Chapter

Role of Androgens in Cardiovascular Diseases in Men: A Comprehensive Review

Dilip Mukherjee, Koushik Sen, Shreyasi Gupta, Piyali Chowdhury, Suravi Majumder and Payel Guha

Abstract

The present knowledge on the androgens role in cardiovascular physiology is not fully completed. It remains unclear whether low serum testosterone concentrations in men are an independent risk factor for cardiovascular diseases (CVDs) or a marker of the presence of CVD. However, we demonstrated that endogenous testosterone levels may be implicated in CVDs. Androgens role in modulating cardiovascular function is one of the highest importances, given that its deficiency is strongly associated with hypertension, atherosclerosis, diabetes, obesity, and cardiac hypertrophy. Although significant and independent association between testosterone levels and cardiovascular events in elderly men have not been confirmed in large prospective studies, cross-sectional studies, however, suggested that low testosterone levels in elderly men are associated with CVDs. The results of androgen therapy are not also conclusive. Perhaps, the effects of testosterone treatment of cardiovascular mortality and morbidity have not been extensively examined in control studies. Data on male animal experimentation of the effect of testosterone replacement therapy are either neutral or beneficial on the development of atherosclerosis. Since circulatory androgen levels modulation is expected to cause many other side effects, it seems to be essential to develop a strategy to target androgen receptor for better treating the CVDs.

Keywords: testosterone, miocardial infarction, men, lipid profile, ROS

1. Introduction

Cardiovascular diseases (CVDs) refers to a class of diseases that involve the heart and/or blood vessels and still the highest leading cause of death in developed and developing countries with earlier onset and possibly of greater mortality risk seen in males compared to females. Approximately 17.5 million people died from CVDs in 2012 representing 31% of all global deaths. It is anticipated that by 2030, the number of death due to CVDs will be reach to more than 23.6 million [1]. Since male gender is one of the risk factors for premature coronary artery disease, stroke, peripheral vascular disease, and heart failure, androgens have often been considered as a cause underlying this male disadvantage [2, 3]. Androgens, mainly

testosterone, may also play in cardiovascular morbidity and mortality by modulating the risk factors of atherosclerosis and vascular functions, lesions to cerebral and peripheral arterial vessel and myocardial infarction leading to heart failure in male [4].

A recent perspective study reveals that testosterone levels in men decline gradually with increasing age and this caused a dramatic increase in the incidence of CVDs [5, 6], but the mechanism of age-related cardiovascular performance remains to be completely understood. However, a protective role of androgen for CVDs in men has been reported and its deficiency may increase the significant risk factor for CVDs. Moreover, controversy also exists whether this age-associated decline in testosterone level is a natural physiologic processes or combination of co-morbidities and life-style choices [7]. With the prospects of much wider therapeutic approaches of testosterone on CVDs, it has become increasingly important to address whether testosterone treatment might increase the risk of severity of CVDs. Considering the importance of therapeutic use of testosterone as have been reflected in several recent studies, it is important to address the issue in a more critical way.

2. Cardiovascular diseases: types and risk factors

CVDs refer to any dysfunctional condition of the heart or the blood vessels (arteries, veins, and capillaries). Coronary heart disease (CHD) and stroke are two fundamental components of CVDs [8]. CVDs can be classified in eight major groups. These are: stroke-disruption of the blood supply to the brain either from blockage or from rupture of blood vessels; CHD-disease of blood vessels, transporting blood to the heart muscle; rheumatic heart disease-caused due to rheumatic fever by streptococcal bacteria when heart muscles and valves are damaged; congenital heart disease-structural malformation of heart; aortic aneurysm-dilation and rupture of aorta; peripheral arterial disease-disease of the arteries that supply blood to arms and legs; deep venous thrombosis and pulmonary embolism-blood clot in leg veins, which can dislodge and move to heart and brain; and other CVDs- tumors of the heart, vascular tumor of the brain, disorder of the heart muscle lining etc.

Risk factors can be categorized as modifiable and non-modifiable risk factors. Modifiable risk factors include; high blood pressure, abnormal blood lipids, tobacco use, physical inactivity, obesity, unhealthy diets, and diabetes mellitus. Non-modifiable risk factors are advancing age, hereditary or family history, gender, and race.

3. Testosterone and its function

Testosterone, a C19 androgen, is the most vital circulating androgens both in male and female. In men, it is mainly synthesized in the testes and a small amount is also derived from adrenal cortex. Testosterone is essential for male sexual differentiation, development and normal function of male reproductive organs, and maintenance of secondary sexual characters. In addition, testosterone promotes many other physiological processes like bone formation, growth of muscle, hair growth, body composition, and erythropoiesis and decreased the risk of osteoporosis [9]. In normal adult men, testosterone concentration ranges between 241 and 827 ng/dl [10]. Secretion of testosterone varies with circadian rhythm.

