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Review

Cardiovascular disease and androgens: A review

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ABSTRACT

Globally, cardiovascular disease is the single largest cause of mortality. The differences in pattern of cardiovascular disease between the two genders have not been explained properly. The spotlight has largely been focused on estrogens but no conclusive evidence has proven its role in reducing the incidence of cardiovascular disease. Consequently, androgens have attracted significant interest in explaining the gender difference in cardiovascular disease. More studies in last two decades have increased our knowledge about the effects of androgens on cardiovascular disease progression. Evidence for age related fall in testosterone levels in males and increasing cardiovascular events with age had lead to the postulation of idea of 'andropause or male menopause'. Unfortunately, for the last few decades the androgens have been highlighted as agents of abuse among athletes all over the world. There have been multiple reports of their association with sudden cardiac death and adverse cardiovascular outcomes when abused. Contrastingly, there has been an increasing prescription use of testosterone supplementation in various conditions related to androgen deficiency state and for many other off-label indications. Human observational studies have mostly concluded that men with lower testosterone levels tend to have higher incidence of coronary artery disease. Emerging evidence supports that lower androgen levels predict poor cardiovascular risk profile. Role with supplementation of testosterone for cardiovascular disease is being studied in both primary and secondary prevention stages and its safety being evaluated. This is an appropriate time to review the role of androgens specifically from a cardiovascular standpoint.

1. Introduction

Globally, cardiovascular disease is the single largest cause of mortality [1]. Hence, it is reasonable to expect that the difference in life expectancy between the male and female gender arise from differential distribution of cardiovascular disease in the two sexes especially in terms of age at onset and in terms of severity. The differences in pattern of cardiovascular disease between the two genders have not been explained properly. The spotlight has largely been focused on estrogens but no conclusive evidence has proven its role in reducing the incidence of cardiovascular disease. In fact, the results from major trials have concluded that postmenopausal estrogen supplementation might be associated with increased risk of cardiovascular disease rather that reducing the risk [2,3]. Estrogen supplementation in males showed clearly worse outcomes [4]. Furthermore, no demographic data shows a point of infliction in the incidence of cardiovascular disease in females after menopause. This has generated more interest on identifying the role of endogenous androgens in cardiovascular disease. Consequently more studies in last two decades have increased our knowledge about the effects androgens on cardiovascular disease progression. Evidence for age related fall in testosterone levels in males (Fig. 1) and increasing cardiovascular events with age had lead to the postulation of idea of 'andropause or male menopause'.

For the last few decades the androgens have been highlighted as agents of abuse among athletes all over the world. There have been multiple reports of their association with sudden cardiac death and adverse cardiovascular outcomes when abused. But recently there has been an increasing prescription of testosterone supplementation in various conditions related to androgen deficiency state. The use of testosterone and synthetic androgens is also extended to a variety of conditions other than symptomatic hypogonadism like hematological disorders, HIV cachexia, cancer cachexia and many other off-label indications (Table 1) [5]. Hence, it is important to review the use of supplemental testosterone specifically from a cardiovascular disease (CVD) standpoint. This review will focus on the effect of androgens on cardiovascular disease and cardiovascular risk factors while trying to underline pathogenetic mechanisms involved in effects of

Abbreviations: CAD, Coronary artery disease; CVD, Cardiovascular disease; DHEA, Dehydroepiandrosterone; SHBG, Sex hormone binding globulin; IMT, Intima media thickness; FMD, Flow mediated dilatation.

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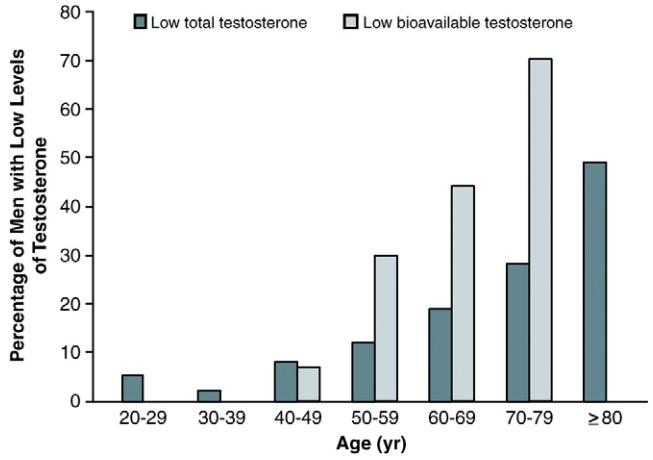

