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Testosterone Deficiency in Male: A Risk Factor for Heart Failure

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Abstract: Testosterone deficiency syndrome (TDS) induces several negative effects that generally involve different organs such as testis, bone, skeletal muscle, and heart, leading to reduction in testis function, causing osteoporosis, strongly reducing muscle mass, decreasing exercise capacity and strength and facilitating heart failure. Approximately 25% of patients affected by chronic heart failure (CHF) is characterized by plasma Testosterone (T) levels below normal ranges also related to disease progression. In addition, reduction of circulating testosterone levels may contribute to some specific features of CHF, such as abnormal energy handling, weakness, dyspnoea and cachexia in particular. According to some recent evidence it has emerged that testosterone replacement therapy (TRT) may improve muscle strength and functional pulmonary capacity in CHF men with TDS.

This review will place emphasis on the pathophysiological role of testosterone deficiency in CHF men as well as the effects of the testosterone replacement therapy.

Keywords: Heart failure, hypogonadism, testosterone deficiency, testosterone replacement therapy.

INTRODUCTION

Chronic heart failure (CHF) is a growing health problem throughout the world, especially as a consequence of the evident ageing of western populations [1]. CHF is a syndrome characterized by an anabolic-catabolic imbalance of both the peripheral skeletal muscles and the heart which might involve the neurohumoral, the endocrine and the metabolic systems. The impairment of major anabolic systems (somatotropic, adrenal and gonadal) may be thought of as widely involved in the CHF pathophysiology and especially low serum Testosterone (T) levels have been correlated to the symptoms severity and the adverse outcomes in men suffering from CHF [2, 3]. This latest assumption was related to the rise in cardiovascular disease (CVD) in men affected by testosterone deficiency syndrome (TDS) and was put forward by various prospective studies carried out for decades [4-23]. On the other hand, it is noteworthy that heart failure (HF) as an illness can affect sex steroid metabolism [24]. Furthermore, patients affected by metabolic diseases, such as diabetes [25], metabolic syndrome [26] and especially obesity [27], which *per se* may favor the onset and progression of CHF, often present low circulating T levels or overt hypogonadism. Elderly men may experience a prolonged mild or severe hypotestosteronemia which can affect metabolic diseases and over the time worsen heart failure outcomes too. Furthermore, the reduction in T levels is a main predictor of decreased peak of oxygen consumption (VO_2), an independent risk marker for impaired exercise capacity and a poor prognostic factor in men with CHF [28-30].

The purpose of this review is to sum up the available evidence on the role of the T deficiency syndrome (TDS) as a modifiable pathogenic factor in HF as well as to highlight both the positive and the potential side effects of T replacement therapy (TRT) in men suffering from CHF.

ANDROGEN DEFICIENCY SYNDROME AND ITS TREATMENT IN MEN

Male hypogonadism is very often a chronic syndrome characterized by low total testosterone (T) levels and its free fractions (FT), being clinical signs dependent on the age of onset. Indeed, if it begins at a very early age, at birth, or at prepuberty, it can easily be diagnosed as most of its symptoms are typical (female or intersexual internal and external genitalia, hypospadias, absent or incomplete pubertal development, eunuchoid body proportions, persistence of prepubertal external genitalia, cryptorchidism, etc). By contrast, the late-onset form is characterized by symptoms and signs that are often unspecific and mimic the natural men ageing (weakness, obesity, fatigue, low libido, depression, mild anemia, sleep disturbances and osteoporosis, type 2 diabetes mellitus, *etc*) and cannot be easily diagnosed [31].

Hypogonadism is classified according to the level of the hypothalamus-pituitary-testis axis involved. We can define a condition of primary hypogonadism when the main problem involves the testis. In this case the Luteinizing Hormone (LH) and the Follicle Stimulating Hormone (FSH) levels are usually elevated (hypergonadotropic hypogonadism). Hypogonadism is defined as secondary when the

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Table 1. Signs and symptoms that characterized T deficiency syndrome in adult and elderly men according to the Endocrine Society.

