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REVIEW

Androgens and cardiac diseases

Androgeni e cardiopatie

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ABSTRACT: ***Androgens and cardiac diseases. V. Bianchi, A. Mezzani.***

Although androgens have been considered deleterious for the cardiovascular system, recent data have demonstrated favourable testosterone effects on cardiac and vascular remodeling and clinical outcome. However, the cardiovascular risk-benefit profile of testosterone therapy remains largely elusive due to lack of well-designed and adequately powered randomized clinical trials. In any case, a large body of clinical evidence underlines that low plasma testosterone levels should be considered a risk factor for cardiovascular disease, and that the evaluation of sex steroids should be included in the routine clinical evaluation of cardiac patients. A better understanding of the mechanism regulating the effects of testosterone on cardiovascular system could lead to novel therapeutic strategies in several cardiac patient populations, such as chronic heart failure patients and those who recently underwent cardiac surgery.

Keywords: testosterone, androgens, cardiac disease, cardiovascular risk.

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Androgens in normal humans

Human androgens comprise testosterone (T), dihydrotestosterone (DHT), androstenedione and dehydroepiandrosterone (DHEA) and its sulfate. Most of T is secreted by the testis in males and by the ovary in females. Approximately 5% of serum T is transformed in DHTby a 5α-reduction process, with DHT having a threefold greater affinity than T and a 15- to 30-fold greater affinity than adrenal androgens for androgen receptors. DHEA and dehydroepiandrosterone sulfate, the most abundant adrenal steroids in humans, are precursors of the intracellular production of androgens and estrogens in non-reproductive tissues. Most T is bound to plasma proteins, namely, 40-50% to albumin and 50-60% to sex hormone-binding globulin, with 1-2% being free [1]. Part of T is converted by the aromatase enzyme in estradiol, so that T is active through three ways: i) by directly activating the androgen receptors, ii) by indirectly activating the androgen receptors as DHT, and iii) by activating the estrogen receptors α and β (ERα and ERβ) after conversion to estradiol [2] (Figure 1).

Androgens and aging

Many cross-sectional studies have demonstrated lower concentrations of circulating and/or free T in elderly men [3-6]. The study by Harman [7] is the largest longitudinal evaluation of the effects of aging on male gonadal hormone function reported to date, strongly supporting the concept of an age-related lowering of both total and bioavailable circulating T levels at a relatively constant rate, independently of obesity, illness, medications, cigarette smoking and/or alcohol intake. Moreover, a prospective cohort study about endocrine functioning in men found that the decline in total and free serum T is associated not only to aging, but to lifestyle as well [8], namely, nutrition and physical activity. Of note, asymptomatic hypogonadism has a high prevalence in the general US population, on average equal to 5.6% in men 30-79 years of age, and increases with increasing age. Hence, the aging of the western countries male population will likely cause a large increase of androgen deficiency [9].

Androgens effects on cardiovascular system

Androgens and heart remodeling

Information about the important role played by the androgen receptors system on cardiovascular function has been gained by male androgen receptors-knockout mice. Experimental use of these mice with inactivated androgen receptors has providedinsights into the functional activities of androgens in adipocytes [10], brain [11], bone [12] and cardiovascular system [13].

Androgen receptors are present in cardiac myocytes of multiple species, including normal men and women, allowing androgens to modulate the cardiac phenotype and produce hypertrophy by direct, receptor-specific mechanisms [14]. The studies of Ikeda [13] demonstrated that in male mice, the androgen receptors system participates in normal