Circulating testosterone is mainly bound to sex hormone binding globulin (SHBG) and albumin and only 1–2% remains as unbound form.

In target cells, testosterone binds to the intracellular androgen receptors (ARs) or is converted to dihydrotestosterone (DHT) catalyzed by 5α-reductase, which then binds to AR. In some target tissues, testosterone is converted to estrogens by cytochrome P450 aromatase enzyme and estrogens then bind to estrogen receptors. Both androgen and estrogen receptors act as transcription factors and mediate genomic effects [11]. In addition, various *in vitro* and *in vivo* studies have shown that testosterone and its derivatives can affect cellular processes in a non-genomic fashion [12]. Testosterone has been shown to regulate cell to cell ion exchange via gap junction in Sertoli cells and cardiac cells in young rats [13]. Testosterone also promotes vasoconstriction [14, 15] and rapid rise of Ca^{2+} in cultured cardiomyocytes by PLC/IP_3-dependent mechanism [16].

4. Circulatory levels of testosterone and CVDs

Association of blood testosterone levels and incidence of CVDs in men with increasing age is based mainly on observational studies and the main disadvantages of such type of studies are the extremely variable endpoints of CVDs, heterogeneous study groups, and diverse selection criteria. A continuous study for months to several years on a particular study group of CVD patient is very difficult for various reasons. Importantly, patients in these study groups are mostly in medications or modified their life style. Moreover, selection of poorly-matched controls and timing of blood sampling are not always standardized for diurnal variation of hormone levels. All these factors have a serious impact to draw a definite conclusion. However, taking all these into consideration, recently, we investigated the relationship between serum total testosterone levels and lipid profiles as well as fasting blood glucose (FBG) levels in elderly men with angiographically confirmed CVDs from two thickly populated and socio-economically backward districts; Nadia and Murshidabad of West Bengal, India. We observed that relationship between sex hormones, lipid profiles and FBG levels of CVD patients is strikingly different from men with no CVDs of similar age group [17]. Considering the previous observational studies along with our study, we presented a comprehensive idea on the relationship between serum testosterone levels and CVDs globally.

In normal men of developed countries, the overall incidence of testosterone deficiency increases with age and approximately one half a million new cases of testosterone deficiency are expected in men aged 40–90 years old (**Figure 1**) [18]. An independent effect of age on serum testosterone in a study of 890 men has also been demonstrated [19]. Prevalence of testosterone deficiency in men aged >45 years is approximately 38.7% based on total testosterone (T) levels and about 36.3% based on bio-available or free T [20]. They have documented that major risk factors such as obesity, diabetes, hypertension, hyperlipidaemia, prostate disease, and asthma or chronic obstructive pulmonary disease are responsible for low testosterone levels in men compared without such conditions. A schematic representation of the association of testosterone and cardiovascular risk factors is depicted in **Figure 2**. It has been reported that low testosterone levels are associated with increased death from CVDs [21]. Whereas, for a long time prospective studies failed to find significant association between testosterone levels and risk of cardiovascular events in middle aged men [22, 23]. However, a study of osteoporotic fractures in elderly men of Sweden reported that high serum testosterone level is associated with reduced risk of cardiovascular events [24]. This is consistent with the influence of testosterone levels on multiple risk factors such as obesity, diabetes, blood

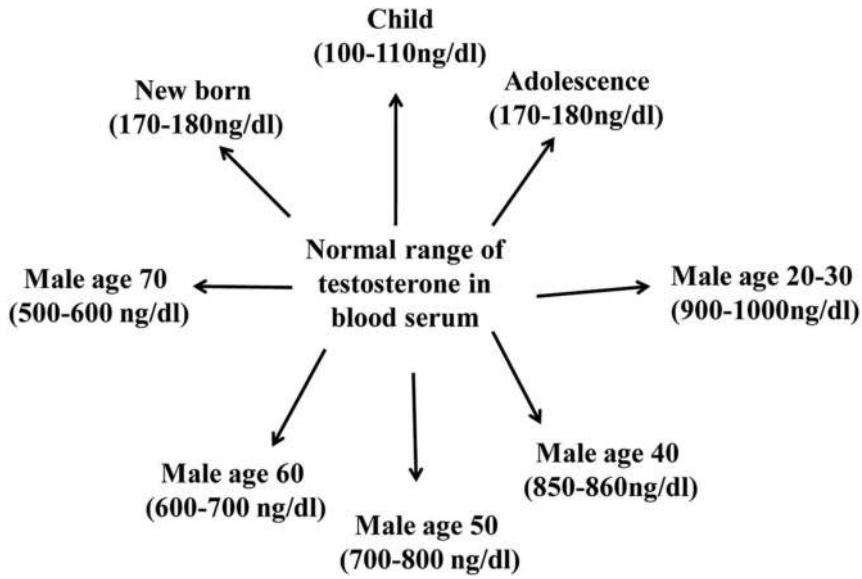

Figure 1.
Testosterone levels in men at different ages of life.

