TESTOSTERONE AND CARDIOVASCULAR DISEASE— A LITERATURE REVIEW

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ABSTRACT

The effects of testosterone on the cardiovascular (CV) system make it a matter of scientific interest. Disturbances in endogenous steroid concentrations are some of the factors involved in the pathogenesis of atherosclerosis and ischemic heart disease. The aim of this article is to summarize the role of hypogonadism in the context of ischemic heart disease development and to review the current evidence on the CV benefits of testosterone replacement. Its low endogenous level is associated with worsened lipid profile, accelerated development of atherosclerotic plaques, high body mass index, metabolic syndrome and, type 2 diabetes mellitus. In light of these facts, some studies look into the benefits of exogenous testosterone replacement in patients with coronary heart disease and heart failure. The results are divergent and a large randomized trial is required to define the link between testosterone replacement therapy and CV risk. New clues present the recent data on the possible adaptive role of hypogonadism in acute coronary syndrome. This has the potential to expand the knowledge on the link between the CV system and gonadal function in men. The role of sex steroids in the pathogenesis of atherosclerotic heart disease and adaptation to acute coronary syndrome is a subject of increasing scientific interest as a result of accumulating evidence in this field.

Keywords: *testosterone, ischemic heart disease, acute coronary syndrome*

INTRODUCTION

The effects of testosterone (T) in ischemic heart disease are of scientific interest on the one hand, because of the undoubted evidence of the modulatory effect of T on the myocardium and, on the other hand, because of the controversial evidence from the existing studies.

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The effects of T on the functional capabilities of the heart is a topic without a unanimous opinion. It is assumed that the higher incidence of myocardial infarction in steroid abusers is a consequence of the adverse effect of their supraphysiological concentrations (1). On the other hand, a number of studies show that low T concentrations are a predisposing factor for a higher incidence of cardiovascular disease (CVD) and death due to the same reason (2). A decline in T with increasing age and incidence of metabolic syndrome is widely known (3–6). Asymptomatic hypotestosteronemia is observed in ca. 5.9% of men between 30 and 79 and has a higher incidence in elderly men (7,8). Despite the fact that many of the physiological effects on tissue level are known, an increasing number of observational and interventional studies present a diverse and even contradictory an-

swers to the question on the role of T in the pathogenetic mechanism leading to the development of coronary artery disease (CAD), acute myocardial infarction (AMI), and the remodeling of the heart.

With the increase in population age in the past 30 years, the prescription of T treatment in the countries of western Europe and the United States has surged (9). The large number of men classified as having late-onset hypogonadism makes the matter of treatment socially important. While in primary and secondary hypogonadism the cardiometabolic benefits of exogenous T replacement are proven, in patients with late-onset hypogonadism the question of whether the benefit of T replacement outweighs the risks, or whether it improves cardiometabolic risk factors remains. Recent data on the potential adaptive role of hypogonadism in acute coronary syndrome (ACS) give new clues to investigate and expand our knowledge on the link between the CV system and gonadal function in men.

Physiology and Pathophysiology

The testosterone is the main androgen in males - it originates primarily from the testes and to a lesser degree from the adrenal glands. Its effects are not limited to the sexual development but extend to extragonadal tissues. Androgen receptors are found in the endothelial arterial macrophages and smooth muscle cells (10–12).

The mechanism of action of T is mediated by genomic and non-genomic effects. The classical genomic pathway requires the binding of endogenous T to a receptor and its internalization in the nucleus. The binding of T to the androgen receptor leads to conformational changes in the latter and the formation of an androgen/androgen receptor complex. Following translocation to the nucleus, dimerization and binding to androgen response elements (ARE), the genetic expression is being modulated (13,14). The described mechanism of action is common to the steroid hormones (15,16). One of the genomic effects of T is the change in the beta-receptor expression in the myocardium (increase in beta2, decrease in beta1) in animal models with medication induced heart faultier (17).

There is growing evidence in the literature that androgens exert their effects on cells independently of ligand-dependent nuclear receptors. Non-genomic actions are defined as such on the basis of the following criteria: if it occurs over a short time period (up to several minutes); if effects are still observed despite blocking transcription and translation (18–20). Examples of such non-genomic effects are the mobilization of the intracellular calcium, activation of the phosphatidylinositol 3-kinase (PI3K) pathway, extracellular signal-regulated kinase (ERK), and probably the activation of G-protein coupled receptors (16).