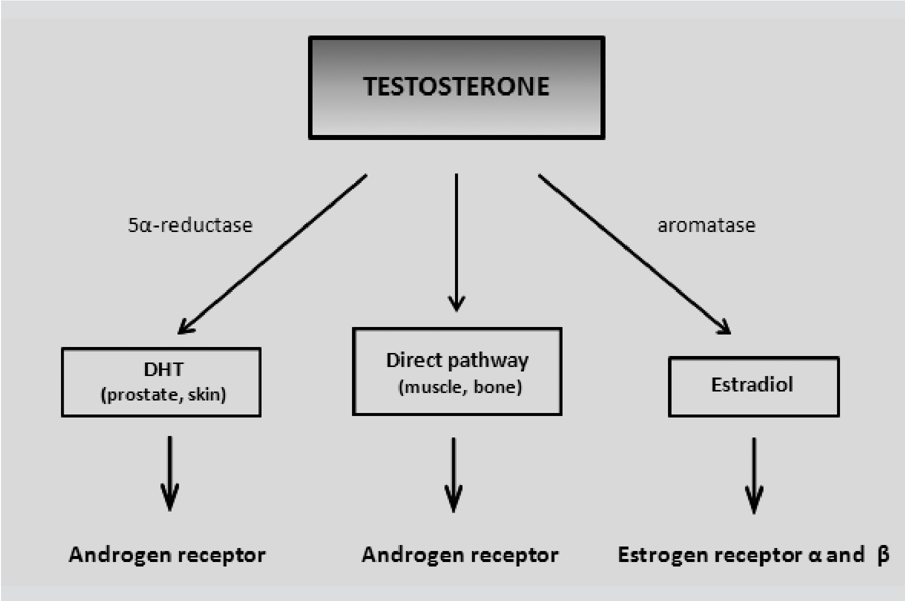

Figure 1. Pathways of testosterone action.

Testosterone directly activates the androgen receptors. In some organs rich of the 5α-reductase enzyme, such as prostate and hair follicles, the effect of testosterone is amplified after transformation in dihydrotestosterone (DHT). Another pathway of testosterone action is through its aromatization into estrogen, that interacts with estrogen receptors α and/or β.

cardiac growth. Moreover, heart androgen receptors modulate adaptive hypertrophy and fibrosis during the process of cardiac remodeling under hypertrophic stress, and protect the heart from both angiotensin II-induced vascular remodeling [15] and doxorubicin-induced cardiotoxicity [16]. Androgen receptors also exist in cardiomyocytes [17] and play an important role in the modulation of cardiac hypertrophy and cardiac remodeling after myocardial infarction (MI) [18, 19]. Of note, when estrogen levels are reduced T worsens cardiac dysfunction and remodeling [20]. Grohe [17] demonstrated that the enzyme cyp450 aromatase is expressed in cardiac myocytes, and that the local estrogen biosynthesis in the heart is effective to activate both the receptor ERα and ERβ. Accordingly, in the myocardium T operates both by activation of androgen receptors and local aromatization in estradiol acting on ERα and ERβ. Many studies have demonstrated the preventive effect of estrogens on myocardial hypertrophy, while androgens induced cardiac hypertrophy [20-22]. These studies evidenced that T and estrogen interact physiologically modulating the effect on cardiac hypertrophy and contractile function, which underscores the need to evaluate both T and estrogen circulating levels in the clinical setting.

Androgens and vascular function

A direct effect of T on vascular function is mediated by the expression of the androgen receptors in vascular cells, which has been demonstrated in rabbits, dogs, monkeys and humans [23] in vascular smooth muscle cells, endothelial cells, macrophages, megakaryocytes and platelets [24]. In addition, these cells express aromatase and 17β-hydroxysteroid-dehydrogenase, so that also estradiol can be produced locally from both T and DHEA [25-27]. ERα, ERβ and membrane estrogen receptors are expressed in endothelial cells, smooth muscle cells, macrophages and platelets as well as in coronary arteries of monkey and man [28-31]. In rabbit aorta, T was found to stimulate the expression of androgen receptors and to inhibit neointimal plaque formation, indicating autoregulatory effects [23].

The effects of androgenson vascular functionare still controversial. It has long been hypothesized that androgens promote atherosclerosis, and several in vitro and in vivo studies have shown that androgens increase expression of atherogenic factors [32-35]. Conversely, other studies have demonstrated a correlation between advanced atherosclerosis and low T levels. Muller showed that serum free T concentrations were inversely related to the mean progression of intima-media thickness of the common carotid artery, independently of cardiovascular risk factors [36, 37]. Low plasma T levels were also associated with endothelial dysfunction and poor vasodilation of brachial artery in men [38]. T-induced vasodilation was first reported in 1945 [39]. This effect involves primarily the vascular smooth muscle cells without requiring the presence of endothelium, and the rapidity of the response evidences that T acts through a non-genomic way. T induces vasodilation in all arterial beds studied, including coronary, mesenteric, iliac, renal, and femoral arteries [40], and thevasodilator responsiveness of coronary arteriesis reduced with age [41]. The direct infusion of T causes acute coronary vasodilation, as demonstrated by intracoronary infusion of T at physiological concentration in patients with coronary artery disease (CAD) [42, 43] and this concept is supported by numerous experimental findings both in animals and humans [32, 42, 44].