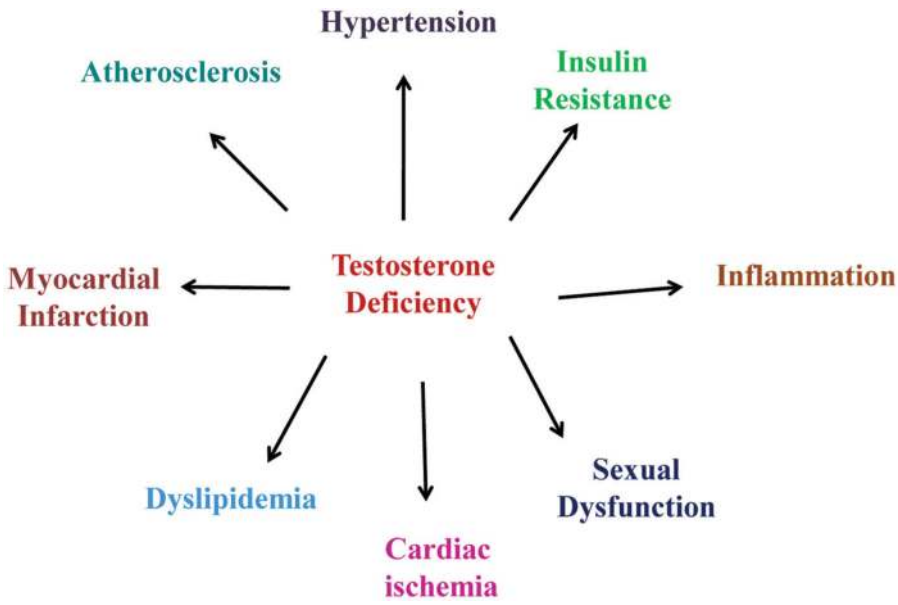

Figure 2.
Association of testosterone deficiency and cardiovascular risk factors.

pressure, and carotid atherosclerosis [25, 26]. A recent meta-analysis showed that low testosterone levels predicted risk for CVDs in elderly men but not middle-aged men [27]. Interestingly, using data from the French Three-City prospective cohort study (3650 men aged >65 years) after adjustment for cardiovascular risk factors, a J-shaped association between plasma total testosterone and incidence of ischemic arterial disease (IAD) in elderly men has been reported [28]. They have suggested that both high and low plasma testosterone levels are associated with an increased risk of arterial ischemic events in elderly men and an optimal range of testosterone levels may confer protection against cardiovascular events. In a recent study, Kelly and Jones [29] observed that testosterone replacement in men diagnosed with hypogonadism shown to be a beneficial effect on several cardiovascular risk factors, cardiac ischemia, functional exercise capacity, and mortality.

5. Association of various risk factors with CVD

5.1 Role of lipids in CVD

It has long been established that lipids play a central role in the initiation and progression of CVDs [30–32]. Dyslipidemia comprises the abnormalities of lipid profiles characterized by high levels of total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL), and very low density lipoprotein (VLDL) along with low levels of high density lipoprotein (HDL) that contributes to the development of atherosclerosis [33]. In older men, reduced testosterone levels are associated with adverse profiles of lipids. Low testosterone level is associated with high TC, high LDL [34, 35], and high TG [36, 37]. Hypo-gonadal men exhibit abdominal or central adiposity [38, 39]. This finding has led to conclude that all parameters of lipid profile except HDL might be more strongly associated with CVD risk, whereas some investigators reported a negative correlation between HDL and CVD [40, 41]. A strong inverse correlation between body fat and testosterone level is also observed [42]. Higher mass of visceral adipose tissue is inversely correlated with bio-available testosterone [43]. In an epidemiological study from our laboratory, we studied the relationship between serum total testosterone levels and lipid profiles in male patients ranging the age group between 40 and 70 years with angiographically proven CVDs from Nadia and Murshidabad district of West Bengal, India and compared the data with normal men with no CVD history. We observed a significantly low serum total testosterone levels in CVD patient group compared to normal group and further demonstrated a significant negative association between serum total testosterone and TC, TG, LDL, and VLDL among CVDs patients. However, a significant positive correlation between serum total testosterone and HDL was observed [17]. Thus, in these two districts of West Bengal, low levels of serum total testosterone in elderly men are associated with CVD that appear together with an atherogenic lipid milieu that may be involved in pathogenesis of CVD. The molecular mechanism of sex hormone-induced changes in the serum lipid profile is incompletely understood [33]. However, there are evidence from animals, cell, and clinical studies that testosterone controls the expression of important regulatory protein involved in lipid and cholesterol metabolism namely, apolipoprotein A-1