More specific
Delayed or incomplete sexual development-Eunuchoidism
Reduction of libido and sexual activity
Gynecomastia
Loss body hair and shaving
Small or shrinking testes
Reduction in sperm count
Osteoporosis, low trauma fracture, height loss
Hot flushes, sweats
Less specific
Feeling sad, depressed mood
Decrese of energy and concentration or memory
Overweight, obesity
Sleep disturbance
Mild Anemia
Diminished physical or work performance

hypothalamus and/or the pituitary are involved and low circulating T levels are commonly associated with low or inadequately normal levels of LH and FSH (hypogonadotropic hypogonadism) [32].

According to the Endocrine Society [33] and recent consensus statements of major Societies in the field [34], a diagnosis of androgen deficiency or hypogonadism requires the presence of typical symptoms besides the establishment of low T levels (< 280 ng/dl) by laboratory assessment. Indeed, it is recommended that serum T should only be assessed in those patients who are affected by clinical disorders at high risk for low serum T, whilst a widespread evaluation of serum T is strongly discouraged (Table **1**). The determination of serum FT is only recommended in the presence of total T levels within the "grey zone" (250-350 ng/dl) or in the presence of remarkable modifications of Sex Hormone Binding Globulin (SHBG) levels such as in obese men [27] or in those who suffer from metabolic syndrome or overt diabetes mellitus [35]. Since the method considered as the gold standard (dialysis method) for the FT measurement is extremely complicated, time consuming and not routinely available in laboratories, the FT evaluation can be calculated by Vermeulen's formula, knowing in advance the circulating levels of SHBG and the total T fraction [36]: FT levels lower than 65 pg/ml (0,225 nmol/l) are suggestive of overt hypogonadism and require TRT [37]. Finally, if low serum total testosterone levels are found (< 150 ng/dl), it is advisable to measure the gonadotrophins and the serum PRL in order to exclude any serious problems at the hypothalamus-pituitary level and/or at the testicular level [33].

Different formulations for TRT have been commercialized so far (Table **2**), although those more recently launched on market (trans-cutaneous T gel and long-acting intramuscular compounds) have documented a greater capability to reproduce the T circadian rhythm and to keep the circulating T levels within the normal range than the older ones [32]. The absolute contraindications to testosterone treatment include prostate and breast cancer as well as erythrocytosis, although severe liver, kidney or pulmonary diseases, uncontrolled hypertension, limitation in mobility and frailty seem to be important factors that one should take into consideration whenever starting the T therapy [32, 33, 52].

PATHOPHYSIOLOGICAL ROLE OF T DEFICIENCY IN CHF MEN

Heart failure (HF) is a common, costly, disabling, and potentially deadly condition in western countries, affecting about 2% of adults and up to 6-10 % of people over the age of 65. The most frequent causes and risk factors which can lead to HF are hypertension, atherosclerosis, obesity, diabetes mellitus, hypercholesterolemia, ischemic heart disease [38]. As hypogonadism in men may favor the onset of abdominal obesity [27] and type 2 diabetes mellitus [35], as well as lead to an unfavorable lipid profile, hypertension [39], atherosclerosis [40] and aortic aneurysm [41], it has been hypothesized that it might be instrumental in the onset and progression of cadiovascular diseases (CVD) and HF.