The mechanism of T action is the arterial androgen receptors mRNA up-regulation, that reduces neointimal plaque formation in male rabbits [23], associated with a 50% increase of the amount of androgen receptor mRNA in the arterial segments treated with T. The beneficial effects of T on post-injury plaque development underlines, at least in males, the important role played by androgens in the vascular system. Physiological levels of DHT attenuated the development of atherosclerosis by androgen receptor-mediated suppression of the formation of intimal foam cells by macrophages [45]. The pathophysiological role of androgen receptors activity in the cardiovascular system has been studied in male androgen receptors-knockout mice under vascular stress [15], that exhibited exaggerated angiotensin II-induced medial thickening and perivascular fibrosis in the coronary arteries and aorta. Furthermore, physiological T supplementation inhibited cholesterol-enriched diet-induced fatty streak formation in mice with a deletion in the gene encoding the classical androgen receptor [46]. These data suggest that androgen exerts an athero-protective effect via androgen receptor-dependent and -independent signaling.

Androgens and cardiac electrophysiology

The effects of T on cardiac electrophysiology are poorly described, but evidence is accumulating about the impact of sex steroids on human cardiac rhythm and arrhythmias [47]. Charbit [48] showed that the difference in QT-interval duration between men and women might be explained by differences in T levels. An involvement of gonadal steroids in morphologic differences in ventricular repolarization between males and females has also been hypothesized [47, 49]. A reduced QT dispersion in heart failure patients treated with T has been observed [50]. Lower QTc intervals in men with higher serum T levels could be due to the association of serum T with prolongation of the RR interval [51]. A non-genomic action of T and progesterone on cardiac ion channels likely contributes to gender differences in cardiac repolarization process [52]. Repolarization of canine ventricular myocardium is significantly modified by T, but not by estrogen, in both genders. This effect is likely due to augmentation of expression of K^+-channel proteins, and thus may provide protection against arrhythmias via increasing the repolarization reserve [53]. The protective role of T in male hearts has been evidenced by [54] and Bigi [55], who demonstrated a QTc interval ≤380 ms among professional bodybuilders abusing of anabolic steroids.

Androgens and cardiac diseases

Coronary risk factors

T plays an important role in metabolism regulation. Low T levels are associated with obesity, metabolic syndrome and diabetes in men [56, 57], and are now recognized as an independent risk factor for such diseases [58]. T replacement improves glycemic control, visceral adiposity and hypercholesterolemia in hypogonadal men with type 2 diabetes [59]. High T levelsare associated to a low incidence of type 2 diabetes in men, but not in women [60]. In a recent review, the current knowledge on the metabolic actions of T, the effects of T deficiency on obesity, metabolic syndrome and type 2 diabetes and the role of T replacement are discussed [61]. In older men, lower total T is associated with insulin resistance independently of measures of central obesity [62]. T is also involved in lipid homeostasis in insulin-responsive tissues, such as liver, adipose tissue and skeletal muscle [63].

Coronary artery disease and estrogens

CAD is the leading cause of death worldwide for both men and women [64], with the prevalence of CAD being significantly higher and the life expectancy significantly shorter in men as compared to women [65]. Historically, the different prevalence of CAD between men and women has been interpreted as an estrogen-induced protective effect against atherosclerosis. This concept has been challenged by randomized clinical trials testing the effects of combined estrogen/progestin therapy in post-menopausal women, that showed no benefits as to CAD incidence [66, 67]. Furthermore, hormone replacement strategies in postmenopausal women have been associated with an increased risk of breast and endometrial malignancy and thromboembolic disease with resulting increased mortality. In a study conducted on 2763 postmenopausal women, the treatment with oral conjugated equine estrogen plus medroxyprogesterone acetate for 4.1 years did not reduce the overall rate of CAD events [66]. In addition, a recent review showed that, in elderly postmenopausal women with established CAD, daily use of conjugated equine estrogen and combination of medroxyprogesterone acetate plus estrogen did not reduce the overall risk of MI and coronary death during an average follow-up of 4.1 years [68]. In men, estrogen plasma level is related to the incidence of CAD [69].

Coronary artery disease and androgens

The effects of androgens on CAD are even more controversial. Previous studies have evidenced an increased risk of cardiovascular risk in all ages in men after administration of T [70-72]. A correlation between the use of androgens and MI has been reported in body-builders using supraphysiological doses of androgens [73-81]. Such doses of androgens were considered toxic on the cardiovascular system [82, 83, 84], but no clear evidence about an epidemic of acute cardiac events has been associated with the increase of anabolic steroids abuse during the last decades [85, 86].