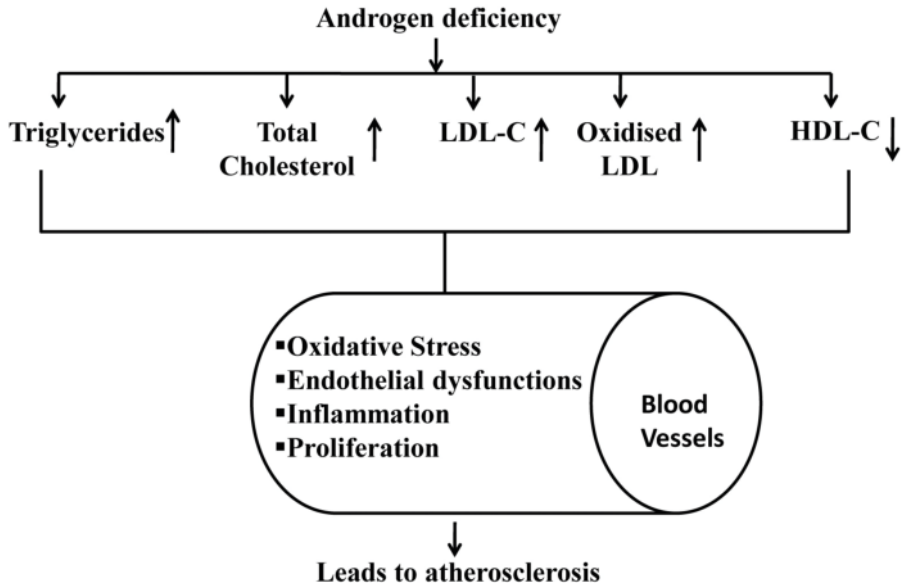

Figure 3.
Changes in lipid profile due to androgen deficiency, leading to atherosclerosis.

(apoA1) [44, 45], and scavenger receptor class B type 1 (SRB1) [46–48]. The major component of HDL is apoA1, which is secreted by the liver in lipid free or minimally lipidated form [44]. The interaction between apoA1 and lipid transfer ABCA1 present in the peripheral tissues results in the formation of minimally lipidated apoA1, which through a series of steps is converted to discoid shaped pre-HDL. This does not possess atheroprotective properties [45]. In addition to apoA1 and SRB1, lipoprotein modifying enzymes are also critical in maintenance of serum lipid homeostasis. One of the most important lipoprotein modifying enzymes is lipoprotein lipase (LPL), present on the endothelial cell surface [49]. Other enzymes are lecithin-cholesterol-acyl-transferase (LCAT) which esterifies the free cholesterol of HDL and cholesterol ester transferase protein (CETP), which mediates the exchange of cholesterol ester between HDL and LDL [44]. Testosterone might promote the expression of SRB1 receptor and facilitate the selective uptake of HDL, thereby exerting an antiatherogenic role [50]. A schematic association of testosterone deficiency and atherogenic lipid profile is depicted in **Figure 3**.

6. Relationship between low testosterone levels and cardiovascular risk factors

6.1 Role of androgens in hypertension

Hypertension is one of the major risk factors for developing CVDs leading to atherosclerosis and sudden cardiac death. Studies with human reveal that hypertension is more prevalent and occurs earlier in men than in women [51, 52]. Sexual dimorphism in blood pressure develops and is maintained until the age of 60 years [53–55]. Epidemiological data further indicate that women older than 60 years, show gradual increase in systolic blood pressure over a period of 5–20 years, until hypertension is highly prevalent in women as in men [55–57]. In hypertensive patients, treatment with antihypertensive drugs can reduce sexual activity and blood concentrations of testosterone [58, 59]. However, treatment of androgen to such patients found to exacerbate hypertension and increase the risk of CVDs [60–62]. There is also higher incidence of hypertension in individual with reduced free testosterone [63].

