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Testosterone, myocardial function, and mortality

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Abstract
The cardiovascular system is particularly sensitive to androgens, but some controversies exist regarding the effect of testosterone on the heart. While among anabolic abusers, cases of sudden cardiac death have been described, recently it was reported that low serum level of testosterone was correlated with increased risk of cardiovascular diseases (CVD) and mortality rate. This review aims to evaluate the effect of testosterone on myocardial tissue function, coronary artery disease (CAD), and death. Low testosterone level is associated with increased incidence of CAD and mortality. Testosterone administration in hypogonadal elderly men and women has a positive effect on cardiovascular function and improved clinical outcomes and survival time. Although at supraphysiologic doses, androgen may have a toxic effect, and at physiological levels, testosterone is safe and exerts a beneficial effect on myocardial function including mechanisms at cellular and mitochondrial level. The interaction with free testosterone and estradiol should be considered. Further studies are necessary to better understand the interaction mechanisms for an optimal androgen therapy in CVD.

Keywords Testosterone · Coronary artery disease · Heart failure · Cardiovascular disease · Cardiomyocytes · Cardiac mitochondria · Cardiovascular mortality

Introduction

The effects of testosterone on myocardial function have generated a great deal of discussion in the literature but remain controversial. Previous studies have found that in men of all range of age the administration of testosterone resulted in an increased cardiovascular risk [1–3]. The abuse of androgens in bodybuilders has been associated with myocardial infarction (MI) [4–12]. Higher doses of androgens have been considered toxic on the cardiovascular system [13–15], but no association between incidence of acute cardiac events among frequent users of androgens has been found [16, 17]. Recently, an increasing number of clinical trials showed lower testosterone levels were observed in men with a greater incidence of CVD and mortality had lower testosterone levels.

The decline of testosterone level in men is a physiological process due to increasing age [18], but many pathophysiologic processes such as malnutrition, sedentary lifestyle [19], and chronic diseases (type 2 diabetes, obesity, etc.) play an essential role [20]. Asymptomatic hypogonadism is observed in men 30–79 years old with an incidence of about 5.6% [21] and is more relevant in aging subjects. In recent years, prescriptions for testosterone replacement therapy have increased tremendously, 500% from 1993 until today [22]. This degree of increase suggests that many are not necessary [23], probably due to self-prescription sustained by advertising. This review provides an update on the implications of testosterone for cardiovascular function and attempts to explain its role at the molecular and cellular level.

Testosterone effects on cardiomyocytes

Testosterone has a substantial protective effect on cardiomyocytes inhibiting apoptosis and cardiac fibrosis through various mechanisms of actions demonstrated at molecular and cellular levels [24]. The administration of testosterone has a significant protective anti-ischemic function on myocardial tissue in rats [25] and in humans [25], as well as in the heart following ischemia/reperfusion [26]. Testosterone exerts a protective effect on cardiomyocytes increasing the the level of peroxisome proliferator-activated receptor α (PPARα), that is an important nuclear regulator of fatty acid metabolism in cardiomyocytes [27] and by reducing the oxidative injury through the stimulation of the NF-κB (nuclear

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factor kappa-light-chain-enhancer of activated B cells) expression [28] and the Akt activity (that promotes survival and growth in response to extracellular signals) [29]. NF-κB is a protein involved in various processes of cell proliferation and survival in response to biochemical or bacterial antigens [30]. NF-κB regulates anti-apoptotic genes, representing a critical molecular key protecting cardiomyocytes and reducing the superoxid cellular injury and necrotic death [28]. By stimulating the sarcoendoplasmic reticulum Ca(2+)-ATPase, testosterone enhances cardiomyocytes relaxation [31] and increases cardiac contraction [32]. These mechanisms in subjects with testosterone deficiency are compromised, but they still remain to be wholly clarified in subjects with testosterone deficiency.

Furthermore, testosterone has a protective effect on mitochondria. The impaired mitochondria function decreases ATP production while increasing the reactive oxygen species (ROS) formation [33] as observed in cardiac aging. In castrated rats, the induction of a myocardial infarction (MI) caused a severe alteration in mitochondrial structures leading to cardiomyocyte apoptosis and impaired cardiac function [34]. These mitochondrial alterations were reversed by testosterone supplementation, with an associated increase in the AMP-activated protein kinase (AMPK, which is essential in the regulation of cellular energy homeostasis stimulated also by caloric restriction) and the activation of peroxisome proliferator-activated receptor-γ coactivator 1 (PGC1α, a co-activator of mitochondrial biogenesis in the cells) [34]. Testosterone administration increased the expression levels of PGC1α, ATP5B (a subunit of mitochondrial ATP synthase), and Cox4 (a terminal enzyme of the mitochondrial respiratory chain) in the skeletal muscle [35]. Apoptosis of cardiomyocytes and oxidative stress is reduced by testosterone upregulation of Akt phosphorylation in cardiac myoblast [36]. Testosterone inhibits the ROS formation at physiological plasma levels; however, a supraphysiologic level has an opposite effect reducing the formation of nitric oxide and increasing oxidative stress at the cellular level [37] and mitochondrial dysfunction as observed in leukocytes during induction to female-to-male transsexuals change [38].