Despite these reports, an increasing body of literature indicates that men with CAD have significantly lower T levels than those without CAD. An increased development of atherosclerosis has been shown in male animals after castration and reversedwith androgen replacement therapy [46] (see above '*Androgens and vascular function*'). The relationship between serum T level and CAD in humans has been evaluated in a complete review by Wu [87]. Thirty-two cross-sectional studies were analyzed; in 16 studies, a lower level of T was found in patients with CAD as compared to controls, whereas other 16 studies showed no differences in T level between patients and controls. The Caerphilly Heart Study enrolled 2512 men [88], showing a modest reduction in T in survivors of MI. The association, however, became not significant when adjusted for plasma insulin and triglycerides. Conversely, Phillips [89] demonstrated a significant relationship between low free T level and the degree of coronary occlusion in 55 men undergoing angiography. Another study on 900 men found that both total and bioavailable T were significantly lower in men with CAD than in those without [90]. Similar results were reported by Dunajska [91], who showed that men with CAD had lower total T levels, T/estradiol ratio and free androgen index as compared to controls; moreover, men with CAD were more insulin-resistant than controls and had an atherogenic lipid profile. A positive association between low serum androgen levels and severe internal carotid artery atherosclerosis in men has been evidenced by Debing at al. [92], suggesting a protective role of physiological levels of androgens from the development of atherosclerosis. Similar results have been evidenced in the study of health in Pomerania [93] and further confirmed recently [94, 95].

In women, the relationship between androgen level and CAD has been poorly investigated. In women with polycystic ovary syndrome, two long-term longitudinal studies showed no significant increase of CAD incidence [96]. High free T and androstenedione levels within the physiological range have also been correlated with reduced carotid artery atherosclerosis in premenopausal and postmenopausal women [97]. More recently, in postmenopausal women decreased T levels have been found to be associated with CAD independently of other risk factors. Hormonal replacement therapy tends to increase T level, which may further support the beneficial role of hormone replacement therapy in postmenopausal women [98]. Evidence of a positive association between low serum androgen levels and severe internal carotid artery atherosclerosis in postmenopausal women has been provided, and suggests that higher, but still physiological, levels of androgens in postmenopausal women have a protective role from the development of CAD [99]. He [100] showed a more complex interaction between sex hormones and CAD. In both men and postmenopausal women with angiographic CAD, there were significant differences (relative to age-matched control subjects) in sex hormone ratios, suggesting that an abnormality in sex hormones could influence coronary health. A lower estradiol-to-progesteron ratio was associated with the predisposition to coronary atherosclerosis in males, whereas lower estradiol-to-progesteronand estradiol-to-T ratios were associated with the same condition in females.

Angina pectoris

Several studies have demonstrated the effect of T therapy in angina pectoris and are reported in Table 1. The first studies were reported in 1942 by Hamm [101] and Walker [102]. These authors showed that T supplementation in patients with angina pectoris produced significant clinical improvement, reduced cardiac symptoms and increased time to ischemia. These date have been confirmed recently [103]. English [104] found that low-dose supplemental T reduces exercise-induced myocardial ischemia in men with chronic stable angina. Long-term benefits of T therapy were observed during 12 months of treatment in men with low T levels and angina; T increased time to ischemia without side effects [105]. In a randomized study on 50 men with exercise-induced ST segment depression, Jaffe [106] showed that a treatment with T cypionate, 200 mg intramuscularly weekly, significantly reduced ST segment depression after 8 weeks of treatment; no effects were observed in the placebo group. In a crossover study, conducted on 62 men with ischemic heart disease treated with T undecanoate or placebo [107], angina pectoris was relieved by 77% and myocardial ischemia in ECG and Holter recordings was reduced by 69% and 75%, respectively. Moreover, administration of low doses of T in men with chronic stable angina reduced exercise-induced myocardial ischemia [104], resulting in an increase in time to 1-mm ST-segment depression after 12 weeks of treatment.