In animal studies, all major mouse and rat models (noncastrated, castrated, and anti-androgen treated) potential role for androgen in the pathogenesis of hypertension have been documented [55, 64]. In mice, castration and subsequent treatment with testosterone at high dose produce the onset of hypertension and further observed that this effect is mediated by androgen receptor [65]. Long back, it was found that *tfm* X chromosome (including a mutated non-functional AR) rats and castrated rats have lower blood pressure than intact control rats, suggesting that androgen/AR signaling pathway might be involved in hypertension [66]. Thus, androgen-AR signaling pathway appears to be involved in the regulation of hypertension in men and as androgen level reduce with increasing age this might have a deleterious effect on the development of hypertension. Antiandrogen treatment might be able to suppress hypertension. Moreover, some recent studies using AR knockout mice in selective cells suggest that AR in individual cell types may have independent role in the development of hypertension [67, 68].

6.2 Testosterone association in type 2 diabetes and insulin resistance, a risk factor of CVD

Low level of testosterone is associated with type 2 diabetes mellitus (T2DM) irrespective of age, race, and obesity [69–72]. High plasma testosterone level is

associated with reduced risk of developing T2DM [73]. Insulin resistance is the most common hyperglycemic condition and hallmark of T2DM [74]. It is a state where target cells are not responding to normal levels of circulating insulin leading to development of T2DM [75, 76]. An inverse relationship between total testosterone concentration and insulin resistance has also been reported in men [77, 78]. Clinical trials have demonstrated that testosterone administration improved insulin sensitivity, reduced glycaemia, and heart failure progression in men [79].

Cohort studies from Farmingham, Heart Study, EMAS, and Osteoporotic Fractures in Men study [80] and Western Australian Health in Men Study [81] reported that men with T2DM have lower testosterone levels compared with men without T2DM. In fact, different earlier studies showed that men with T2DM have 30–40% lower circulatory testosterone levels than that of healthy men [82–84]. In a study of 3156 men from various ethnic backgrounds, aged 45–84 years and after adjusting for age, ethnicity, BMI, it has been shown that T2DM and FBG levels are inversely associated with total testosterone concentration [70]. In a recent study with elderly male patients (40–70 years of age) of two district of West Bengal, we observed a highly significant negative correlation between serum total testosterone and FBG levels in CVD patients compared with non-CVD patients of same locality [17]. Our results further indicate that low levels of serum total testosterone might have role in the development of hyperglycemia as evidenced from high FBG levels in elderly men. Moreover, a recent study demonstrated that insulin resistance, hyperinsulinemia, and associated hyperglycemia can promote the development of specific form of cardio-morphopathy, which is independent of coronary artery disease and hypertension and a major cause of morbidity and mortality in developed countries [85]. It is characterized by myocardial insulin signaling, mitochondrial dysfunction, activation of sympathetic nervous system, activation of renin-angiotensin-aldosterone system, and male adaptive immune responses [86]. These patho-physiological changes result in oxidative stress, fibrosis, hypertrophy, cardiac diastolic dysfunction, and eventually systemic heart failure [87].

Association of testosterone deficiency with hyperglycemia has also been observed in animal model [88]. It has been demonstrated that castration-induced testosterone deficiency not only enhanced the hepatic gluconeogenesis but also decreased extra-hepatic insulin sensitivity in aged male rats [89]. Unpublished data from our laboratory also demonstrate that castration in adult male mice is followed by an increase in FBG level compared to sham operated control group and this increase in serum FBG levels was reversed after treatment with testosterone.

The mechanism linking androgen with T2DM and insulin receptor is not fully understood. Testosterone administration up-regulate the expression of GLUT-4, insulin receptor substrate-1 (IRS-1) in cultured adipocytes, and skeletal muscle cells [90]. Another study showed that testosterone promotes AKT and PKC phosphorylation, the major mediator of insulin receptor signaling, which regulate GLUT-4 translocation (**Figure 4**) [91]. The beneficial effects of testosterone on diabetes through increasing the metabolic rate in muscle promoting gain of energy from adipose tissue resulting decreased fat mass concentration has also been reported [92]. *In vitro* study of murine model also demonstrated that testosterone administration reduces β cell apoptosis [93], whereas, testosterone deficiency promote elevation of the expression of RBP4, which increases insulin resistance [94]. On the contrary, several studies demonstrate a non-positive correlation between testosterone supplementation and heart failure. Several clinical trials led to propose that testosterone supplementation at physiological doses could be a treatment for men with metabolic syndrome and heart failure [95].