Concerning low serum T levels and mortality in men, current evidence has been conflicting until now. As a matter of fact, some studies carried out in elderly men in particular, showed increased mortality rate [22, 42-46]. Furthermore, in men with coronary heart disease or CHF, low serum T levels resulted to be related to higher mortality [47] and disease severity [48]. On the other hand, several other studies have reported no correlation between low T levels and mortality [49, 50] most likely because the examined population was younger than in previous studies. A recent meta-analysis and a cross-sectional study, both conducted by Ruige *et al.*, [51, 52], have provided no association between endogenous T and CVD risk in middle-aged men, whilst in elderly men it is unclear whether low T may have a direct negative effect on CVD or should it be considered as a poor general health parameter. In addition, this issue remains rather conflicting in the light of recent results from a randomized controlled trial (RCT) which reported a high rate of testosterone replacement therapy-associated cardiovascular adverse events in those elderly men suffering from hypogonadism (serum T below 12 nmol/l) and chronic diseases with important limitations in mobility [53]. In men with CHF, low serum T and low calculated T/ Estradiol (E_2) ratio can be also due to an increased peripheral aromatization of T to E_2 [24], even more in those suffering from metabolic diseases such as obesity and overt type 2 diabetes mellitus [24-25]. A recent meta-analysis [54] has led to the conclusion that there are no evident harmful or beneficial effects of augmented serum E_2 in men at risk for incidental CVD and an increased level of E_2, if present, might be correlated with Body Mass Index (BMI). Therefore, these results focus our attention on alterations of gonadic sex steroids pattern as a parameter of poor general health in men [26] which can negatively

Table 2. Routes of administrations, half lives and doses of current T formulations.

	Generic Name	Commercial Name	Doses
INJECTABLE	*Testosterone propionate*	Testovis®	100 mg every 2-4 weeks
	Testosterone enantate	Testoviron® Dep.	200-400 mg every 2-4 weeks
	Testosterone undecanoate	Nebid®	1000 mg every 10-14 weeks
ORAL	*Testosterone undecanoate*	Andriol®	120-240 mg /day
TRANS-DERMAL	*Testosterone patch*	Androderm® Testopatch®	2.5-5 mg/day 1.8-2.4 mg/day
	Testosterone gel	Testogel® Androgel® Testim®	50-100 mg/day
		Tostrex®	60-80 mg/day
BUCCAL	*Buccal Testosterone*	Striant®	30 mg 2 times a day

influence different risk factors (hyperlipemia, hypertension, hyperglycemia *etc*). In turn, this might contribute to worsen the metabolic syndrome, obesity and diabetes mellitus [27, 55-57] that often lead to complications such as CVD and HF. As a result, in men with diabetes mellitus and hypogonadism the TRT might be aimed at improving metabolic control and reducing CV risk and microvascular complications eventually [32, 35].

It is commonly accepted that anabolic/catabolic imbalance which facilitates catabolism, is the main pathophysiological factor that can impair heart compensation in patients with advanced CHF [58, 59]. Different studies showed a significant reduction in serum concentrations of anabolic hormones, including testosterone, in men affected by CHF as well as a direct and independent relationship between serum T reduction and both the peak oxygen consumption and the peak oxygen pulse in men with CHF. This may indicate that low T might be a marker of poor prognosis, independent of conventional risk predictors and of the underlying cause of CHF [28, 30]. Moreover, low T levels seem to account for the magnitude of deterioration in peak VO_2 over time, whilst other indices related to the progression of heart disease, did not predict the deterioration of exercise capacity, thus indicating that T deficit plays a crucial role in the progressive deterioration of functional capacity in male affected by CHF. Anabolic hormones are determinants of exercise capacity and the age-related decline in circulating T and in other anabolic hormones such as weak androgens (dehydroepiandrosterone and its sulphate) and insulin-like growth factor 1 (IGF-1) may contribute to gradually impaired exercise tolerance in elderly men [60, 61]. Androgen receptors are present in myocytes from multiple species including humans [62] and, in this context, they can modulate both ventricular structure and function [63, 64]. Testosterone can stimulate hypertrophy of both type I (oxidative ‘‘slow twitch’’) and type II (glycolityc ‘‘fast twitch’’) muscle fibers, although the former may be quite sensitive to anabolic agents than the latter, given that type II muscle fibers are able to enlarge only in response to the administration of high testosterone doses [65, 66]. Furthermore, T effects on muscle fibers might involve modifications in the expression of many muscle growth regulators such as IGF-I, IGF-binding protein-3, and myostatin [67]. Testosterone also seems to have positive effects on the cardiomyocyte function as documented by different researches in rats and in humans [68, 69]. This protective effect consists of a reduction in QT interval and arrhythmia susceptibility, modulating the early phase of ventricular repolarization by increasing NO production, channel K^+ kinetics [68] and intracellular calcium [69]. Moreover, it may inhibit the cardiomyocyte apoptosis and the damage of both ventricles during HF and/or myocardial injury modulating local cytokine production such as the Tumor Necrosis Factor-alpha (TNF-α), interleukins (IL-1 and IL-6), *etc* [70, 71]. Finally, although androgens are not synthesized at the heart tissue level [72], T can protect rat cardiomyocytes from sorbitol apoptosis induction by an interaction among T activity, myocardial mineralcorticoid production and its blockade. In this last respect, the protective T effects against myocyte apoptosis are antagonized by spironolactone [73].

