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REVIEW

Testosterone and heart failure

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Abstract Testosterone deficiency is a generalized phenomenon seen in the course of chronic heart failure (CHF). Reduction in circulating testosterone level is a predictor of deterioration of functional capacity over time, underscoring the role of testosterone deficiency in CHF. Anabolic hormones are determinants of exercise capacity and circulating levels of anabolic hormones strongly determine muscle mass and strength. Testosterone deficiency is involved in the pathophysiology of CHF, contributing to some features of this syndrome, such as the reduced muscle mass, abnormal energy handling, fatigue, dyspnea and, finally, cachexia. This review summarizes current knowledge on the role of testosterone deficiency in the pathophysiology of CHF, gaining insights from the potential implications of testosterone as supplementation therapy.

Keywords Heart failure · Testosterone · Exercise capacity · Muscular function

Established evidence indicates that chronic heart failure (CHF) is a syndrome involving not only the failing heart but also peripheral skeletal muscles as well as neurohumoral, endocrine, and metabolic systems. These include, among others, a decrease in testosterone levels. Low plasma levels of testosterone have been reported in patients with CHF [1–3] and it has been hypothesized that a relative hypotestosteronaemia could be involved in the impairment of skeletal muscle function and exercise tolerance which occur in the CHF syndrome [4]. Indeed, approximately 25 % of men with CHF have biochemical evidence of testosterone deficiency, and low levels have been related to disease progression [5]. Relative testosterone deficit reflects one aspect of anabolic insufficiency that leads to a metabolic shift favoring catabolism, a major underlying mechanism for tissue wasting seen in CHF.

This review summarizes current knowledge on the role of testosterone deficiency in the pathophysiology of CHF, gaining insights from the potential implications of testosterone as supplementation therapy.

Pathophysiologic mechanisms sustaining CHF: role of testosterone

Anabolic/catabolic imbalance, which favors catabolism, is a key pathological feature of patients with advanced CHF [1, 6]. In an unselected cohort of men with CHF, Jankowska et al. [7] have demonstrated a high prevalence of reduced serum concentrations of anabolic hormones, including testosterone, which were markers of a poor prognosis, independent of conventional risk predictors and of the underlying cause of CHF. This finding suggests that testosterone deficiency is a generalized phenomenon seen in the course of CHF. Recently, the same group reported that circulating level of testosterone is directly and independently related to peak oxygen consumption and peak oxygen pulse in men with CHF [8]. In the same study a reduction in circulating testosterone level was the only predictor of the magnitude of deterioration in peak VO_2

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over time, whereas other indices related to the progression of heart disease, could not predict the deterioration of exercise capacity, a finding that underscores the pathophysiological role of testosterone deficiency in the progressive deterioration of functional capacity in male patients with CHF.

Anabolic hormones are determinants of exercise capacity. Age-related decline in circulating testosterone, dehydroepiandrosterone sulfate, and insulin-like growth factor 1 (IGF-1) contribute to gradually impaired exercise tolerance in elderly men [9–11]. Hence, it is not surprising that the deficiency in testosterone levels may significantly contribute to some features of advanced CHF, which mainly effects elderly patients, such as the reduced muscle mass, abnormal energy handling, fatigue, dyspnea and, finally, cachexia. Indeed, circulating levels of anabolic hormones strongly determine muscle mass and strength. Testosterone induces hypertrophy of both type I (oxidative "slow twitch") and type II (glycolityc "fast twitch") muscle fibers, but type I muscle fibers seem to be more sensitive to anabolic agents than type II muscle fibers [12]. It has been shown that the administration of testosterone induced an increase in the area of type I muscle fibers at low doses, whereas type II muscle fibers enlarge only after administration of high testosterone doses [13]. Probably, the effects of testosterone involve modifications in the expression of many muscle growth regulators, including IGF-I, IGF-binding protein-3, and myostatin [14]. Several studies are in agreement that testosterone directly stimulates intra muscular IGF-I mRNA and down-regulates respective binding proteins [15–17].