Androgen receptors and cardiovascular system

Testosterone effects on the CVD system in men are mediated by its direct interaction with androgen receptor (AR) and, after its aromatization in 17β-estradiol, with estrogen receptors (ER) (Fig. 1). The expression of the AR has been demonstrated in vascular cells in rabbits, dogs, monkeys, and humans [39], and in endothelial cells, macrophages, and platelets [40] and has permitted investigations on how androgens modulate the cardiac phenotype and predispose to cardiac hypertrophy [41]. In animal models, inactivation of AR in the heart reduces the cardiac growth significantly [42] while the activation of AR modulates the hypertrophic and fibrotic response to cardiac remodeling under stress conditions [43]. AR activation

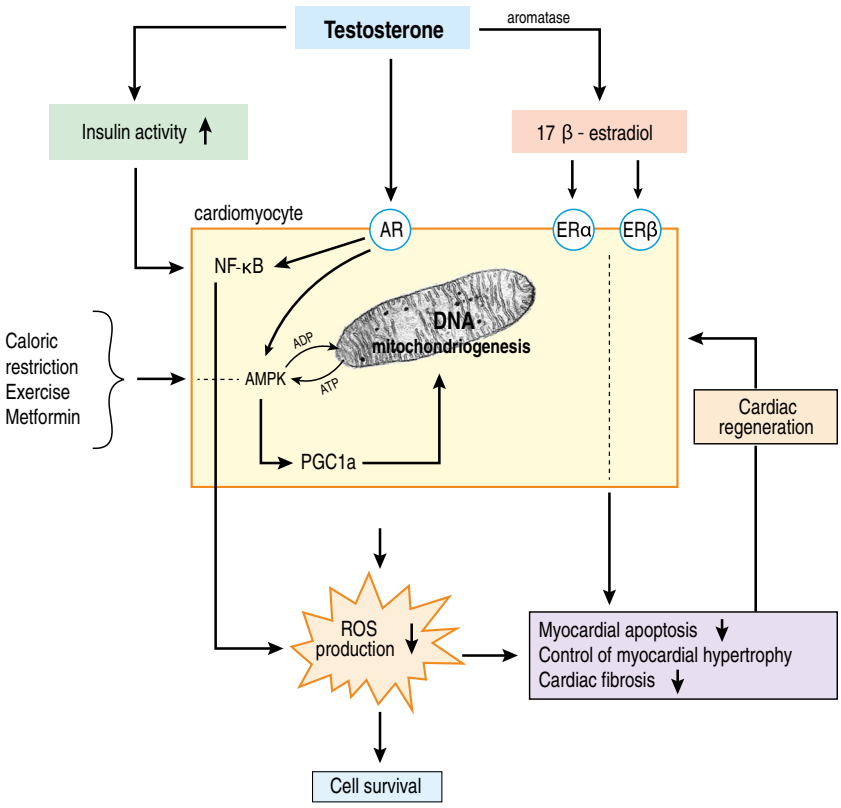

Fig. 1 Testosterone improve insulin sensitivity and acts directly on cardiomyocytes activating AR (androgen receptor), AMPK, and PGC1 that increase mitochondrial biogenesis and autophagy. Testosterone after the conversion in 17β-estradiol due to aromatization activates the ERα and ERβ. The increased efficiency of mitochondria reduces the release of ROS and apoptosis

protects from cardiotoxicity [36] and senescence induced by doxorubicin [24]. Low expression of AR in a coronary artery is highly correlated with CVD and sudden death [44]. In men, physiological levels of androgens inhibit the development of atherosclerosis [45] and AR expression is associated with reduced incidence of coronary artery disease (CAD) [44] and modulate angiogenesis in a sex-dependent manner [46].

The role of estrogen receptor

Estrogen receptors, both type α (ERα) and type β (ERβ) are also expressed in cardiomyocytes [47], and on coronary arteries of monkeys and humans [48–51]. The presence of aromatase, the enzyme that converts testosterone in 17β-estradiol in the heart, has been demonstrated [52] evidencing the importance of estrogen activity in the myocardial tissue. Estradiol is involved in cardiac growth [53] and modulates the extension of the ischemic lesion in the infarcted heart [54]. Estrogen receptors (ERα and not ERβ) are essential in the regulation of myocyte contraction [55] and improve cardiac function after MI in both sexes by the reduction in -cardiac fibrosis [56]. It seems that androgens are involved in the process of myocardial hypertrophy [57–59] while estrogens have a preventive effect. So that estrogen deficiency is deleterious on cardiomyocytes function and the androgen-to-estrogen conversion is of pathophysiologic and clinical importance. The effects of testosterone on cardiomyocytes are modulated by estrogen, suggesting the need to determine both testosterone and estradiol circulating levels during a clinical evaluation.