Myocardial infarction

A limited number of studies are available on the relationship between T levels and MI. After MI in male patients, a transient decrease in T has been observed [112]. Chronic T administration showed no detrimental effects on left ventricular remodeling

Table 1. - Effect of testosterone treatment in men with coronary artery disease

		Patient n.	Dosage	Treatment duration	Clinical effect
Chronic administration	Hamm L [101]	7	75 mg/week	1/2 months	⇑
	Walker TC [102]	12	100 → 10 mg/day	4 months	⇑
	Sigler LH [108]	16	50 mg/week	6/7 weeks	⇑
	Jaffe MD [106]	50	200 mg/week	2 months	⇑
	Wu SZ [107]	62	40-120 mg/day	1 month	⇑
	English KM [104]	46	5 mg/day	3 months	⇑
	Mathur A [105]	15	1 g/3 months	12 months	⇑
Acute administration	Webb CM [109]	14	2.3 mg i.v.	10 min	⇑
	Rosano GM [110]	14	2.5 mg i.v.	5 min	⇑
	Thompson PD [111]	32	2-6 times baseline plasmatic level	20 min	–

The clinical effect cumulates the reduction of the number of anginal episodes and both the prolongation of time to and the increase of heart rate at ischemic threshold during ergometric stress test.

⇑ = clinical improvement; - = no effect.

after MI [113]. In a study conducted on 65 regularly menstruating women aged 33-48 years with recent MI, a significantly higher concentration of T was found in women with a family history of CAD than in those without [114]. Due to the young age of these women, data are not conclusive and need verification.

Chronic heart failure

Several authors have considered the effects of T administration in chronic heart failure (CHF) patients at physiological doses, evidencing positive clinical outcomes [115-119]. In patients with CHF, a low level of plasma T has been observed [120-122]. Particularly, CHF due to idiopathic dilated cardiomyopathy is associated with a significant decrease in growth hormone, insulin-like growth factor 1 and T concentrations [122], underlying the concept that a catabolic state is strictly related to this clinical condition. Wehr [123] showed that low free T level is independently associated with increased CHF mortality, with no association with total T levels. The T treatment in men with CHF determined a significant improvement in exercise capacity and symptoms [115]. Anabolic hormones (T, DHEA sulfate, insulin-like growth factor 1) are related to physical capacity in healthy men, and in CHF patients low circulating T are independent predictors of exercise intolerance [124].

In a randomized double-blind placebo-controlled trial, T administration for a 12-month period in men with moderate-to-severe CHF was associated to an improvement in exercise capacity and symptoms, without changes in muscular strength [115]. In a similar protocol, T replacement was studied in men with moderate-to-severe CHF; T therapy improved exercise capacity and NYHA class compared with placebo [117]. Pugh [118] demonstrated that the administration of T increases cardiac output acutely, apparently via a reduction of left ventricular afterload. In a recent review [125], T appears to be a promising therapy to improve exercise capacity in patients with CHF. Caminiti [116] showed that long-acting T therapy improves exercise capacity, muscle strength, glucose metabolism and baroreflex sensitivity in men with CHF. T therapy improved both peak VO_2 and ventilatory efficiency, as assessed by the VE/VCO_2 slope.

T benefits seem to be mediated by metabolic and peripheral effects. Recently, T supplementation has been used in a 12-week program of exercise rehabilitation in elderly male patients with CHF and a low T status,positively impacting on a range of key health outcomes [126]. Iellamo [119] showed that women with stable CHF who received T transdermal patch, improved functional capacity, insulin resistance and muscle strength without side effects. In a recent meta-analysis, Toma [125] observed that T appears to be a promising therapy to improve exercise capacity in patients with CHF.

Testosterone and prognosis

Recent epidemiological studies revealed that low T levels in men were associated with higher cardiovascular mortality rates [90, 127-131]. Low plasma level of T and estradiol predict mortality in elderly men [129]. Furthermore, anti-androgen therapy in men affected by prostate cancer is associated with significant increases in the risk of CAD and incident heart failure [132]. Moreover, in men treated by orchiectomy, a twofold increase of CAD mortality over a 10-year period has been demonstrated [133].

Shores [134], using the Veteran's Affairs clinical database, reported that men with low T level had a 88% relative increase in all-cause mortality risk when compared with those with normal T levels, and concluded that hypotestosteronemia was a marker of increased mortality risk. An increased risk of death associated with the decline in anabolic hormone levels during a 6-year follow-up was reported in the InChianty study [135]. Laughlin [128] studied a group of 794 men for 20 years, and found that the risk of death was 44% greater between the lowest and highest quartiles of total T after adjusting for age, adiposity and lifestyle choices. The European Prospective Investigation in Norfolk [127] investigated all-cause and cardiovascular mortality in 11606 healthy men between 40 and 79 years of age, observing a statistically significant association between baseline serum T level and all-cause, cardiovascular- and cancer-related death. The authors concluded that T concentrations are inversely related to cardiovascular and all-cause mortality. Recently, Malkin [90] followed 930 men with angiographycally proven CAD over a 7-year period, and found that in androgen-deficient men the mortality was 21% versus 12% in the eugonadal group. Furthermore, the biological available T – and not total T – was significantly associated to all-cause and cardiovascular mortality (Figure 2). This data suggest that bioavailable T is the most sensitive assay for mortality risk stratification.