Objective morphological and functional abnormalities, relatively independent of reduced blood flow are present in the muscle of CHF patients [18]. These maldaptive changes in the muscles, which include fibers athrophy and a prevalence of type II fibers with a predominance of glycolitic over oxidative metabolism, have been consistently involved not only in symptoms development, but even in the pathophysiology and worsening of the HF syndrome, the so-called "muscle hypothesis" of CHF [19–21], in which a key role is played by an enhanced activation of the muscle metaboreflex mechanism in the control of cardiorespiratory function. In short, by the muscle hypothesis, structural and functional alterations in peripheral muscles occurring in CHF would elicit in time—an enhanced muscle metaboreflex (also called ergoreflex [21]) activation even at moderate levels of exercise. While the muscle metaboreflex is initially beneficial to compensate for reduced cardiac output by vasoconstricting inactive vascular beds and increasing HR, in time it would be responsible for the prolonged neurohumoral activation and abnormal hemodynamic, autonomic, and ventilatory responses to exercise that characterize CHF [20–22].

By the muscle hypothesis, the neurohormonal activation and an altered balance between catabolism and anabolism (in favor of catabolism) would contribute to disease progression and also to the transition from nonwasted HF to cardiac cachexia [19–21, 23, 24]. Indeed, the ergoreflex has been shown to be particularly enhanced in the cachectic subjects and to be accompanied by more marked muscle mass depletion, supporting its contribution to the progression of the syndrome of heart failure [1, 20]. Interventions specifically targeted at reversing peripheral muscle alterations such as exercise training have been shown to improve muscle structure and function and reduce muscle metaboreflex overactivity and ventilatory response to exercise in CHF, in addition to improve VO_2 [18, 21, 25]. The increase in leg muscle strength and work output that has been reported after testosterone supplementation [26], which reflects an improvement in muscle function, might have acted in the same manner, by decreasing the muscle metaboreflex overactivity. In support of this concept, anabolic administration at replacement doses has been shown to accelerates fast- to slow-oxidative fiber type conversion [27], which are typically reduced in CHF patients [21] and to increase the number and size of type I slow-oxidative fibers [28], which imply an improved oxidative capacity of skeletal muscles and a higher aerobic potential with a delayed fatigue and a reduced stimulation of muscle afferents. The favorable effects of testosterone on exercise capacity in CHF might thus result also from interaction with peripheral mechanisms involved in the pathogenesis of CHF syndrome, such as improvement in insulin sensitivity [26, 29]. Improved insulin sensitivity, with the attendant increased availability of glucose as an energy source for the skeletal muscle cells, might have contributed to the reduced fatigability and might have also acted by promoting peripheral vasodilation resulting in an increase in blood flow to exercising muscle. Finally, an improvement in endothelial function [30–32] cannot be ruled out.

Testosterone as a supplementation therapy in CHF: pathophysiological insights and clinical benefits

An improvement in survival rate has been reported in CHF in the last decade, which should be ascribed mainly to therapeutic strategies targeted to the pathophysiological mechanisms sustaining the progression and worsening of the disease, mainly the prolonged neurohumoral activation.

Insights into the role of testosterone in the HF syndrome come from studies investigating testosterone as supplementation therapy. In fact, the notion of testosterone deficiency in CHF and its relation to poor prognosis encouraged studies of testosterone replacement in patients with HF.