Testosterone and cardiac electrophysiology

Sex steroids govern the human cardiac ventricular repolarization and arrhythmias [60]. Prolongation of the QT interval represents a risk factor for ventricular arrhythmias, including Torsade de Pointe [61]. Sex steroids are involved in determining morphologic differences of the ventricular repolarization between males and females [60, 62]. The QT interval in men is shorter than that in women (450 versus 470 msec), and the difference may be explained by differences in T levels [63]. A shorter QT interval is observed in healthy men of all age corresponding to the maximum level of serum T level from the ages of 9 up to 50 years [64] while lower levels of testosterone were correlated with more prolonged QT intervals. Hypogonadal men have been shown to have a significantly higher incidence of a prolonged QT [65, 66] [67], although this is not consistent in all studies [68] while estrogen and progesterone do not affect QT interval [69]. The administration of testosterone enanthate at the dose of 240 mg in a single intramuscular injection in nonobese men with hypogonadism decreased the QT interval length [63] and this has also been observed in patients with HF after testosterone administration [70]. In men with higher testosterone level, a shorter QTc interval can be explained by the prolongation of the RR interval [71]. How testosterone influences the mechanisms of ventricular repolarization remains to be elucidated, but it seems that testosterone activates the potassium channel [72] and simultaneously reduces the activity of L-type calcium channels [73] and increases the repolarization reserve [74]. Among professional bodybuilders ingesting supraphysiological doses of anabolic steroids, a shorter QTc of ≤ 380 ms was observed [75, 76].

Testosterone and coronary artery disease

In castrated male animals, it was observed an increased development of atherosclerosis and reversed with testosterone replacement therapy showing an evident association between low serum testosterone level and the development of atherosclerosis [77]. In men under anti-androgen therapy due to prostate cancer, an increased incidence of heart failure (HF) [78–81] and cardiovascular mortality [82] has been observed. Diabetic patients with a low serum testosterone level have a higher incidence of CAD than in those with a normal testosterone level [83].

Various clinical studies have investigated the correlation between testosterone level with CAD in men [45, 84–96] and are reported in Table 1. In male patients evaluated with coronary angiography, the severity of the coronary atherosclerosis was highly related to a lower testosterone levels [94–96]. Other studies were conducted evaluating the carotid artery through ultrasonography and evidenced that low total testosterone level was associated with carotid intima-media thickness [45, 86, 92, 97], with total carotid plaque area [91], and with intermittent claudication [93]. Testosterone administration inhibited the progression of non-calcified coronary plaque progression [85]. Taken together, these studies demonstrated that androgens had a protective effect on the development of CAD. However, Srinath et al. [89] did not find any correlation between low testosterone level with carotid intima-media thickness (cIMT). Basaria et al. [88] did not result in a significant change in either common carotid artery intima-media thickness or coronary artery calcium after testosterone therapy. Khazai et al. [87] found that in men without CVD, a lower free testosterone was correlated with the higher coronary artery calcium score (CACS) and total testosterone with the log of CACS, while it had an opposite effect on coronary intima-media thickness. Furthermore, Budoff et al. [84] found that testosterone therapy determined a significant increase in coronary artery non-calcified plaque volume. Interestingly, the Chun study [86] put in evidence a difference between patients with or without CAD in middle-aged men. The associations between testosterone, DHT, and 17β-estradiol with cIMT and carotid plaque differ according to the presence or not of premature

Table 1 Correlation between testosterone level and coronary artery disease (CAD)

Authors	Patients	Age	BMI	Type of study	Methods of investigation	Clinical effects
Budoff 2017 [84]	170 M T deficiency	70.5	30.6	Double-blinded, placebo-controlled trial	Coronary computed tomographic angiography	T therapy associated with a significantly greater increase in coronary artery non-calcified plaque volume.
Khazai 2016 [87]	3164 M Without CAD	62.2	27.8	Prospective studies	Ultrasonography	Lower FT was associated with higher RR of CACS and lower TT is associated with higher log CACS. Lower BT and TT are associated with lower cIMT.
Abd Alamir 2016 [85]	165 M T deficiency	71.1	28	Double-blind, placebo-controlled trial	Coronary computed tomographic angiography	T therapy inhibited non-calcified coronary plaque progression.
Chan 2015 [86]	492 M without CAD 426 (B) M with CAD	53.8 49.6	26.8 CRP 2.-8	Cross-sectional study	Ultrasonography	Higher T was associated with reduced CIMT lower prevalence of carotid plaque while higher E2 is associated with worse CIMT.
Srinath 2015 [89]	1558 M with CHD	63.1	___	Cross-sectional study	Ultrasonography	Low T was correlated with CVD risk factors, but no association with cIMT, cardiac events, or mortality.
Yeap 2013 [93]	268 M intermittent claudication	70–89	>25	Cross-sectional study	Edinburgh Claudication Questionnaire	Lower T or DHT levels, but not E2, were associated with symptoms of intermittent claudication in older men.
Basaria 2015 [88]	156 M T deficiency	66.9	28	Randomized controlled trial	Ultrasonography	T therapy in men with low T levels did not show significant difference in either common CMT thickness or coronary artery calcium score
Soisson 2012 [92]	354 M	64	___	Multicenter study	Carotid ultrasonography	Low plasma T associated with elevated CMT thickness only in those with low-grade inflammation and depended on C-reactive protein.
HU 2012 [95]	87 M CAD	51	24.5	Cross-sectional study	Coronarography	In men with CAD, a low T level was correlated with the severity of coronary artery stenosis (Gensini score).
LI 2012 [94]	803 M	66	25.5	Cross-sectional study	Coronarography	Lower T level was correlated with coronary artery stenosis and higher Gensini score.
Vikan 2009 [91]	1101 M	66.3	26.9	Prospective study	Ultrasonography	An inverse association between testosterone levels with iCMT and total carotid plaque area, but no prospective associations were found.
Ouyang 2009 [90]	1947 PMW	65.6	28.3	Cross-sectional study	Ultrasonography + computed tomographic chest scans	In postmenopausal women, T was correlated with greater cIMT while SHBG is negatively correlated. SHBG and T were associated with extent of coronary calcium but in the opposite direction compared to cIMT.
Debing 2008 [86]	124 M Carotid atherosclero-sis			Case-control study	Ultrasonography	Low serum TT levels was correlated with severe internal carotid atherosclerosis.
Svartberg 2006 [45]	1482 M Trompso study	60.3	26.1	Population-based cross-sectional study	Ultrasonography	Inverse association between TT levels and cIMT in men but was not independent of BMI.
Phillips 1994 [96]	55 No previous MI	60.7	26.9	Cross-sectional study	Coronarography	Low T was correlated with the degree of coronary artery stenosis and inflammatory markers.