Testosterone demonstrates a protective effect in the myocardium by increasing the level of PPAR-α (peroxisome proliferator-activated receptor alpha) and by reducing oxidative stress (21). Interestingly, mitochondrial disruption following an AMI is normalized after T infusion in animal models. Apoptosis and cell necrosis through NF-kB and Akt signaling pathways were restricted, and the expression of genes regulating mitochondrial biogenesis was increased (adenosine monophosphate protein kinase pathway; PGC1α-coactivator of PPARγ) (22,23). There is a stimulation of calcium-dependent ATPase in the sarcoplasmic reticulum (leading to increase in contractile ability) (24) and relaxation of vascular smooth musculature mediated by nitric oxide synthesis (25,26).

Another animal model investigates the lack of T on the heart in the context of gender affirming therapies. When supraphysiological levels of androgens are achieved in transgender males, induction of mitochondrial dysfunction consisting of altered mitochondrial membrane potential, impairment in the redox system, and reduced electron transport in the respiratory chain is observed (11,27). At the moment there is no definitive evidence that testosterone therapy used for gender reassignment has any negative effects on the CV system. The available evidence suggests an increased risk of ACS and stroke in transwomen using estrogens (28).

Influence of Testosterone on CV Risk Factors

The fact that men, compared to premenopausal women of similar age, suffer more often from ischemic heart disease and myocardial infarction is attributed to the effect of male sex steroids or to the lack of estrogen protection (29,30). Available is a multitude of data on the deleterious effect of hypotestosteronemia on the development of atheromatous plaques (31).

In terms of the physiological effect of T on the lipid profile, favorable effects are observed. There is a positive correlation between T and HDL and inverse correlation between T and LDL cholesterol, triglycerides, fibrinogen, tissue plasminogen activator-1 (32). Correspondingly, HDL and lipoprotein A levels increase with exogenous testosterone replacement (33). However, the clinical implications as well as the underlying mechanisms are still unclear (34). The higher frequency of hypotestosteronemia in combination with high body mass index (BMI) is undeniable (35,36). Phenotypically, hypogonadism and metabolic syndrome have similar manifestation. It is known that T, through relevant genomic mechanisms, leads to an increase in lean body mass and a decrease in the number of adipocytes. This in turn leads to an improvement in insulin sensitivity, decreasing serum insulin and leptin levels. One mechanism explaining hypotestosteronemia in obese men is the aromatization of testosterone to estradiol in adipose tissue. On the other hand, concomitant hyperinsulinemia, especially in abdominal obesity, exerts a direct negative effect on SHBG production in the liver. As a consequence, changes in total T concentration occur, while the free and the bioavailable fractions are not significantly altered (37,38). Other publications indicate a correlation between newly discovered glucose intolerance and the low T in the phase of AMI (39). This is consistent with the fact that diabetes mellitus is an independent risk factor for hypogonadism irrespective of BMI (40).

In light of this evidence, it is possible that the commonly observed association between normal or high T and lower CV risk is a reflection of better health status rather than a beneficial physiological effect of testosterone (41). Various observational clinical trials show a more significant correlation between BMI and T, rather than the lipid profile and T. There is no doubt that sex steroids play a role in the process of atheroma formation, but because of its complexity and multifactorial nature, the current experimental settings do not provide a unanimous answer to the effect of T. Depending on sex, differences in the mechanisms relevant to atherosclerotic plaque formation been identified (31). The fibrinolytic system plays an important role in the development of ACS as imbalance between thrombogenic factors, fibrinogen, PAI-1, and t-PA determines the increased risk (42). In experimental studies supraphysiological levels of T (but not dihydrotestosterone) lead to increase in fibrinogen, antithrombin 3, decreased PAI, protein C and S (43).

Multitude of research - both experimental and observational, with various designs and outcomes have shown the divergent effects of testosterone. Some are favorable with respect to cardiovascular disease risk factors, others seemingly negative. Because of the aforementioned multifactorial nature, the multiple variables, and the interplay between risk factors (change in lipid profile or hemostasis), the literature data is currently insufficient to provide an estimate of the net effect of testosterone on cardiovascular risk profile.

Testosterone Replacement and Ischemic Heart Disease

In practice androgen abuse is common and often doses higher than the physiological are administered in order to achieve an anabolic effect. In that specific population, increased risk of left ventricular hypertrophy, AMI, and sudden cardiac death has been proven (1). In contrast to that, several diverse interventional studies conducted from 1970 to 2010 demonstrated a possible vasodilatory effect of high doses of testosterone on coronary vessels (44–46).

