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Review

Cardiovascular effect of testosterone replacement therapy in aging male

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Abstract. Cardiovascular diseases (CVD) are the most important causes of morbidity and mortality in the developed and developing world. Particularly, coronary heart disease is the commonest cause of death worldwide. Testosterone (T) is an anabolic hormone with putative beneficial effects on men's health and restoration of normal T levels in deficient men represents an important key-point of male well-being. In the lasts years it has emerged a possible linkage between androgen deficiency and CVD. Many studies noted that T deficiency might contribute to increased risk of CVD. Furthermore, androgen deficiency is frequently associated with increased levels of glucose, total cholesterol, low-density lipoprotein, increased production of pro-inflammatory cytokines, and increased thickness of the arterial wall that all contribute to worsen endothelial function. The clinical and epidemiological studies discussed in this section give an update on the interplay between late onset hypogonadism (LOH) and CVD. The linkage between androgen deficiency and men's vascular health has a great impact in the modern approach to the ageing male, and should be further investigated to determine the therapeutic potential of androgens in men with vascular disease. (www.actabiomedica.it)

Key words: Late onset hypogonadism, metabolic syndrome, atherosclerosis

Introduction

It has been observed that ageing men experience gradual declines in serum testosterone (T) levels (1). This age-related decline, defined as late onset hypogonadism (LOH), and confirmed in several cross-sectional and longitudinal studies (2) can occur both because of defects at testicular or hypothalamic-pituitary functions. It is established that T levels decrease about 1-2% per year after age 40 (3), and only a subset of aging men exhibit levels clearly below the lower limit of the normal range for healthy, young men (4). It is estimated that hypogonadism affects between 19–34% of men over the age of 60 (5). Consequently, understanding this phenomenon is important because of the associated conditions including metabolic syndrome (6, 7) type 2 diabetes mellitus or impaired fasting glucose (8, 9), atherosclerosis (10), myocardial infarction (11), chronic heart failure and unwanted effects with a range of medications (12). Currently, low T levels are gaining recognition as an independent risk factor for these conditions. In fact it has been demonstrated that T plays a key-role in the development of insulin resistance/Metabolic Syndrome (MS) (13), and increased risk of cardiovascular disease (CVD) as confirmed by the hypogonadal state occurring in men undergoing androgen suppression as treatment for prostate cancer (14). It is unclear, however, whether declines in T are primarily associated with normal aging *per se* or rather with age-related changes in overall health and lifestyle; but it is certain that male hypogonadism has a multifactorial aetiology that includes genetic condi-

tions, anatomic abnormalities, infection, neoplasm and injury.

Diagnosis and treatment of Late onset Hypogonadism (LOH)

Diagnosis of hypogonadism is based on clinical symptoms and laboratory determinations of serum T, usually total T (TT) levels. Typical symptoms include change in mood and cognitive function disorders (15), decreased bone mineral density (16), increased visceral adiposity and body mass index (BMI) (17), decreased muscle mass and strength (15), and sexual dysfunction (18). In order to discuss the biochemical diagnosis of hypogonadism it is necessary to outline the usual carriage of T in the blood. Serum TT consists of free testosterone (FT) (2%–3%), testosterone bound to sex hormone binding globulin (SHBG) (45%) and testosterone bound to other proteins (mainly albumin –50%) (19). Measuring bioavailable T, or FT, is expensive and time-consuming, but may more accurately detect hypogonadism. The normal range for serum TT levels in early morning hours in healthy, young men, 20 to 40 years of age, is approximatively 320 to 1000 ng/dL (11-35 nmol/L). Levels TT falling below 320 ng/dL (11 nmol/L) or FT 70 pg/ml (0.255 nmol/l) clearly indicate hypogonadism and the need for hormone replacement therapy. TT levels between 320 and 400 ng/dL (11-14 nmol/L) should be repeated and followed up by calculation of FT using sex-hormone binding globulin (SHBG) concentrations, or by measurement of FT levels by equilibrium dialysis or bioavailable T by the ammonium sulfate precipitation method.

Treatment for hypogonadism is usually by mean of testosterone replacement therapy (TRT). The routes of administration which are currently available are oral, transbuccal, injectable, implants and transdermal (20).

By restoring serum T levels to the normal range using TRT, many of these symptoms can be relieved. Emerging evidence suggest that TRT improves the main components of MS: insulin resistance and lipid profile, possibly improving the cardiovascular risk profile. Treatment with T in hypogonadal men has shown an improvement in cognitive, verbal and visual memory, mental status, visual-motor scanning and attention, verbal knowledge/language, spatial abilities and memory for both verbal and visual information (21). While many studies of TRT in older men suggest a potential beneficial effect on cognition, most studies to date have been small and need further replication with larger sample sizes (22). In addition, it is difficult to define the psychosocial impact of both hypogonadism and TRT. However, sexual hormones largely influence mood, well-being, and quality of life in the internal medicine patients. For this reason, despite the methodological difficulties of assessment, TRT may have a deep impact on the social, psychological and sexual life of the treated patient (23).