Fig. 1. Prevalence of low levels of total and bioavailable testosterone as an index of male hypogonadism according to decade of life. (with permission from NEJM).

testosterone on cardiovascular system. Safety of testosterone use and possible future roles in CVD will be discussed as well. Most of the data available in this regard is still limited to the retrospective observational studies and hence the conclusion from the review of these data will be largely hypothesis generating.

2. Physiology of endogenous androgens

Testosterone is the most important endogenous androgen that exhibits many of its effects through a physiologically active dehydrogenated metabolite dehydrotestosterone. The other major physiologically active androgen precursor is dehydroepiandrosterone (DHEA), which is produced in the adrenal glands. Additionally, testosterone is converted peripherally and in the adrenals to estradiol, which may be responsible for some of the physiological effects of testosterone. Circulating testosterone is present in the form of free testosterone (fT) and bound forms. Only 2–3% of all circulating testosterone is present as fT and is responsible for most physiological effects. About 60–70% of all testosterone is bound to sex hormone binding globulin (SHBG) and about 30% is bound to albumin. As a result any illness or disease affecting the levels of albumin and globulins may alter the total and free testosterone levels. Hence, there can be a false change in the levels of fT in patients with chronic disease processes. Measurement of both free testosterone and bound testosterone is an acceptable way to overcome the anomalies due to altered SHBG and albumin levels [6,7]. In clinical settings, the diagnosis of hypogonadism is based on measurement of serum testosterone and not other endogenous androgens. The testosterone is measurable by a variety of assays and indirect immunoassays are considered better than direct immunoassays [8]. Chromatography and mass spectroscopy are considered as gold standards but the best available standard test is exchange dialysis.

Table 1
Possible uses and benefits of testosterone therapy.

1. Increased lean muscle mass and strength
2. Erectile dysfunction
3. HIV cachexia with increased sense of well being, and muscle strength and mass
4. Increased bone density
5. Improvement in mood and cognition
6. Improvement in libido
7. Increased erythropoesis

The levels of testosterone undergo age related decline. Longitudinal studies in men between 5th and 8th decades suggest that the level of testosterone in human males fall by about 1.6–3% every year from the fifth decade onwards [9]. The actual decline however may start happening much earlier, almost at the same time when cardiovascular differences start to appear in the adult males and females. Based on the total serum testosterone levels, the prevalence of asymptomatic hypogonadism is estimated to be about 20% in men over 60, 30% in men over 70 and 50% in men over 80 years of age [10]. These numbers may be even more if free testosterone is used to diagnose hypogonadism instead of total testosterone levels.

The physiological effects of testosterone can be divided into genomic and non-genomic effects. The androgens are steroid ring compounds and like all other steroids mainly act through receptors located in the cell nucleus. The major receptor for androgens is appropriately called as androgen receptor (AR), which mediates the effects through modulation of transcription of the genes. These genomic effects are inhibited by transcription blockers. The androgens also exhibit certain other effects like arterial vasodilatation that are not mediated by transcription or protein synthesis and are referred to as non-genomic effects. These effects have much faster onset and are noticed within a few minutes after intravenous infusion of androgens while the genomic effects are noticed after a gap of a few hours.

3. Androgens and epidemiology of heart disease

The data from recent world health reports reveals an average 5.6 year difference in life expectancy between men and women in most of world health organization (WHO) member nations [11]. Differences in mortality between the two genders exist despite adjustments of risk factor variables. These differences most likely result from differential pattern and the incidence of ischemic heart disease that has been clearly observed in epidemiological studies [12]. In the last two decades, the role of sex hormones has been studied prospectively with respect to the incidence of specific cardiovascular events. Estrogen clearly has not been shown to have any beneficial effect on the cardiovascular diseases in females [2,3]. Initial studies on association of androgen levels and cardiovascular disease incidence and prevalence didn't show any positive or negative association. In a large study on 1009, 40–79 year old men, the androgen levels (testosterone, estriol and androstenedione) were not found predictive of the prevalence of cardiovascular disease at the beginning of the study or cardiovascular disease incidence at twelve year follow-up [13].

