy showed that lower testosterone level is associated with higher incidence of hypertension, hyperlipidemia, and obesity, all risk factors for cardiovascular disorders [46]. Increased incidences of diabetes, obesity, lipid disorders, and cardiovascular death, have also been noted in patients with prostate cancer on ADT [47]. Furthermore, data from Surveillances, Epidemiology, and End Results (SEER) had shown an increased incidence of DM and CVD in men who underwent orchiectomy for treatment of prostate cancer [48,49]; all these outcomes were adjusted for baseline comorbidities. Similarly, a population–based study using linked administrative database from Ontario, Canada, studying men age>66 with prostate cancer who had either orchiectomy, or receiving at least 6 months of continuous medical ADT (either GnRH agonists, steroidal antiandrogens, non steroidal antiandrogens, alone or in combination) reported an increased risk of DM, with no evidence of enhanced CVD outcomes after a mean observation of 6.5 years [50]. We are learning that low testosterone levels induced by medical or surgical castration in men with low grade prostate cancer is linked to increased incidence of obesity, insulin resistance and DM; however, not every study reports the increase rate of CVD in this group of individuals.

Among many interventional trials, a recent prospective study on hypogonadal men with T2DM who either received testosterone therapy or placebo and who were followed for 5.8+1.3 years, testosterone deficiency was associated with increased risk of mortality including death due to CVD. Risk of mortality increased by 2 fold (17.2% vs. 9%) in men with DM and testosterone levels <300ng/dl compared to those with testosterone levels >300ng/dl (10.4nmol/l). In this study data were adjusted for related covariates [51]. Of interest, testosterone therapy in this cohort was associated with a decreased mortality compared to placebo, 8.4% vs. 19.2%, respectively [51]. Moreover, a double-blind placebo controlled study in 184 hypogonadal men with metabolic syndrome had shown that testosterone replacement therapy decreased the levels of insulin and leptin, markers of metabolic syndrome and decreased body mass index, as well as waist and hip circumferences compared to

placebo treated group [52]. In summary, there is strong evidence that hypogonadism increases the incidence of DM, hypertension, and obesity, all risk factors for CVD.

To further support the association between low testosterone and development of DM, metabolic syndrome, and lipid metabolism disorders, many investigators studied the association between testosterone levels and various components of metabolic syndrome (MS) and insulin sensitivity. In a cross-sectional and longitudinal study of 60 obese and 20 of non-obese men of <40 years with and without MS [53], increasing BMI was positively correlated with serum leptin, TG, and insulin levels coupled with lower testosterone levels and insulin sensitivity (assessed by HOMA). The inverse association was more pronounced in people with MS compared to obese subjects without MS. In addition, the negative association was significantly higher between the two obese groups (with and without MS) compared to those in control group (none-obese) [53]. This finding supports the hypothesis that the incidence of low testosterone is significantly higher in men with metabolic syndrome, while low testosterone level worsens the intensity of insulin resistance. Moreover, others have shown that aged hypogonadal men with MS receiving testosterone replacement therapy for sixty months will have a significant reduction in waist circumference, body weight, HbA1c, triglyceride and total cholesterol/HDL in addition to a significant improvement in insulin sensitivity as assessed by HOMA-I and blood pressure [54]. Furthermore, in an observational study (cumulative registry study) of 255 men age 33-69 years with low testosterone level whom received testosterone replacement therapy to increase the level of testosterone to mid normal typically found in younger individuals, Traish et al. reported a significant improvement in lipid, blood pressure, HbA1Cand C-reactive protein [55]. Furthermore, in a sub group analysis from two observational and longitudinal studies, a total of 156 obese hypogonadal individuals with DM, out of a cohort of 561, showed that testosterone therapy caused a significant and sustained weight loss accompanied by improvement of HbA1c, lipid profile, CRP, and liver enzymes [56]. Of interest, testosterone therapy of hypogonadal individuals with diabetes and moderate to severe CHF, improved insulin resistance and reduced HOMA-IR, decreased fasting blood sugar, increased muscle mass, and decreased fat mass [57]. However, not all researchers agree on the beneficial role of testosterone therapy. For example Basu et al. reported no improvement in insulin secretion and action, hepatic insulin clearance, and glucose tolerance in elderly men with LOH after two years of testosterone therapy [58]. Based on the evidence provided in these studies, we can draw two conclusions. First, the incidence of hypogonadism is higher in men with obesity, DM, or MS probably due to disruption of HT-PIT-T axis function. Second, low testosterone level increases fatty deposit, enhances insulin resistance and incidences of DM and finally, it worsens lipid metabolism.