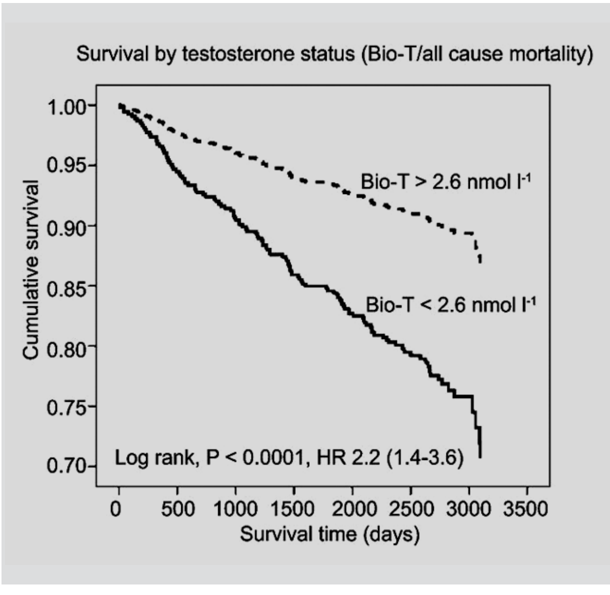

Figure 2. - Survival curves of all-cause mortality based on bio-available testosterone (Bio-T) levels.

The solid line represents patients with baseline Bio-T less than 2.6 nmol/l, the broken line represents patients with Bio-T greater than 2.6 nmol/l. Follow-up duration was 6.9±2.1 years.
HR = hazard ratio.
Reproduced with permission from Malkin [90].

Conclusions

Although androgens have been considered deleterious for the cardiovascular system, recent data have demonstrated favorable T effects on cardiac and vascular remodeling and clinical outcome. However, Ruige [136] in a recent review affirms that the cardiovascular risk-benefit profile of T therapy remains largely evasive in view of a lack of well-designed and adequately powered randomized clinical trials. Discrepancies between studies might be explained by differences in methodology, dose and duration of T administration, and effects of other important hormones, such as estrogens and insulin-like growth factor 1. In any case, a large body of clinical evidence underlines that low plasma T levels should be considered a risk factor for cardiovascular disease, and that the evaluation of sex steroids should be included in the routine clinical evaluation of cardiac patients. A better understanding of the mechanism regulating the effects of T on cardiovascular system could lead to novel therapeutic strategies in several cardiac patient populations, such as CHF patients and patients who recently underwent cardiac surgery.

Riassunto

Sebbene gli androgeni siano stati considerati dannosi per il sistema cardiovascolare, dati recenti hanno dimostrato effetti favorevoli del testosterone sul rimodellamento cardiaco e vascolare e sulla prognosi. Tuttavia, il rapporto rischio-beneficio cardiovascolare della terapia con testosterone rimane elusivo per la mancanza di trial clinici randomizzati ben disegnati e dotati di adeguata potenza statistica. In ogni caso, una notevole evidenza clinica suggerisce che bassi livelli di testosterone plasmatico dovrebbero essere considerati un fattore di rischio cardiovascolare, e che il dosaggio degli steroidi sessuali dovrebbe essere incluso nella routine clinica dei pazienti cardiopatici. Una miglior comprensione dei meccanismi che regolano gli effetti del testosterone sul sistema cardiovascolare potrebbe condurre a nuove strategie terapeutiche in molte popolazioni di pazienti cardiopatici, quali quelli con scompenso cardiaco cronico e quelli recentemente sottoposti a cardiochirurgia.

Parole chiave: testosterone, androgeni, cardiopatia, rischio cardiovascolare.

ABBREVIAZIONI

T = testosterone
DHT = dihydrotestosterone
DHEA = dehydroepiandrosterone
ERα = estrogen receptors α
ERβ = estrogen receptors β
MI = myocardial infarction
CAD = coronary artery disease
NYHA = New York Heart Association

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