More recent studies however have shown surprising results. Prospective studies on DHEA sulfate (DHEAS) have consistently suggested negative correlation between the levels of DHEAS with cardiovascular disease [14,15]. A relatively recent meta-analysis of four case-control and eight cohort studies had shown that lower DHEAS levels (2 μmol/l difference) was associated with 13% increase in fatal and non-fatal coronary events [14]. Smoking is known to reduce the DHEAS levels and was considered as a possible confounder [16]. The data from the Massachusetts Male Aging Study (MMAS) focusing on middle-aged men confirmed similar results after controlling for smoking and for use of cardiac, vasodilator, antihypertensive, or lipid-lowering medication which have often been implicated to cause reduction in endogenous androgen levels [15]. No other endogenous androgen has been shown to have such a strong correlation with incidence of cardiovascular disease as DHEAS.

It still is relatively premature to implicate low circulating androgen levels in pathophysiology of cardiovascular disease. Studies done in women have not found similar association of DHEAS levels with incidence of CVD [17]. Japanese men who have a very low incidence of cardiovascular disease are known to have low DHEAS levels [16]. It is uncertain whether the increased incidence of cardiovascular disease accelerates the age related decline in androgen levels or lower androgen concentration accelerates the cardiovascular disease

process. The fall in DHEAS levels probably are markers of aging body and lower levels may be markers of faster aging thus associated with an increased incidence of cardiovascular disease. Based on above data, it is reasonable only to consider low DHEAS levels as marker of increased cardiovascular disease and mortality in men. Implications of androgens in the pathogenesis of cardiovascular disease are discussed later in the article.

4. Androgens and metabolic risk factors for CVD

The association of androgens with major cardiovascular risk factor reduction appears to be strengthening. Relationships of testosterone with incidence of obesity, insulin resistance, lipids and diabetes have been studied. Results from National Health and Nutrition Examination Survey (NHANES-III) revealed that among 1413 men 20 years or older, those in lowest tertile based on levels of testosterone had maximum prevalence of diabetes [18]. Prospective data from Multiple risk factor intervention trial (MRFIT), MMAS and Rancho Bernardo studies have prospectively confirmed that low levels of testosterone were associated with increased incidence of diabetes [19–22]. Similarly, associations have also been noticed between androgens and risk of metabolic syndrome. A study on 711 Finnish men had shown that men with free and total testosterone levels in lowest quartile had significantly higher incidence of both diabetes and metabolic syndrome [22]. This association has been confirmed in non-obese men [23]. The concurrence of low androgens with metabolic syndrome is well established and is referred to as Hypoandrogenic Metabolic (HAM) syndrome [24]. In addition to the androgens, SHBG is considered to be an independent predictor of metabolic syndrome and insulin resistance [22].

Lipid abnormalities are considered as cornerstone of pathogenesis of atherosclerosis and coronary heart disease (CHD). Sex hormones and their relationship with lipid abnormalities is well established. Multiples observational studies in men have shown that testosterone levels in higher range of normal correlate with favorable lipid profile including high HDL, low VLDL and low triglycerides [25–29]**.** Absolute LDL levels may not be affected significantly but Haffner et al. have reported that lower total testosterone levels and high normal SHBG are associated with high levels of more atherosclerotic small dense LDL in normoglycemic males [30]. Longitudinal data on participant of MRFIT also noted that high normal testosterone levels in men predicted better lipid profile in future [31]. One can argue that some of these effects may be linked to the reduction in insulin resistance, obesity and lean mass and diabetic control. However, the relationship holds true despite adjustment for age, body mass index and alcohol consumption and can't be explained by differences in blood glucose levels, differences in physical activity and prevalence of insulin resistance [25,26,28,29]. The data from a recent meta-analysis of interventional trials shows that supplementation is not associated with any statistically significant deterioration of lipid profile [32]. An average reduction in total cholesterol by 16 mg/dl was observed in men with low normal or normal testosterone levels at the beginning of intervention in this meta-analysis. Hence the current evidence supports an association between with high normal levels of testosterone with favorable lipid and cardiometabolic profile without proving a definite cause–effect role in pathogenesis of dylipedemia or CVD.