The influence of testosterone on inflammatory process in atherosclerosis: The impact of testosterone on pathogenesis of atherosclerosis remains controversial. However, among various anti-inflammatory factors, decreased testosterone level was found to be a risk factor for development of atherosclerotic [59]. Many studies have established that atherosclerosis is characterized by endothelial cell dysfunction, vascular inflammation, and lipids build up within the intima of the arterial walls. Increased plaque formations on the wall of various arteries were noted in animals on high fat diet which could be reduced with testosterone therapy [60]. Additionally, testosterone therapy prevented arterial injury plaque induced by endothelial denudation of rabbit's aorta [61]. Although the presence of androgen receptors on male rabbit's arteries suggested a possible influence of testosterone on arterial wall [62], it was later shown that testosterone modulates the development of atherosclerosis via both androgen dependent and independent fashions [63]. Furthermore, in a study cited before, while testosterone replacement therapy decreased weight and insulin level, it also decreased various inflammatory markers such as IL1 β, TNF – α, and C reactive protein [52]. Farias et al. reported a reverse association between total and free testosterone levels with C-reactive protein and carotid intima media thickness (IMT) and endothelial dysfunction in 115 male subjects. After adjusting data with other co-factors, they found that low total testosterone remained independently associated with thicker IMT [64].

The presence of a significant negative correlation between testosterone levels and the number of coronary vessels with more than 75% occlusion in men with coronary heart disease and the levels of IL6 and IL10 (major inflammatory markers), strongly suggests, that low testosterone is associated with inducing inflammatory reaction on the vessel walls in patients with arteriosclerosis [65]. In addition, it has been shown, that medically induced hypogonadism with GnRH agonist in healthy elderly men increased the level ofIL6 and tumor necrosis factor α (TNF α) while testosterone replacement therapy could reverse the level to normal [66]. Other studies have also demonstrated that testosterone therapy in hypogonadal men decreased the levels of TNF α, IL6, sICAM, matrix metalloproteinase (MMP2) -an enzyme largely responsible for vascular remodeling - whereas, the addition of flutamide - a testosterone receptor antagonist – increased the level of these inflammatory markers to the baseline [67,68]. In summary, based on the findings from selected representative studies on animal and human subjects, we can conclude, that although the lack of testosterone exacerbated the inflammatory process of atherosclerosis, testosterone replacement therapy effectively reversed this process.

Summary

Historically, testosterone therapy was either a fountain of youth or a source of sudden death or other morbidities. During the past several decades, conflicting data resulting from research characterized by diverse study designs, has exacerbated the uncertainty around the topics related to the diagnosis and treatment of LOH. While several studies reported an increase of cardiovascular events resulting from testosterone therapy, others did not show any changes or even identified a beneficial effect of TRT on cardiovascular outcomes. Finally, many smaller clinical trials or studies focused on the basic science of these issues, have demonstrated that TRT may be advantageous for patients as it reduces the ill-effects of CAD risk factors such as lipid levels, HTN, metabolic syndromes, DM, or it may improve the pathogenesis of arteriosclerosis.

In this brief review, we tried to focus on several representative studies investigating the link between testosterone level/testosterone treatment and CAD. To better understand the relationship between testosterone and CAD, we also discussed the role of testosterone in various cofounders of CAD such as MS, DM, , and hyperlipidemia. Currently, we follow the Endocrine Society of America's guidelines

and offer TRT to those individuals properly diagnosed with LOH. At the same time, we continue to follow patients for adequacy of treatment by: periodically assessing testosterone levels, evaluating a clinical response, and avoiding the over-treatment and side effects. Nevertheless, we look forward to more long-term and prospective studies designed properly enough to answer our various concerns and inquiries. These studies could help clinicians in resolving the dilemma we currently face and eventually lead to a consensus in medical field about the potential risk and/or benefit of testosterone therapy for older individuals.

For clinicians, many questions remain unanswered. Who should be treated? How long should this treatment last? What level of testosterone should be the safe target during therapy? Is there a redline that should not be crossed during the therapy? What do we tell our patients about the risks and benefits of TRT?

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