In men with ST depression of at least 1 mm on exercise, electrocardiographic improvement was demonstrated after 8-week administration of i.m. T cypionate. An average reduction of 51% in the ST depression on exercise was observed compared to the baseline ECGs (47). In another study, after application of low dose testosterone patches (5 mg daily) in men with stable angina and serum T levels in the low end of the reference range, the time to 1mm ST-depression was increased with no change in the incidence of angina onset. The positive effect was most significant in men with lower baseline serum T. In the same study, no systemic effect on hemodynamics was observed, suggesting a greater sensitivity of the coronary circulation to T (48). In other interventional studies, the i.v. administration of T compared to placebo in both eugonadal and hypogonadal subjects resulted in an increase in the time to ST depression during exercise (44,45). This effect is more pronounced in subjects with lower baseline serum T concentrations (45).

In contrast, after application of estradiol (E), such (short-term) effect has not been observed, which implies that it is not mediated by the aromatization of T to E (49).

These results point toward the fact that the coronary circulation is more sensitive to the vasodilatory effect of T. This is confirmed by another small study with 13 men with angiographically proven coronary artery disease and testosterone deficit. Vasodilation was induced by intracoronary infusion of T in both physiological and supraphysiological doses (46).

The described studies are interventional, aiming to account for the therapeutic effect rather than the underlying pathophysiological mechanisms. More information in this regard is provided by basic science research. Many of these are in castrated rats representing a commonly used experimental model to study the role of androgen deficiency (50). For example, an in vitro study confirms a vasodilatory role of T that is independent of sex, and is much more pronounced on the coronary vessels compared to the aorta (51). Another in vivo study also demonstrates the vasodilatory effect of T (12,52).

Overall, these mechanistic interventional studies suggest that testosterone replacement may be beneficial with respect to the CV system. The results, however, should be interpreted with caution because only a small number of participants is included and not all participants had low serum T at baseline. These studies also include T administrations in ways that are difficult to replicate in clinical practice (53). In all these studies, the role of T in the onset and development of the CAD is being investigated. Another less studied issue is the relationship between androgen levels and the adaptation of the hypothalamic-pituitary-gonadal axis to an acute CV event. Because of the disparate data, a definitive answer can be given only by a large prospective, randomized trial. Exactly that is the ongoing TRAVERSE trial, designed to characterize the CV risks and benefits of T replacement by gel in a cohort of patients with low baseline T and with an already established CV event or a high risk for a CV event. It will potentially provide clarity on the matter if low T is an independent predictor for a CV event, what the frequency of CV events is in men with low T and underlying CVD or high risk for a CV event (54).

Testosterone and Myocardial Remodeling—Changes in the Conditions of Ischemia/Reperfusion

The data on the effect of T in the conditions of ischemia/reperfusion derive from experimental animal models. The physiological concentrations of T in combination with conditional training exert a positive effect on the infarction zone, while supraphysiological concentrations do not (55). Other studies report cardioprotective effect of chronic T application measured by reduction of LDH, increase in the expression of catalase, stimulation of angiogenesis trough hypoxia-inducible factor 1 (HIF1a), reduction of expression of hypoxia-inducible factor 1, reduction of caspase 3 (caspase 3 plays a role in apoptosis) (56–58). Again, in three settings of ischemia/reperfusion, T exerts positive inotropic effect regardless of the dose (physiological or supraphysiological). The intracellular transduction cascades engaged by T (non-genomic signalization) include protein kinase signal pathways (protein kinase A and C, mitogen-activated protein kinase (MAPK)), adenylate-cyclase, and the increase in intracellular Ca^{2+} (15,59,60). Conflicting evidence comes from M. Cavsin et al. (61). Additional replacement with T in their experimental model dramatically increases the rate of heart rupture and death in female mice with or without ovariectomy, whereas castration significantly reduces these complications in mice. The data derived from this series of experiments suggest an increased inflammatory response to higher T levels. This is objectivized by the greater neutrophil infiltration and more active degradation of the extracellular matrix.

All these results are a product of fundamental research in rodents. The consequences of T treatment on the development of CVD are still unclear. For this reason, more dose-dependent, time-dependent statistical analyses and molecular studies are needed to clarify the effect of T replacement therapy.

Testosterone and Hearth Failure

Testosterone level is usually low in patients with heart failure (HF) and correlates positively with the ejection fraction (62). This observation is the rationale for a number of studies with T replacement therapy in patients with HF. Despite the significance of the problem, studies evaluating the effect of exogenous T replacement on the cardiac muscle in the setting of HF are few. Testosterone replacement in pa-

tients with reduced ejection fraction resulted in improvements in walking ability, muscle strength, oxygen consumption, functional capacity, and insulin resistance (63–67).