5. Androgens, atherosclerosis and coronary artery disease (CAD)

The role of testosterone in development of atherosclerosis has been evaluated in several studies. Males in animal studies tend to develop atherosclerosis earlier and more rapidly independent of lipid levels and evidence of intimal injury. The same holds true for humans as well. The understanding of the pathways mediating effects of androgens on atherosclerosis is still evolving. Testosterone levels in higher range of normal may have a preventive role in coronary disease. In the Rotterdam study involving 1032 men and women older than 55 years, testosterone levels in highest tertile were predictive of reduced prevalence of severe atherosclerosis detected by aortic calcification on radiography [33]. This is difficult to explain considering the fact that testosterone has been shown to facilitate the initiation of atherosclerosis. Testosterone tends to increase the cholesterol uptake and foam cell formation responsible in fatty streak formation, the earliest step in atherosclerosis [34]. This effect is mediated through androgen receptors (AR) the expression of which is higher in macrophages in males [34]. Other effects of testosterone such as increased apoptosis of endothelial cells [35] and increased activation and migration of vascular smooth muscle cells [36] also play an important role in atherosclerotic process. Estrogens have an opposing effect on atherosclerotic process and tend to reduce the smooth muscle proliferation and activation [37]. All these mechanism may explain gender differences in atherosclerosis disease patterns, including the earlier onset and faster progression of atherosclerosis in males compared to females.

However, the above phenomena can't explain the result of the Rotterdam study. Other human observational studies have also concluded that low levels of testosterone may be associated with increased sub-clinical atherosclerosis evaluated by measuring intima media thickness (IMT) and also predicted progression of sub-clinical atherosclerosis [38]. Men with angiographic coronary atherosclerosis have lower levels of testosterone compared to those with normal coronaries [39]. Compared with age-matched controls, men with complete androgen deprivation were found to have significantly higher central pulse wave velocities (PWV) indicating increased stiffness of central arteries in hypogonad men [40]. Interventional studies in animals have also indicated the possible benefit of testosterone in atherosclerotic process by showing that the accelerated atherosclerosis in castrated cholesterol fed male rabbits is reduced by testosterone and DHEAS supplementation [41,42]. New information has emerged from more recent animal studies that can explain the cellular mechanism associated with beneficial effects observed with higher testosterone levels. Vascular cell adhesion molecule (VCAM) mediates the migration of macrophages into the intima media and is an integral part of the pathogenesis of fatty streak formation. The levels of this VCAM have been shown to be inversely related to fT [43]. Replacement of testosterone has also been shown to reduce the levels of inflammatory mediators like TNF-alpha and IL-beta that are now considered as important players in atherosclerosis [44]. Although, testosterone or DHEAS levels have been shown not to be associated with hs-CRP levels in men [45], in postmenopausal women however lower testosterone and SHBG levels are associated with increased hs-CRP levels [46]. Indeed, results from INVADE study group do suggest that hs-CRP is independently associated with carotid atherosclerosis progression when ascertained by IMT but only in women and not in men [47]. Hence, it is reasonable to assume at this point that androgens, especially testosterone, have a permissive role in evolution of atherosclerosis at a cellular level. However, reduction of testosterone levels may play a role in the age related atherosclerosis in both men and women which is most likely related to increase in pro-inflammatory mediators and atherosclerosis mediating molecules like VCAMs.

In spite of the evidence favoring possible involvement of reduced endogenous androgens in pathogenesis of atherosclerotic vascular disease, there is no certain role of exogenous testosterone supplementation in normal or hypogonadal males to slow down the progression of atherosclerosis. A review of studies of testosterone supplementation in patients with peripheral vascular disease (PVD) showed no improvement in any clinical parameter such as claudication distance or pain [48] despite supplementation. There is some data to show that testosterone supplementation in large doses may improve quality of life and exercise tolerance in males with coronary

artery disease with chronic stable angina (CSA) [49–51]. However, it is uncertain if these results are related to the effect of testosterone on reduction of atherosclerosis alone. Coronary vasodilator properties of testosterone seen after high dose intravenous infusions may play a role. An angiography based study done by Webb and colleagues showed that infusion of testosterone over 3 minutes into the coronary arteries of 13 men with established CAD to achieve supraphysiological levels during coronary angiography increased coronary vessel diameter by 3.1–4.5% over the pre-infusion levels [52]. Coronary artery blood flow also increased by 12–17.4% compared to the pre-infusion flow. The mechanism probably involves endothelial and non-endothelium mediated coronary vascular dilatation [53]. However, these effects require large doses and supraphysiological levels of testosterone and this strategy may not considered as a reasonable therapeutic option due to possible side effects of high doses.