M men, *PMW* postmenopausal women, *T2D* type 2 diabetes, *T* testosterone, *FT* free testosterone, *TT* total testosterone, *DHT* dihydrotestosterone, E2=17beta-estradiol, SHBG=sex hormone binding globulin, *CACS* coronary artery calcium score, *cIMT* carotid intima-media thickness, *BMI* body mass index

CAD. Furthermore, the level of estradiol and free testosterone are more informative than only total testosterone. In the Basaria et al. [88] and Budoff et al. [84] study, the level of estradiol were low (19.7 and 21.8 pg/mL) and 31% of patients were diabetics and 40% obese respectively and no inflammatory markers were detected.

In postmenopausal women, the impact of androgen on the development of CHD remains controversial. In postmenopausal women, testosterone was positively correlated with a

greater cIMT [90] and a meta-analysis showed that increased androgen levels and SHBG were correlated with CHD [98].In women with polycystic ovary syndrome (PCOS), no significant rise in CAD incidence was found [99]. In women of all ages, a high (but in the physiological range) free testosterone and androstenedione were correlated with the lower prevalence of atherosclerosis [100, 101] and a lower rate of coronary events [102]. The Rotterdam Study, a prospective population-based cohort study, found no increased risk for CVD in postmenopausal women with the higher androgen levels and better cardiovascular health in PCOS women [103]. The reduced frequency of fatal cardiovascular events in women compared to men is attributable to the interaction between androgen and estrogen which has an intrinsic cardioprotective effect and explains such sex dimorphism [104].

Angina pectoris It has long been known that both acute and chronic testosterone administration is beneficial in angina pectoris. The direct infusion of testosterone at physiological concentration caused acute coronary vasodilation in patients with CAD [105–108]. The acute effects of testosterone administration intravenously (time ranging from 5 to 20 min) have shown a significant vasodilator effect. Chronic administration of testosterone in men with chronic stable angina reduced the myocardial ischemia during the maximal exercise testing and the onset of ST depression [109–111]. In a crossover study, testosterone therapy in men with ischemic heart disease reduced angina pectoris by 77% and myocardial ischemia on ECG and Holter by 69 and 75% respectively [112]. Thompson et al. [108] in men without CAD the infusion of testosterone study had inconclusive data without beneficial or deleterious effect. The vasodilation induced by testosterone is evident in coronary, mesenteric, iliac, renal, and femoral arteries, and involves the vascular smooth muscle cells primarily [113]. The vasodilatory effect induced by testosterone on the peripheral vasculature is AR-independent, promotes nNOS activation, and results in hypotensive systemic impact [36, 114]. The responsiveness to testosterone appears to be reduced with age [115] (Table 2).

Testosterone and chronic heart failure

Chronic heart failure (CHF) is the most severe consequence of MI, and over the age of 60 years, about 10% of men and 8% of women are affected [116]. The mortality rate with CHF is high, approximately 50% of the patients will die in the 5 years following the diagnosis. Generally, a low testosterone level has been observed in patients with CHF [117–119]. Only a few studies have evaluated the effect of testosterone administration in CHF patients at physiological doses [120–126] and these are summarized in Table 3. Three hundred and five patients have been assessed with a mean age of 64.1 ± 3.2 and a mean ejection fraction of 32.9. The duration of follow-up varied from 6 weeks to 12 months, only one study evaluated short term (2 day). After testosterone therapy, an increase in physical capacity and improvements in clinical signs and muscular strength were reported, without changes in ejection fraction. Pugh et al. [123] demonstrated that the acute testosterone administration (60 mg for 2 days) induced favorable hemodynamic alterations with an increase in ejection fraction and reduced left ventricular afterload. In CHF patients, a complex hormonal imbalance is observed, mainly due to testosterone deficiency [119]. The low testosterone level in CHF patients is an independent predictor of exercise intolerance [127] and is associated with increased mortality [128].