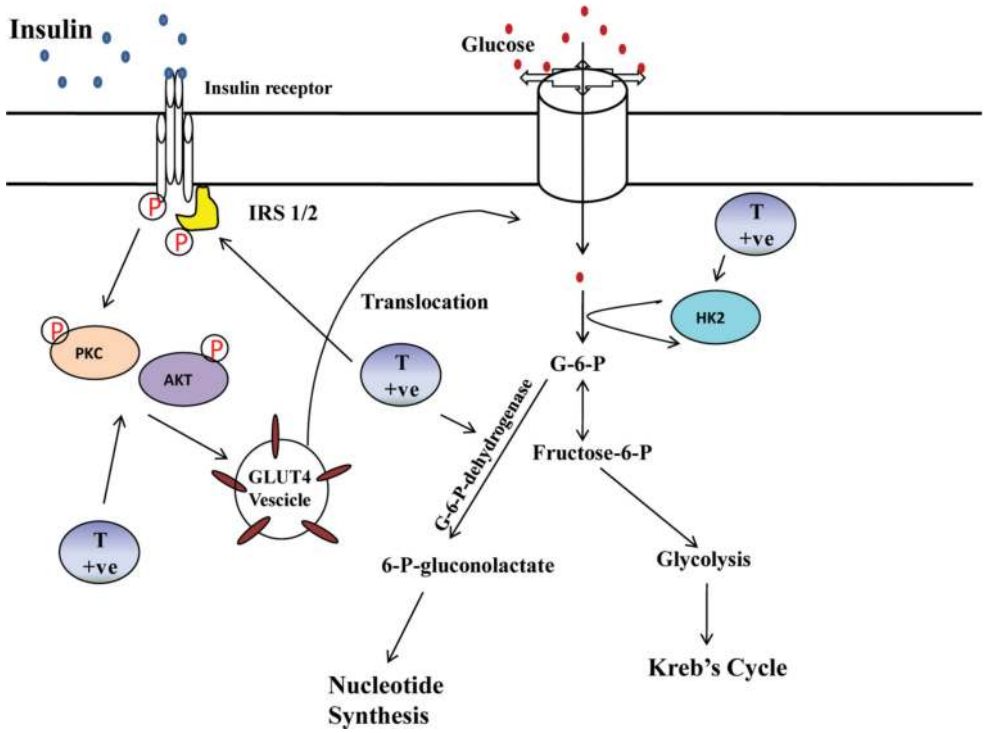

Figure 4.
Proposed mechanism of action of testosterone on cellular IRS activation leading to glucose homeostasis. Testosterone increases GLUT4 expression and membrane translocation which increases cellular uptake and utilization of glucose. Abbreviations: GLUT4, glucose transporter 4; G6P, glucose-6-phosphate; HK2, hexokinase 2; IRS, insulin receptor substrate; T +ve indicates targets or activity increased by testosterone PKC and AKT.

6.3 Testosterone and vascular inflammation

It is now well accepted that atherosclerosis is a chronic inflammatory disease. Individuals with hyperlipidaemia and signs of systemic inflammation develop atherosclerosis, with specific defects in lipid processing and immune activity consequentially occurring at the vessel wall. It is known that the activation of endothelial cells promotes the adhesion of leukocytes to the blood vessel wall as an early atherogenic event leading to increased vascular permeability for not only the inflammatory leukocytes, but also the circulating lipid components, such as LDL [96]. It has been suggested from observational studies that many pro-inflammatory cytokines like interleukin 1β (IL-1β), IL 6, TNF-α, C-reactive protein (CRP), and serum testosterone levels are inversely related in patients with CVDs and T2DM [97–99]. These inflammatory cytokines are known to modulate lipid metabolism, endothelial functions, and atherosclerosis [100]. Testosterone has been reported to reduce the levels of TNF-α and elevated circulating anti-inflammatory IL-10 [101, 102] and circulating CRP [102] in hypogonadal men with CVDs. *In vitro* studies also support the protective effect of testosterone supplementation on atherosclerosis, but the mechanism is not fully known [103, 104].

7. Testosterone deficiency and vascular functions

A negative correlation between testosterone and hypertension has already been discussed. In a subpopulation study of 206 aged males, it was shown that serum testosterone level is an independent negative predictor for developing arterial

stiffness and this association remained after adjusting for the other risk factors [105]. Carotid-intima media thickness (IMT) is a marker for CVDs [106]. The relationship among the progression of carotid-IMT, atherosclerotic plaque formation, and total testosterone was investigated and an inverse relationship between this hormone and atherosclerotic plaque formation was observed. This study also reported for a positive co-relation between carotid-IMT and atherosclerosis [107]. Men with low serum testosterone level exhibit higher IMT compared to normal control [108–110]. Long term testosterone administration reduced carotid-IMT in men with CVDs [111, 112]. Animal models also demonstrated that castration or hypogonadism in mice or rabbits fed a pro-artherogenic diet results in increased atherosclerosis and testosterone supplementation inhibits plaque formation [113]. The cellular and molecular mechanism by which testosterone induced IMT is little understood. Other studies, however, have shown that testosterone may reduce IMT by down regulating the inflammatory response or acting as a regulator of apoptosis or increasing vascular smooth muscle cell stability [7].