The differences between the effects of testosterone administration on myocardial ischemia may also depend on whether the exposure is acute and chronic. Brief sudden exposure to testosterone is known to increased myocardial damage during ischemia [54]. This mechanism is implicated in myocardial damage in athletes abusing testosterone. Chronic testosterone therapy increases while acute testosterone therapy decreases the T type calcium channel currents in mammalian myocytes that are thought to mediate HTN and angina [55], hence the speculations about possible benefit in improvement of anginal symptoms with testosterone therapy. This effect may occur with supratherapeutic doses in humans. Supplementation with physiological doses of testosterone is not found clinically beneficial when used in addition to anti-ischemic therapy [56].

The first randomized placebo-controlled double-blind study investigating the effects of testosterone in ischemic heart disease looked objectively at men with CAD proven with positive exercise ECG stress test [57]. After 4 and 8 weeks of supplementation with testosterone cypionate on repeated stress testing, the ST-segment depression in leads II, V4, V5, and V6 immediately and 2, 4, and 6 min decreased by 32% and 51% from baseline in the supplementation group with no change in the placebo group. However, no symptomatic improvement was noticed in the treatment group compared with the placebo group. Improvement in myocardial perfusion by adenosine myocardial perfusion scan had been observed after orally administered low doses of testosterone but clinical benefit is uncertain [58]. The effects on primary factors of cardiovascular disease like lipids, insulin resistance, metabolic syndrome and diabetes may explain increased incidence of CAD in hypogonad males compared to eugonad males. It is reasonable to conclude that testosterone levels in lower range of normal act as markers of progression of atherosclerosis and CAD, and may have a role to play in its pathogenesis. Despite this, there doesn't seem to be enough data to support testosterone therapy for treatment of CSA symptoms or slowing the progression of atherosclerosis safely even in hypogonad men or in men at higher risk for CAD with low normal testosterone levels.

6. Androgens and hypertension (HTN)

The presentation of HTN is different in males and females. There an early onset of HTN in males [59], the equalization of incidence of HTN doesn't occur until the 7th decade. The average blood pressures are consistently higher in males after puberty. In human observational studies, levels of testosterone relate inversely to systolic blood pressure [60,61]. Some of this inverse relationship may be due to reductions in the testosterone levels due to medications used to treat HTN that are known to affect the sexual function in hypertensive men on therapy [62]. The same relationship is not observed between the blood pressure and levels of DHEAS, estradiol or estrogens [63]. No effect on systolic or diastolic blood pressure was however found in a recent meta-analysis of interventional trials using testosterone supplementation to treat hypogonadism [33]. Thus the cause–effect relationship is not established. There is some evidence that suggests that HTN itself may hasten the age related fall in testosterone levels [64,65].

Animal studies indicate possible role on androgens in pathogenesis of HTN. Experimental studies on murine models have revealed that HTN is prevented by orchidectomy and that testosterone supplementation reproduces HTN [63]. These effects may be mediated through androgen receptors as evident from the fact that flutamide tends to reverse the blood pressure difference between male and female mice models [66]. The androgen receptors seem to stimulate the adrenergic system causing the effects of testosterone on blood pressure [67]. Gonadectomy is known to abolish the excess ACE pathways activation [68] and cellular ACE mRNA production [69]. Testosterone induces the renin angiotensin aldosterone system (RAAS) activation in humans [70] although the lack of any gender specific differences in the effects of ACE inhibitors on blood pressure [71] would mean that this effect is unlikely to have any clinical significance. There is weak data to suggest that the adrenal cytochrome P-450 [11] may be involved in testosterone-mediated hypertension [72].