The effect of testosterone on cardiomyocytes and cardiac function in CHF patients is not fully understood. Only Pugh et al. [123] has reported an increased cardiac output after testosterone administration in patients with HF. The majority of studies have shown improvements in protein synthesis, muscle mass and strength, and baroreflex sensitivity [121, 124].

Table 2 Effect of acute and chronic administration of testosterone on angina pectoris. *M* men, *CAD* coronary artery disease

Authors	No. of patients	Dosage	Duration	Effects
Jaffe 1977 [109]	50	200 mg/week	1 month	Reduced post-exercise ST-segment depression.
Wu 1993 [112]	62	40–120 mg/day	1 month	T improved myocardial ischemia in ECG and Holter recordings .
English 2000 [110]	46	5 mg/day	3 months	Low doses T treatment in men with chronic stable angina reduced exercise-induced myocardial ischemia.
Mathur 2009 [111]	15	Nebido 1000 mg	12 months	T increased time of exercise-induced ischemia .
Webb 1999 [107]	13 CAD (61 years)	2.3 mg iv	10 min	Administration of T-induced coronary artery dilatation and coronary blood flow in men with established CAD.
White CM 1998 [106]	15 CAD	300 μg iv	10 min	No hemodynamic differences or side effects were noted.
Rosano 1999 [105]	14 CAD (58 years)	2.5 mg iv	5 min	Beneficial effect on exercise-induced myocardial ischemia in men with CAD onset of 1-mm ST-segment depression.
Thompson 2002 [108]	32 M (69 years)	2–6 time normal level	20 min	Neither a beneficial nor a deleterious effect on the onset of ST-segment stress were induced.

Table 3 Effects of testosterone administration in CHF patients

Authors	Patients	Age	Androgen therapy	Follow-up duration	Ejection fraction	Clinical effects
Pugh 2003 [123]	12, M	62.8	T 60 mg/day buccal	2 days	30.9	Cardiac output increased
Pugh 2004 [120]	20, M	62	Sustanon 100 mg/every 2 weeks	12 weeks	35	Distance walked increased. No changes in cardiovascular function
Malkin 2006 [122]	76, M	64	5 mg/day transdermal	12 months	32.5	Exercise capacity increased for one functional class. No change in muscle strength
Caminiti 2009 [121]	70, M	70	T undecanoate (Nebido) 1000 mg/baseline/6/12 weeks	6 months	31.8	VO2max, muscle strength increased. IR improved.
Iellamo 2010 [124]	36, W	62.2	Transdermal patch 300 μg/twice/week	6 months	32.9	VO2max, distance walked, and muscular strength increased. IR improved.
Stout 2012 [125]	41, M	67.2	Sustanon 100 mg fotnight	12 weeks	21.3	VO2max, ejection fraction and muscle strength increased.
Mirdamadi 2014 [126]	50, M	60.8	T enanthate 250 mg/every 4 weeks	12 weeks	34.5	Functional capacity and muscular strength increased no changes in hemodynamic parameters

M men, *W* women, *IR* insulin resistance, *T* testosterone

Testosterone therapy in male CHF patients, when combined with a program of exercise rehabilitation, demonstrated favorable clinical outcomes with increased VO2 max and ejection fraction [125] and improved exercise capacity [129, 130]. Iellamo et al. [124] showed that transdermal administration of testosterone in women with stable CHF enhanced functional capacity, insulin resistance, and muscle strength and was well tolerated. Testosterone administration in CHF patients with hypogonadism improved the regulation of the beta-adrenergic system [131]. The modest number of clinical studies available for testosterone prescription in HF patients suggests that cardiologists have generally not considered testosterone a useful and safe therapy to this point.

Testosterone level and mortality risk

A physiological level of testosterone maintains normal health conditions and reduces the risk of mortality. Low testosterone level, as observed in men undergoing anti-androgen due to prostate cancer, causes a significant increase in the incidence of both CAD and CHF frequency [79], and a two-fold rise in cardiac mortality over a 10-year period [82]. Testosterone therapy in hypogonadal men reduced significantly the mortality rates [132].

The main clinical studies examining the relationship between serum level of testosterone and mortality risk are depicted in Table 4. Only two studies reported no association between testosterone level and mortality [133, 134]. The overall evidence indicates that low serum testosterone levels in men is associated with higher mortality rates; [89, 118, 133–165]. Shores et al. [166] found an 88% higher incidence of all-cause mortality in men with low testosterone level. Laughlin et al. [136] in a 20-year follow-up study reported a 44% higher risk of death among men with the lowest testosterone levels. The InChianty study [167] reported that low testosterone levels were associated with an increased risk of death during a 6-year follow-up. The European Prospective Investigation in Norfolk [135] observed an inverse correlation between serum testosterone level and cardiovascular and all-cause deaths in 11,606 healthy men. Malkin et al. [140] followed a group of men with angiographically demonstrated CAD for 7 years and found that testosterone-deficient men had higher mortality compared to those with normal T (21 versus 12%). Importantly, only biological and free testosterone were significantly associated with cardiovascular and all-cause mortality, but total testosterone was not [151, 162] suggesting that the free form of testosterone is a more significant predictor of mortality risk.