Testosterone and cardiovascular system

Cardiovascular disease, and its underlying pathological process atherosclerosis, is an important cause of morbidity and mortality in the developed and developing world. Coronary heart disease in particular is the commonest cause of death worldwide (24, 25). As well as increasing with age, this disease is more common in the male versus female population worlwide, which has led to interest in the potential role of sex hormones as possible modulators for the risk of development of atherosclerosis. MS is commonly defined as a cluster of risk factors that include increased central abdominal obesity, elevated triglycerides, reduced high-density lipoprotein, high blood pressure, increased fasting glucose, and hyperinsulinemia which are all closely associated with insulin resistence (26). MS indicates a high risk for the development of both type 2 diabetes mellitus and CVD. Several studies have demonstrated an increased risk of CVD in men with either MS or type 2 diabetes mellitus (27). Studies have also shown that low T levels in men can predict the development of insulin resistance, the basis of MS, and possible progression to overt type 2 diabetes mellitus (28). Essentially, hypotestosteronemia is associated with an increase in many of the known cardiovascular risk

factors (29). Therefore TRT could be a potential treatment that could be offered for improvements in glycaemic control, insulin resistance, cholesterol and visceral adiposity and reduction in cardiovascular morbidity and mortality (30), particularly in diabetic men (31).

Recent studies have also shown that men with CVD have significantly lower levels of bioavailable T than men with normal coronary angiograms (32), and the presence of hypogonadism in a population of men with CVD is about twice that observed in the general population (33). Androgens have also been found to inhibit male atherosclerosis in rabbits (34) and reduce vascular resistance in rat pulmonary and coronary arteries (35). Recent animal and *in vitro* studies have further documented that T up-regulates the expression of arterial androgen receptor mRNA and is associated with an inhibitory effect on neo-intimal plaque formation (36). Additionally, positive acute hemodynamic effects of T on coronary vasomotion and stress-test induced ischemia were reported (37). Several studies have shown that acute administration of T induces a rapid relaxation in vascular tissues of different species including humans (38, 39), suggesting a non-genomic effect of this hormone on vascular reactivity (40). Different mechanisms have been proposed to explain T-induced vasodilatation (41) but it remains a matter of debate which is the effective mechanisms and which are the mediators involved of the T-induced vasorelaxation. Furthermore men given a testosterone injection prior to exercise testing showed improved performance, as assessed by ST changes compared to placebo (42). Administration of one to three months of testosterone treatment has also been shown to improve symptoms of angina and exercise test performance (43). T inversely correlate with the severity of atherosclerosis and has beneficial effects upon vascular reactivity, inflammatory cytokine, adhesion molecules, insulin resistance, serum lipids, and haemostatic factors (44). Interestingly, men with established coronary heart disease display reduced circulating T levels (45) that are often associated with a certain degree of endothelial dysfunction independently of other vascular risk factors, suggesting a protective role of endogenous T on the endothelium (46). Many studies have found that testosterone levels are negatively correlated with carotid intima media thickness (IMT) (47), an early sign of atherosclerosis shown to predict cardiovascular mortality (48). Epidemiological studies have also assessed links between serum testosterone and non-coronary atherosclerosis. A large study found an inverse correlation between serum total and bioavailable testosterone and the amount of aortic atherosclerosis in men, as assessed by radiological methods (49). A 4-year follow up study of the latter population showed that free testosterone was also inversely correlated with the rate of increase of IMT (50).

The evidence of the beneficial effects of TRT on central obesity and diabetes, raises the question whether T treatment could be beneficial in preventing or treating atherosclerosis. No trial of sufficient size or duration has investigated the effect of TRT in primary or secondary prevention cardiovascular disease. Epidemiological data shown that low T levels are associated with an atherogenic lipid profile, including lower HDL cholesterol and higher total cholesterol, LDL cholesterol and triglyceride levels. Furthermore, these relationships are independent from other factors such as age, obesity and glucose levels (51, 52). Also interventional trials of TRT have shown a decrease in total cholesterol, confirmed by a recent meta-analysis (53). Also specific data referred to the ageing male population suggest a consistent negative correlation between T and blood pressure, in particular for systolic hypertension (54), but interventional trials have not found a significant effect of TRT on blood pressure (55). T levels are negatively correlated with plasminogen activator inhibitor-1 (PAI-1), the major prothrombotic factor known to be associated with progression of atherosclerosis; and positively correlated with tissue plasminogen activator (tPA), one of the major fibrinolytic agents were found (56). Interventional trials have shown a neutral effect of physiological TRT on the major clotting factors (57) but supraphysiological androgen administration can produce a temporary mild pro-coagulant effect (58). A more recent study show an inverse correlation between total serum T and the pro-inflammatory soluble interleukin-6 receptor, but no association with interleukin-6 (IL-6), highly sensitive CRP (hsCRP), tumor necrosis factor-α (TNF-α) or interleukin-1β (IL-1β)

(59). Malkin et al. demonstrated that T treatment in hypogonadal men, mostly with known coronary artery disease, induced anti-infl ammatory changes in the cytokine profile reducing IL-1β and TNF-α and increasing IL-10 (60).

In conclusion, low T may concur to determine additional cardiovascular risk and contribute to the progression of endothelial dysfunction. Therefore, TRT seems to play a key-role to improve endothelial function via genomic and non-genomic pathways. Further controlled studies are necessary to demonstrate the risk/benefit ratio of T therapy in the CVD patient.

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