Contrary to the effect of testosterone in enhancement of hypertension, its direct effect on vascular smooth muscles in vitro is vasodilatation rather than vasoconstriction. This effect is endothelium mediated through the nitrous oxide (NO) pathway activation. Blockade of the calcium ion influx via voltage gated membrane calcium channels [73] and potassium ion efflux via the voltage gated and ATP-sensitive potassium channels [52,74] may also be involved. These effects are reproducible after intravenous infusion of testosterone to achieve supraphysiological levels in vivo in animal models. In contrast, supplementation of testosterone in physiological doses reduces flow mediated dilatation (FMD) of blood vessels [75]. Impairment of FMD is usually an early indicator of atherosclerosis in adults. Chronic androgen deprivation appears to increase flow mediated dilatation (FMD) of blood vessels. We need better elucidation of the physiological effects of testosterone and androgens before a premise can be reached. In the light of present data it is reasonable to assume that there is no definite association between systolic blood pressure and testosterone levels although testosterone may facilitate the endogenous pathways that generate hypertension.

7. Androgens, myocardial protection and heart failure

Congestive heart failure (CHF) is a major health problem and among the most common reason for hospitalization worldwide. CHF has a very poor prognosis and 1-year mortality after hospital admission for heart failure may be as high as 30%. The role of androgens, especially testosterone, in heart failure has been studied in recent past. Speculations about possible beneficial effects of testosterone in heart failure that are based upon facts that androgens tend to favorably affect the metabolic parameters that play a significant role in the evolution of myocardial dysfunction and establishment of heart failure. Additional direct effects may be non-genomic direct cytoprotective effects mediated through cell surface molecules and channels and not by genetic expression.

The gender difference in cardiac mass emerges after puberty and is maintained for the duration of life. It is contentious if this is a compensatory phenomenon related to the physiological differences like early onset of hypertension, higher blood pressure and differential volume status between the men and women [76]. Marsh et al. confirmed presence of androgen receptor genes in cardiac myocytes [77]. Hence, there is a possibility that androgens may affect remodeling and modulate the cardiac response to stress.

The nature of modulating effects of androgens on mammalian cardiac myocytes is not clearly elucidated. Animal studies by Rocha et al. have shown testosterone-induced activation of cardiac renin angiotensin aldosterone system (RAAS) in rats [78] with increased maladaptive remodeling. These harmful effects may explain the increased frequency of adverse cardiac events in athletes abusing androgens.

However, in humans, testosterone supplementation in men with low testosterone reduces remodeling and improves left ventricular ejection fraction [79]. This effect is mediated by optimization of the balance between IL-10 and TNF-alfa [79]. There is evidence to suggest that testosterone has a beneficial effect on myocyte survival at the cellular level. Testosterone induces heat shock protein 70 (HSP-70) in myocytes and plays important role in preconditioning for delayed cardio protection in settings of ischemia [80]. This preconditioning might reduce the chance of cellular death during additional ischemic stress in hearts with relative ischemia. This effect is genomic and is abolished by androgen receptor blockers. Induction of ATP-sensitive potassium channels in the cardiac mitochondrial inner membrane may be another mechanism of cytoprotection conferred by testosterone [81]. Acute administration of testosterone increases contractility of mammalian myocytes, an effect that explains the benefit of testosterone for performance enhancement in athletes [82].

These effects of testosterone at molecular level form the basis of theoretical benefit of testosterone supplementation in heart failure. Additionally, observational studies in humans reveal that the levels of testosterone are lower in patients with severe heart failure. This may nonetheless be secondary to chronic cachexia from heart failure and its effects on the hypothalamic–pituitary–gonadal axis. The results of studies looking into the role of testosterone supplementation in heart failure patients bring optimism. An interventional pilot study that randomized 20 men with chronic heart failure to receive weekly injections of testosterone enanthate (100 mg) or placebo for 12 weeks found that testosterone treatment significantly improved left ventricular ejection fraction and exercise capacity compared with placebo [83]. In contrast, Chung et al. found no improvement in 2D-ECHO finding of heart failure in CHF patients treated with 4 weeks of testosterone or nandrolone [84]. The limited follow-up period of 4 weeks was probably too short to notice any change in echographic parameters in this study. No significant adverse effects were noticed in these or other similar studies [83–85]. A more recent double-blind randomized control trial (RCT) by Malkins et al. addressed some of the deficiencies in the previous trials and showed significant clinical benefit in exercise tolerance in patients of moderately severe heart failure with testosterone supplementation for twelve months [86]. This study used testosterone patches rather that injectable testosterone preparations and duration of therapy was probably long enough to notice the benefit. Thus, the role of testosterone supplementation in hypogonad patients with heart failure is promising. Trials are underway on the adjuvant role of androgens in heart failure may provide more information for future use [87].