Endothelial cells play an important role in atherosclerosis, regulation of vascular tone and forming a barrier that regulates the uptake of cells and macromolecules into the vessel wall [114]. Clinical evidence suggests a link between testosterone deficiency and endothelial dysfunction [115–117]. Flow-mediated dilation (FMD), which represents endothelial dysfunction is decreased in men with testosterone deficiency and increased after exogenous administration of the steroid [118, 119]. Testosterone can exert direct effects on various cells of vascular wall by activation of androgen receptor or by non-genomic effects on plasma-membrane receptors and channels [114]. Testosterone can modulate calcium flux by mechanism that is independent of androgen and estrogen receptors in macrophages and endothelial cells [120]. Androgen receptors are expressed in endothelial cells, smooth muscle cells, and cardiomyocytes and all of these are relevant to atherosclerosis and heart failure [121]. It has also been demonstrated that testosterone may improve endothelial function through modulation of nitric oxide (NO) release. Endothelium-produced NO plays a variety of roles in vascular function maintenance like vasodilatation, inhibition of cell death, and platelet aggregation [96, 122].

8. Role of androgens in cardiac hypertrophy

Cardiac growth can be divided into two categories: normal growth in the developmental process and cardiac hypertrophy induced by hemodynamic overload. Since cardiomyocytes are terminally differentiated and lost their ability to multiply soon after birth, they respond to increased workload by an increase in cell size (hypertrophy), not by an increase in cell number (hyperplasia). Cardiac hypertrophy is prevalent in men with hypertension and recognized as an independent risk factor for congestive heart failure and sudden cardiac death [123]. The most impressive evidence of the effect of androgens on heart is the case of highly conditioned athletes, who died by sudden cardiac death. Examination of such death indicated anatomical abnormalities in heart, known as hypertrophy-cardiac myopathy [124]. Since, the net weight of heart is increased as a result of individual cardio-myocyte, the cardiac hypertrophy is assessed as heart weight to body weight ratio and left ventricular hypertrophy (LVH). LVH is the most potent predictor of adverse cardiovascular outcomes in hypertensive populations and is independent risk factors for coronary heart disease, sudden death, heart failure, and stroke. Clinically LVH is diagnosed by evaluating ventricular functions, such as left ventricular ejection fraction, left ventricular shortening fraction, end-systolic, and end-diastolic volume by electro physiological studies. Although directly related to

systolic blood pressure, other factors including age, sex, race, body mass index, and stimulation of renin-angiotensin-aldosterone system and sympathetic nervous system play an important role of pathogenesis of LVH. LVH is associated both with hypertension and increased cardiovascular morbidity and mortality [125], and it has been suggested that testosterone could be influential in modulating left ventricular mass [126]. Low level of testosterone in male is associated with high blood pressure and left ventricular mass [127]. Interestingly, this association is mediated through obesity. Very recently, it has also been suggested that testosterone can induce hypertrophy in rat heart, which is independent of exposure duration [128].

A central link for the development of skeletal muscle hypertrophy is the activation of mammalian target of rapamycin (mTOR) [129, 130], which also have been reported in testosterone-induced cardiomyocyte hypertrophy [131]. Both type I and type II skeletal muscle fibers have shown to respond in testosterone treatment increasing muscle mass, cross-sectional areas (CSA), and satellite cell number after hormone administration [132]. Testosterone and its synthetic cognates have been used both clinically and illicitly to increase muscle mass [133]. However, the cellular mechanism explaining these effects is not completely understood. Different cellular and molecular mechanisms are shown to be involved in skeletal muscle hypertrophy induced by testosterone, including promotion of nuclear accretion, entry of satellite cells into cell cycle [132–134], and activation of intracellular androgen receptor [135]. Besides regulating gene expression via AR, testosterone also produces fast, non-transcriptional responses involving membrane-linked signal transduction pathways [12]. A rapid non-genomic action exerted via G-protein coupled receptor, intracellular calcium increases, and extracellular signal regulated kinase ½ (ERK 1/2) activation has been described for the action of testosterone in skeletal myotubes [136]. Recently, a cellular lineage of myoblast, which lack the classical AR (L6 myoblast), testosterone has shown to promote the proliferation and differentiation of L6 cell via G-protein coupled receptor [137]. Altogether, these data suggest that in men testosterone, increased cardiac hypertrophy and aside from classical mechanism of action of testosterone, non-classical actions are also implicated in development of cardiac hypertrophy.