Some objective morphological and functional abnormalities were found in the muscle of CHF patients, relatively independent of a reduced blood flow [74]. These changes which are characterized by fiber atrophy and the prevalence of type II fibers with a predominance of a glycolitic over an oxidative metabolism, seem to account for a maladaptive condition of muscle mass, being instrumental not only in symptoms development, but even in the pathophysiology of the HF syndrome (‘‘muscle hypothesis’’ of CHF) [75-77]. In this condition a key role is played by an increased activation of the muscle metaboreflex mechanism (also called ergoreflex [77]) in the control of cardiorespiratory

function. This ergoreflex may represent a beneficial reflex which initially enables the cardiovascular system to compensate for a reduced cardiac output by vasoconstricting inactive blood vessels and rising the heart rate. However, with time it is responsible for the sustained and prolonged neurohumoral activation which generates some abnormal hemodynamic, autonomic, and ventilatory responses to exercise that characterize the worsening of HF process and even facilitate cardiac cachexia [76-78]. In fact, in cachetic patients the ergoreflex is particularly enhanced, being coupled with a more marked muscle reduction which, in turn, can aggravate HF. Therefore, every intervention especially aiming at improving muscle structure function (exercise training) has been shown to decrease the metaboreflex activity and ventilatory response to exercise in CHF, improving VO_2 [74, 76, 79]. Given that T therapy has been able to improve the leg muscle strength and workout, one can hypothesize that it might similarly decrease the muscle metaboreflex activity causing an improvement in muscle function [80]. As a result, TRT has been shown to facilitate the conversion of the fast-oxidative-type fibers to the slow-oxidative ones [81, 82] which are found to be reduced in muscle mass of CHF subjects [76]. Moreover, it can increase the number and activity of type I slow-oxidative fibers which can improve the skeletal muscle oxidative capacity and aerobic potential, thus delaying muscle fatigue. Other possible effect of TRT on exercise capacity in CHF syndrome is the reduction in insulin-resistance. It can favour glucose availability as a prompt energy source for muscle mass and promote peripheral vasodilation by improving endothelial function that, in turn, causes a rise in blood flow to muscle mass [83-85].

TESTOSTERONE REPLACEMENT THERAPY IN CHRONIC HEART FAILURE MEN: PATHO-PHYSIOLOGICAL INSIGHTS AND CLINICAL BENEFITS

Given the role of TDS on different pathophysiological mechanisms facilitating and/or generating negative metabolic effects on HF outcome, studies of T replacement in HF patients have been encouraged. Furthermore, some data showing a positive effect of T supplementation on muscular performance even in CHF men with normal T levels and the fact that three meta-analysis investigating the adverse effects of T therapy did not find any important ones even in men affected by CVD [86-88], have definitively given weight to the T therapy in CHF men independently of their T levels [80].