Controversies

The benefit of testosterone therapy on CVD progression remains controversial. However, testosterone replacement therapy has shown evidence of benefit in hypogonadal men [168] and to be safe with no detrimental effects on cardiovascular function [169] and left ventricular remodeling after MI or stroke [2, 170–173] and does not increase mortality risk [174] or incidence of MI [175]. Conversely, other studies found that testosterone therapy increased the incidence of cardiovascular events [176–179]. Schooling et al. [179] in a meta-analysis reported that in trials without pharmaceutical support, the administration of testosterone appears to be associated with a higher rate (8 vs 4%) of cardiovascular events. Vigen et al. [180] in a study including 8709 men, aged ≥ 60 years, found that testosterone administration increased the risk of a cardiovascular event by 5.8% compared to the subjects not receiving testosterone. One of the most critical points made in this study is that most men remained hypogonadal after testosterone therapy and some incorrect data (number of

Table 4 Relationship between serum level of testosterone and mortality

Authors	No. of patients	Mean age	Type of study	Range hormonal level	Time of follow-up	Comments
Jankowska 2006 [127]	208 M, HF	63	Follow-up	TT = 11–9 nmol/L DHEAS = 1411–310 ng/mL IGF-1 = 258–168 ng/mL	6 months	Deficiency of each anabolic hormone was a marker of higher mortality.
Shores 2006 [166]	858 M veterans	63.3	Clinical database	TT = < 6.6 nmol/L FT = < 0.015 nmol/L	4.3	Low T level was correlated with increased mortality risk
Araujo 2007 [149]	1709 M	40–70	Population-based cohort study	TT = ≥ 13.9 nmol/L FT = ≥ 0.28–12.0 nmol/L DHEAS = ≥ 21–32 nmol/L	15.3	Only free testosterone level positively associated with IHD mortality.
Laughlin 2008 [136]	797 M	73.6	Prospective, population-based study	TT = < 8.4 nmol/L BioT = 8.3 ng/dL	11.8 years	TT level in the lowest quartile was highly correlated with mortality rate.
Lehtonen 2008 [142]	187 M	71.5	Follow-up	TT = 20.2 nmol/L	10 years	TT was inversely associated with mortality, independent of confounding factors.
Khaw 2007 [135]	11.606 M	67.7	Prospective	TT = 15.8 nmol/L DHEAS = 2.82 ± 1.96 SHBG = 45.4 ± 18.3	7 years	Lower TT correlated with higher mortality for any cause (cardiovascular and cancer).
Carrero 2009 [147]	126 M, HD	66	Observational	Low TT = 6.3 nmol Low FT = 0.15 nmol/L	41 months	T concentrations inversely correlated with all-cause and CVD mortality.
Vikan 2009 [148]	1586 M	59.6	Population-based prospective cohort study	TT = 13.3 nmol/L FT = 0.20 mmol/L E2 = 0.06 nmol/L SHBG = 52.2 nmol/L	11.2 years	FT levels in the lowest quartile was correlated with increased risk of all-cause mortality, while TT was not.
Tivesten 2009 [137]	3014 M	75.4	Large prospective cohort study	TT = 15 nmol/L E2 = 20.9 pgr/ml FT = 0.28 nmol/mL FE = 0.36 pgr/mL	4.5 years	Low levels of TT and E2 were highly related to mortality risk.
Haring 2010 [134]	1954 M	63.1	Prospective population-based study of health in Pomerania	TT = 7.6 nmol/L DHEAS = 1.2 mg/mL	7.2 years	Low TT levels was associated with increased CVD and all-cause mortality rate.
Ohlsson 2010 [146]	2644 M	75.4	Observational	DHEA = 1.76 ng/mL DHEAS = 0.70 μg/mL TT = 15.6 nmol/L E2 = 20.9 pg/mL	4.5 years	Low serum levels of DHEA and DHEAS predicted death from all causes.
Menke 2010 [144]	1114 M	40	Prospective	TT = 11.1–27 nmol/L FT = 0.20 nmol/L BioT = 1.4 > 3.9 ng/mL SHBG = 19.8 > 59.1 nmol/L	16 years	Low FT and bioT levels were correlated with higher mortality risk. Not the other sex steroid.
Malkin 2010 [140]	930 M, CHD	60.7	Longitudinal	TT = 13.9 ± 7.4 nmol/L BioT = 4.3 ± 2.5 nmol/L	6.9 years ± 2.1	Low T level was common and correlated with mortality.
Corona 2010 [139]	1687 M, ED	66.2	Observational	TT = < 8 nmol/L	4.3 years	Fatal CV events were correlated with low T level and higher score of ANDROTEST
Ponikowska 2010 [150]	153 M, T2D, CAD	65	Follow-up	TT FT SHBG	19 months	T and DHEAS deficiencies were correlated with higher CV mortality
Militaru 2010 [145]	126 M, post MI	61.7	Observational	TT = Survivors 14.9 nmol/L Non survivors 7.3	30 days	Serum testosterone was significantly related to mortality, independent of confounder factors
Wu 2011 [160]	175 M, HF	68.5	Follow-up	TT = 20.3 nmol/L eFT = 0.28 nmol/L	3.46 years	TT and eFT were commonly decreased in elderly patients with systolic CHF and related to disease severity, but they were not independent predictors for mortality.
Wehr 2011 [128]	875 M, HF	61–74	Prospective	TT = 4.9–14.6 nmol/L SHBG = 91–> 37.8 nmol/L	7.7 years	No correlation of FT, TT, and SHBG levels with mortality was found, but low FT correlated with increased all-cause mortality in post-menopausal diabetic women.
Hyde 2012 [151]	3637 M	77	Population-based cohort study	TT = 15.4–> 14.8 nmol/L FT = 0.28 nmol/L SHBG = 41.7–> 46.4 nmol/L LH = 5.5–> 7.8 IU/L	5.1 years	Low FT predicteds mortality from CVD. Higher SHBG and LH were correlated with death from other causes.
Shores 2012 [161]	1031 M	40	Observational cohort	TT ≤ 8.7 nmol/L	4 years	The mortality in testosterone-treated men was 10.3% compared with 20.7% in untreated men
Haring 2013 [164]	254 M	75·5		TT = 14.9 nmol/L DHEAS = 78.9 mg/dL	10 years	