8. Miscellaneous effects on cardiovascular system and safety of androgens

The effects of testosterone are not limited to the basic pathogenesis of cardiovascular disease. They also tend to have adverse effects that may not be explained by any known mechanism. Cardiomyopathy, ruptured aortic aneurysm [88], stroke and myocardial infarction [89], and precipitation of atrial fibrillation [90], have been rarely reported with testosterone supplementation. Lower testosterone levels may be associated with prolongation of QTc. Women have longer QTc after puberty and persisting after menopause and hence higher propensity to have torsade de pointes. However, intravenous administration of testosterone is not associated with any changes in electrocardiography parameters including QTc [91].

The most worrisome aspect of androgen administration is the reporting of sudden cardiac death in athletes abusing anabolic androgenic steroids. The abuse of anabolic steroid hormones or androgens is prevalent among athletes since 1950's. The dose of androgens used by these athletes is several times the standard testosterone doses recommended for hypogonadism [92]. Hence a lot of side effects seen in this population group may be related to the supraphysiological levels of testosterone levels. Non-cardiac side effects including virilization in women, polycythemia, acne and hepatotoxicity have been reported. The data on side effects seen in these individuals should not be extrapolated to those using physiological replacement doses. A recent meta-analysis on interventional trials of testosterone replacement in humans supports safety of testosterone to a reasonable extent, although a non-significant trend increase in cardiovascular events was noticed [33]. Nonetheless, with available data it is reasonable to consider that supplementation of testosterone and related compounds when used in usual pharmacological doses may not be associated with significant increase cardiovascular morbidity.

9. Conclusion

Androgens have attracted significant interest in the last two decades in explaining the gender difference in cardiovascular disease. Testosterone affects the cardiovascular system through both genomic and non-genomic phenomena. Animal and human research on androgens has shown molecular effects of androgens on cardiovascular system are variable in nature and are concentration dependent. The degree of clinical importance of each of these cellular effects is uncertain. The observed gender difference in patterns of cardiovascular disease is only partially explained on the basis of known effects of androgens in humans pointing to our incomplete understanding in this field. Human observational studies have mostly concluded that men with lower testosterone levels tend to have higher incidence of cardiovascular disease including HTN, dyslipedemia and coronary artery disease. However, intervention with supplementation of testosterone has been clinically found beneficial only in improving performance in patients with heart failure and reducing exertional angina threshold. This data although promising is scarce at this time for recommending use of testosterone supplementation in these patients. Furthermore, the subgroup of patients that would benefit from these interventions has not been clearly defined. Thus, despite recent advances in our understanding of effects of androgens on cardiovascular system, the future role of androgens in cardiovascular therapeutics needs better elucidation. Nonetheless, there is reassuring evidence that testosterone supplementation can be used with therapeutic intention without significant adverse effects despite reported idiosyncratic complications. The reported side effects in athletes abusing androgens and anabolic steroids are observed mostly in supraphysiological doses. Improved formulation of androgens are now available that can overcome any practical problems in safely achieving physiological concentrations of hormone. There is good evidence that lower androgen levels predict poor cardiovascular risk profile, something that internists, cardiologist and endocrinologist should be made aware of so that these patients get optimum benefit of cardiovascular preventive strategies. In summary, there has been significant increase in our understanding of role of androgens in cardiovascular disease. More strides need to be taken before our understanding role of androgens has therapeutic implications in cardiovascular diseases.

Conflict of interest

We verify that there is no financial conflict of interests of any authors and that all the authors had complete access to all the information presented in the article.

Acknowledgment

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [93].

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