Testosterone supplementation at doses maintaining its serum levels within the physiologic range has been shown to ameliorate some indices of physical performance in CHF patients in several studies [80, 82, 89, 90]. Both intra-muscular testosterone preparations and transdermal testosterone patches have been administered to CHF patients, with the result of improving exercise tolerance, as evaluated by the increased distance walked at the shuttle walking test, with a positive correlation with the increase in T serum levels [78, 90]. A long-acting intramuscular testosterone preparation significantly improved ventilatory efficiency as well as the performance of leg muscles in patients with moderately severe CHF in a double-blind, placebo-controlled randomized study [80]. These studies demonstrated that the anabolic actions of T could have beneficial effects on the muscle wasting of CHF patients, in particular in those with lower baseline T levels, and their results should be undoubtedly regarded as of clinical relevance since ventilatory parameters (VO_2 peak and VE/VCO_2 slope) can discriminate those HF patients at higher or lower risk for cardiac mortality [91-93]. Indeed, a recent meta-analysis has confirmed those promising results highlighting that the benefits of T supplementation do not involve significant changes in central hemodynamic as no detection of left ventricular improvement has been found [94]. The improvement in muscle strength and effort tolerance could be also related to the positive effects of testosterone supplementation on insulin sensitivity, in particular at muscular level, with an increased availability of glucose and a nitric oxide-mediated vasodilation leading to an increase in blood flow and oxygen availability to exercising muscle, contributing to reduced fatigability [47, 80, 88, 89, 95]. Another positive effect of TRT on HF might be the one on the neuronal cardiovascular regulation. Caminiti *et al* [80] reported an improvement in baroreflex sensitivity that is a prognostic marker in CHF, in a subgroup of HF patients treated with T therapy. Finally, TRT makes some positive modifications to cardiovascular risk factors (obesity, hyperlipemia, metabolic diseases and diabetes mellitus, etc) that are involved in the atherogenesis process and its progression [26, 32, 35].

Even though some animal studies have reported that testosterone might induce hypertrophy, fibrosis, and apoptosis in cardiomyocytes [96, 97] and some authors have raised some concern to treat hypogonadal elderly men ($T < 12$ nmol/L) with cardiovascular disease and mobility limitation [53], there is no evidence of either deleterious or positive direct effects of testosterone administration on the left ventricular function in humans. Furthermore, no significant adverse cardiovascular effects were noted in those HF patients enrolled in a recent meta-analysis [94] as they did not suffer from severe HF form (only 2% of those HF subjects presented NYHA IV class symptoms) or showed impaired metabolic parameters (creatininemia, fasting glucose, serum PSA) as an indication that they were not frail and/or affected by severe chronic diseases [94, 98].

CONCLUSION

HF is one the most common causes of life expectancy reduction in western countries the incidence of which is raised by age. Many metabolic diseases such as obesity, hyperlipemia, metabolic diseases and overt diabetes mellitus that are more prevalent in old men, might underpin and/or worsen the HF outcome. Similarly, hypotestosteronemia has been found in men suffering from HF especially in the elder ones. Given that TRT has shown positive effects on improving exercise tolerance and ventilatory efficiency as well as metabolic parameters and insulin sensitivity in HF men, especially in younger ones and in those affected by less severe forms of HF, nowadays, testosterone therapy might be regarded as an auxiliary treatment in CHF patients, especially for those with TDS. However, larger double-blind placebo controlled studies with well defined clinical

outcomes as endpoints should be performed to establish long-term efficacy and safety of this treatment.

CONFLICT OF INTEREST

The author(s) confirm that this article has no conflict of interest.

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ABBREVIATIONS

CHF	=	Chronic heart failure
CVD	=	Cardiovascular disease
E_2	=	Estradiol
FSH	=	Follicle Stimulating Hormone
FT	=	Free Testosterone
IGF-1	=	Insulin-like growth factor 1
LH	=	Luteinizing Hormone
SHBG	=	Sex Hormone Binding Globulin
T	=	Testosterone
TDS	=	Testosterone deficiency syndrome
TRT	=	Testosterone replacement therapy
VE/VCO_2	=	Ventilation relative to Carbon Dioxide production
VO_2	=	Oxygen Consumption

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