Table 4 (continued)

Authors	No. of patients	Mean age	Type of study	Range hormonal level	Time of follow-up	Comments
			Longitudinal epidemiological study	E2 = 21.8 pg/mL FSH = 7.2 IU/L LH = 8.8 IU/L		No significant association between sex steroids, gonadotrophins or their trajectories, and mortality.
Muraleedharan 2013 [154]	581 M, T2D	59.5	Follow-up	TT = 12.4 nmol/L SHBG = 32.2 nmol/L	6 years	Low T levels predicted an increase in all-cause mortality during long-term follow-up.
Yeap 2104 [162]	3690 M	70–85	Follow-up	TT = 12.8 nmol/L DHT = 1.4 nmol/L E2 = 71.6 pg/mL	10 years	Higher T and DHT correlated with the lower mortality rates from any cause.
Pye 2014 [155]	2599 M	60	Prospective study (European Male Aging Study)	TT = 16.56 nmol/L FT = 0.25 nmol/L SHBG = 53.3 nmol/L	4.3 years	Low T level was associated with substantially higher risks of all-cause and cardiovascular mortality.
Khurana 2014 [143]	2419 men, CKD stages 3–4	67.3	Retrospective studies	TT < 12.1 nmol/L	5.9 years	Low total testosterone level were associated with higher mortality in men with CKD stages 3–4
Shores 2014 [141]	1032 M	76	Longitudinal cohort study	TT = 9.6 nmol/L FT = 0.20 DHT = 45 ng/dL FDHT = 0.26 ng/dL	9.2 years	DHT and calculated free DHT were associated with incident CVD and all-cause mortality.
Srinath 2015 [89]	1558 M	63.1	Cross-sectional study	TT = 13.1 nmol/L Carotid IMT= 0.91–0.88 mm	12.8 years	Neither high nor low T levels directly predict atherosclerosis, but are a marker for other cardiovascular risk factors.
Holmboe 2015 [152]	5350 M, random	30–70	Prospective cohort study	TT = 20.6–> 18.9 nmol/L SHBG = 34.5–> 29.6 nmol/L FT = 0.15 nmol/L E2 = 96.5–88.6 nmol/L	30 years	Positive association of LH and LH/T with all-cause mortality. Lower CVD mortality was seen for men with T in the highest quartile compared to lowest.
Sharma 2015 [165]	83.010 M	66	Prospective studies	TT = Under normal limit	6.3 years	Normalization of TT levels after TRT was associated with a significant reduction in all-cause mortality, MI, and stroke.
Daka 2015 [159]	1109 M, T2D	62	Retrospective studies	TT = 13.5 nmol/L FT = 0.26 nmol/L SHBG = 39.2 nmol/L	14.1 years	Low T level predicted MI in men with type 2 diabetes independent of other risk factors.
Hacket 2016 [157]	857, M, T2D		Clinical trial	TT ≤ 12 nmol/L or FT ≤ 0.25 nmol/L	3.8 years	T was independently associated with reduced mortality in men with T2DM.
Tint 2016 [158]	531 M, T2D	66	Prospective studies	TT = 11.9 nmol/L SHBG = 37 nmol/L	7.6 years	Negative correlation of TT and SHBG with mortality.
Hamilton 2016 [156]	788 M, T2D	65.8	Longitudinal study	TT = 13.1 nmol/L	4 years	T level < 10 nmol/L was the cut-point in identifying an increased risk of anemia and death in men with type -2 diabetes,
Hsu 2016 [153]	958 M	76.9	Follow-up	TT = 4.1 ng/mL DHT = 0.4 ng/mL/L E2 = 25.2 pg/mL	5 years	Lower T and E2 was associated with all-cause mortality Not SHBG, LH, FSH, estrogen.
Yoshihisa 2018 [163]	618 M, HF	65.9	Follow-up	TT = 827.2 ng/dL (1st Q), TT = 546.6 ng/dL (2nd Q), TT = 376.6 ng/dL (3rd Q) TT = 165.1 ng/dL (4th Q)	8 years	TT level was associated with myocardial damage, lower exercise capacity, and was an independent predictor of all-cause mortality.