The short-term application of T in the setting of HF resulted in an increase in the stroke volume by the mechanism of reducing systemic vascular resistance (68).

In HF the expression of metalloproteases is increased. They have a negative influence on the process of remodeling, disturbing the structure of collagen and connective tissue (69). Testosterone replacement therapy significantly reduces the expression of metalloprotease genes, and increases the expression of genes that reduce hypertrophy. The net effect is reduction in apoptosis and fibrosis (70,71). Chronic hypogonadism leads to the development of proarrhythmogenic state, impairment of myocardium relaxation (Ca^{2+} influx is reduced) and decrease in the size of cardiomyocytes (decreased synthesis of myosin chains) (72).

These effects of T in the cardiomyocytes may become the rationale for T replacement therapy in elderly patients with atrial flatter, osteoporosis and progressive muscle atrophy. In the future additional investigations are required in order to determine the significance of these findings.

Role of Testosterone in the Adaptation to Acute Coronary Syndrome

The relationship between acute illness and transient disorders of the hypothalamic-pituitary-gonadal axis is known and has been repeatedly confirmed. In men after ACS, gonadal dysfunction associated with tissue resistance to luteinizing hormone or with altered affinity for sex hormone-binding globulin has also been described (73,74). The incidence of erectile dysfunction is increased (75). It is unclear if this transient hypogonadism has an adaptive or maladaptive role. This issue is complicated by the unclear incidence of hypogonadism preceding acute cardiovascular event.

G. Corona and associates did a follow-up for a period of 4 years of patients with erectile dysfunction after an ACS. Their study was based on the possibility that AMI is the cause of the subsequent hypogonadism. In this longitudinal study BMI, testicle size, lipid profile, glycemic parameters, total and free T were measured with the primary endpoint being the occurrence of nonfatal CV events. For a total of 1687 patients, no correlation was found between hypogonadism and the incidence of events.

However, after dividing the participants into groups depending on the presence or absence of previous CV event, it was found that in those with a previous acute CV event the presence of hypogonadism was associated with a significantly lower risk for a new accident. The relationship was even stronger adding reduced testicular volume to low T (hypogonadism was defined as total T < 12nmol/L) (76). Based on this observation, the authors conclude that that an adaptive low T syndrome is possible, similar to the low T3 syndrome in acute systemic illness.

A similar conclusion was reached by the authors of another prospective study in which total T and CV mortality rates were monitored in men after the occurrence of ACS. Patients with a decrease in T to normal-to-low levels (9–15 nmol/L) had a lower risk of CV death over the 6-year follow-up period compared to those whose T concentration remained stably high. In the same study, a decrease in T below < 10.4nmol/L only in the age group above 65 was an independent predictor of mortality (77). There is also disagreement between different research groups on this issue, as it can be seen in the Swiss prospective study by B. Gencer and collaborators. In it 1054 men we followed. At baseline they were divided into a group with high and a group with low testosterone (cutoff defined as 300 ng/dL or 10.5nmol/L). After adjusting for confounders such as systemic inflammation and GRACE-score, the authors concluded that low T is not significantly associated with survivability in these groups (78).

In addition to T, higher estradiol concentration is also associated with a more severe form of ischemic heart disease—higher levels of myocardial necrosis enzymes, impaired left ventricular systolic function, and a more intense inflammatory response (79). Increased aromatization of androgens is associated with increased inflammatory markers in the setting of AMI and is one explanation for the progression of CHD in elderly men (80,81).

Despite conflicting results and different designs, these studies highlight the likelihood that the changes occurring in gonadal function are a conse-

quence of an event, whether adaptive or not, and a reflection of the patient's general health status rather than a cause of the development of ACS. This conclusion is supported by observations in patients with ischemic stroke (82).

CONCLUSION

The contemporary opinion of leading investigators regarding the effect of T in the setting of myocardial hypoperfusion is controversial. These differences stem, on one hand, from the variable study designs—some evaluate the effects of chronic testosterone administration, with a variety of doses and durations. In others it is substituted in physiological or supraphysiological doses over a short time interval. It is possible that acute and chronic change in testosterone level produce different effects, leading to inconsistent results depending on the study design. The role of sex steroids in the pathogenesis and adaptation to CV and metabolic diseases is a subject of increasing scientific interest as a result of accumulating evidence in this field.

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