9. Testosterone replacement therapy in CVD patients

Testosterone replacement therapy (TRT) is increasingly promoted and suggested to be a possible curative way for the adverse effect of low testosterone on CVDs in elderly men. Whereas, the effectiveness of TRT in hypogonadal men has been shown to be effective in alleviating the symptoms of fatigue, sexual dysfunction, depression, decreased bone density, decreased muscle mass, among others [138–141], uncertainties remain with respect to cardiovascular safety for its use. In 2004, a committee on assessing the need for clinical trial of testosterone replacement therapy by Institute of Medicine (IOM) in a review concluded largely based on placebo control trials and show that there is no clear evidence on benefit of the heath outcome examined. In fact, no positive effect of TRT on cardiovascular events was observed [142–144]. Observational studies evaluating the cardiovascular safety of TRT in men have also generated inconsistent results [145, 146]. An independent review conducted by European Medicines Agency (EMA) also found a lack of consistent evidence for TRT increasing cardiovascular risks (European Medicines Agency (EMA)), 2015 [147]. Very recently, in systematically review and meta-analysis by various authors did not find any significant association between exogeneous testosterone treatment and myocardial infarction, stroke or morbidity of randomized control trials [148, 149]. But, a recent study demonstrated that testosterone treatment in men with low

endogenous testosterone shows improved survival rate in CVD patients [150]. Physiological replacement of testosterone has been shown to decrease cholesterol level and LDL concentration in men [101, 151]. Studies on the effect of TRT on HDL concentration yielded conflicting result with either a decrease [152] or no changes [102, 153]. Other investigators observed an increase in concentration of HDL level after testosterone administration [154]. In a recent study on the effects of TRT on lipid metabolism in hypogonadal men with T2DM, it has been hypothesized that because the relationship between lipid metabolism and artherosclerosis are unequivocal, TRT, which ameliorates lipid metabolism, may decrease the morbidity and mortality of CVD in hypogonadal men with T2DM by preventing atherogenesis [155]. Data from randomized placebo-controlled trials (RCTs) suggest that treatment with testosterone is not effective in reducing CV risk; however, when TRT is correctly applied, it is not associated with an increase in CV risk and it may have beneficial effects in sub-population [156]. On the contrary, available reports indicated that TRT is positively correlated with increased cardiovascular risk [157]. It has been reported that those who are under TRT showed increased risk of CVDs [158, 159]. A systemic review and meta-analysis of the effect of testosterone therapy on cardiovascular events showed that testosterone increases cardiovascular related events among men. The risk of TRT was particularly marked in trials [160].

10. Effects of testosterone on myocardial infarction

The myocardial cells undergo a dynamic repair process after myocardial infarction (MI), which is also regulated by hormonal factors and characterized by removal of necrotic tissue and chamber dilatation for so-called "cardiac remodeling" [161]. Recent cohort studies and meta-analyses of randomized clinical trials reported that testosterone therapy is associated with an increased risk of MI, ischemic stroke, and overall mortality [157, 159]. Supplemental testosterone treatment dramatically increased cardiac rupture and mortality in female mice with or without ovariectomy, whereas castration significantly decreased both the events in males [160]. This indicates role of testosterone is sex specific and even hypotesteronemic condition is good for MI associated cardiac remodeling. Findings suggest that testosterone may adversely affect myocardial healing and early remodeling during the acute phase of MI, causing the observed "gender difference." However, this is highly controversial and association between testosterone therapies and cardiovascular disease is complex and need more dose-specific and time-specific statistical analyses and molecular studies to conclude that whether TRT is beneficial or not.

11. Conclusion

For last two decades, androgens have attracted significant interest in explaining the gender difference in CVDs. Although, strong evidences show that testosterone is associated with prevalence of CVDs and affects several key cardiovascular risk factors and increase the risk of cardiovascular mortality, significant independent association between androgen levels and cardiovascular events in men have not been confirmed in large prospective studies. Effects of testosterone therapy on cardiovascular mortality have not also been definitely confirmed in prospective controlled studies. Testosterone administration in men and animal induces both beneficial and deleterious effects on cardiovascular risk factors. Further research in this field is necessary to know the real cardiovascular effects of androgen and to understand the role of androgen in therapeutic applications in CVDs.

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