M men,*T2D* type -2 diabetes, *TT* total testosterone, *FT* free testosterone, *E2* 17-β estradiol, *DHT* dihydrotestosterone, *DHEAS* dehydroepiandrosterone, *SHBG* sex hormone-binding globulin, *HF* heart failure, *CKD* chronic kidney disease, *Q* quartile

patients excluded and included) make the results inconsistent. Finkle et al. [177] found that, in a cohort study of 55.593 patients, the first 90 days of testosterone therapy in younger and older men, there was an increased number of non-fatal MI. However, the validity and conclusions of the study are limited because it was used a large database not including information about metabolic and hormonal data and the clinical indications for the therapy. So that, it was not possible to discriminate if the excess of MI was correlated to a previous hypogonadism condition or to the level of testosterone following the therapy. Shores et al. [178] confirmed the difficulty establishing precisely the relationship between testosterone levels and mortality, in patients given testosterone, due to various confounding factors, and suggested that more specific clinical trials are necessary. Budoff et al. [84] found that testosterone administration in elderly men with low testosterone level was correlated with a significant increase in non-calcified coronary plaque volume. No acute cardiovascular events have been observed during the period of treatment. However, some criticism have been raised. First of all, the

coronary artery calcium score is more predictive than a non-calcified plaque in favoring future cardiac events [181]. Low total testosterone [182, 183] and low free testosterone levels [87] were associated with coronary artery calcification score but not with carotid intima-media thickness. The soft non-calcified plaque may suggest technical errors related to increased fibrous component useful to plaque stability [184]. Snyder et al. [185] did not find significant benefits on physical capacity and only moderate benefits on mood and sexual function in hypogonadal men treated with testosterone gel (Androgel for 1 year). However, in the study, neither free testosterone and 17β-estradiol nor inflammatory markers were detected, considering that 63% of patients were obese. As observed in other studies, the therapy with transdermal testosterone gel may be insufficient to cause metabolic changes (reach an effective metabolic activity). The normalization of serum testosterone level, although it is effective at the cellular level, per se, does not mean that it involves clinical improvement. The association of a hypocaloric diet and regular exercise are essential to reduce the inflammatory markers and potentiate the life-threatening testosterone effects. The relationship between testosterone and the development of atherosclerosis is complex and can be explained by the interference of various cardiac risk factors.

Further investigations are needed to establish the benefit of testosterone therapy in patients with increased cardiac risk factors and the modality and dosage of administration [186].

Future perspectives

Conflicting results about the benefit of testosterone therapy in patients with CVD are caused by the lack of well-designed protocols and large long-term, placebo-controlled, randomized clinical trials with an adequate statistic power [187]. Differences in methodology, including the influence of other hormones, such as free testosterone, 17β-estradiol, and IGF-1, can affect the results of these studies because it can give more information than only serum testosterone level. Furthermore, nutritional condition, weight changes and pro-inflammatory cytokines (IL-6, TNF-α, leptin, adiponectin) levels, and physical activity should be considered.

Conclusions

The conclusion derived from meta-analysis studies should be interpreted with caution because of the potential to overstate benefits of treatment from these studies [188]. However, the majority of clinical studies have demonstrated that androgen therapy yields positive effects on cardiac function and clinical outcomes. Nevertheless, the bulk of the evidence suggests that low testosterone level is deleterious for the health and may increase the risk of CAD, whereas the administration of testosterone therapy causes coronary vasodilation and cardioprotection in men. HF patients exhibit low testosterone levels and testosterone replacement improves physical capacity and clinical conditions. The low testosterone level in men is correlated with an increased cardiovascular risk and mortality rate.

A physiologic testosterone level is indispensable to maintain various important cellular and mitochondrial activities at the cardiomyocytes level. So that, the program of cardiac rehabilitation in CHF is deeply influenced by an adequate testosterone level. The current clinical evidence has shown that testosterone therapy is safe and does not support increased health risks. Finally, in CVD patients, the addition of dietary intervention and regular exercise improved the clinical outcomes significantly [189]. Low testosterone level should be considered a cardiovascular risk factor. Knowledge of the specific mechanisms by which testosterone acts on myocardial tissue are necessary and can bring about novel therapeutic strategies in CVD patients.

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