In the last few years, several studies have indicated the effectiveness of testosterone supplementation, within the physiological range, in patients with CHF [4, 26, 29, 33]. Pugh et al. [4] showed that intra-muscular testosterone therapy improved exercise tolerance, as evaluated by the distance walked at the shuttle walking test, without effects on muscle strength. Subsequently, the same group [22] reported the first randomized double-blind placebo-controlled trial of testosterone therapy, administered via transdermal patches for a 12-month period, in men with moderately severe systolic CHF and demonstrated a 40 % increase in serum level of testosterone which was associated to an improvement in exercise capacity, as indicated by the increased distance walked in an incremental shuttle walk test, and in forearm muscle strength. The increase in walking distance was positively correlated to increase in testosterone levels. In a recent 12-week double-blind, placebo-controlled randomized study, Caminiti et al. [26] showed that very long-acting intramuscular testosterone supplementation, requiring only few intermittent administrations (i.e., three), significantly improved both peak VO_2 and ventilatory efficiency, as assessed by the VE/VCO_2 slope, in patients with moderately severe CHF. These finding are of clinical, in addition to pathophysiological, relevance since both VO_2 and VE/VCO_2 slope discriminate individuals at high and low risk for cardiac mortality in CHF [34–37]. The significant correlation between increase in testosterone level with increase in functional capacity observed in this [26], as in previous, studies [4, 29] would support the hypothesis that the improvement functional capacity was related to testosterone administration. The lack of any change in the placebo groups in the above studies is consistent with this assumption. Thus, the improvement in functional capacity and ventilatory efficiency induced by testosterone supplementation might positively affect the prognosis in patients with moderate HF. Importantly, Caminiti et al. [26] also observed a significant improvement in both static and dynamic leg muscular performance in testosterone treated patients, as assessed by isometric and isokinetic maximal efforts, and the increase in muscle strength was positively related to the increase in testosterone levels. Moreover, also the work output and the fatigue index improved with testosterone administration. These findings imply an improvement in peripheral muscles function, particularly of large, weight-bearing, muscles which are the more relevant to the early fatigue and effort intolerance tolerance experienced by patients with CHF.

Hence, testosterone administration at doses within the physiological range could have direct beneficial effects on the muscle wasting of CHF patients through its anabolic action. It is worth of note that the improvement in VO_2 and in muscle strength was greater in patients with lower baseline testosterone levels but that the improvements in ventilatory efficiency, 6-min walking test and dynamic muscular performance did not differ significantly between patients with low and normal testosterone levels [26]. This would indicate that the benefits of testosterone supplementation are not entirely confined to CHF patients with low baseline testosterone.

Similar to the gradual decline of testosterone observed with aging in men, an age-dependent decline in endogenous total and free testosterone occurs also in women [38, 39]. Testosterone therapy in both sexes augments anabolic function, leading to increased muscle mass and physical strength. Indeed, in recent investigations, testosterone replacement therapy at physiological levels increased muscle mass and improved some cardiovascular risk factors in women with androgen deficiency [40, 41].

A recent study by Iellamo et al. [42] was the first to show that testosterone supplementation therapy at replacement doses administered via transdermal patches applied twice a week, has the same beneficial effects in postmenopausal women with moderate CHF like in men, despite much lower replacement doses.

In that study a significant 23 % relative increase in 6-min walking time coupled with a parallel increase in peak oxygen consumption (VO_2) was achieved, analogous to that found in a previous study in men by the same laboratory [26]. Like in man, a positive correlation was found between the change in free testosterone levels and the increase in walking time. In addition, both muscle strength and performance improved in patients supplemented with testosterone. These effects were not associated to any deleterious effect on lipid profile, or signs of virilization. On the contrary, testosterone supplementation was associated with significant increase in HDL-cholesterol. This finding confirms previous studies indicating that low-dose transdermal testosterone replacement has no deleterious effects on HDL, LDL, or triglycerides [43] and may even increase HDL-cholesterol. The controversial data on the effect of testosterone supplementation on HDL-cholesterol could be related to the route of administration, since HDL reductions has been reported with oral androgens administration [44].

Interestingly, testosterone supplementation induced an improvement in insulin sensitivity both in men and women with CHF [26, 42, 45, 46]. The prevalence of insulin resistance in CHF and its role on CHF development have been elucidated [47, 48]. Indeed, more than 40 % of HF patients manifest disorders of glucose metabolism [46], including women [49], and insulin resistance, leading to an inability of insulin to promote glucose transport into skeletal muscles, has been proposed as a mediator of skeletal muscle fatigue and wasting of CHF, linking these processes directly to the metabolic disturbances in HF patients [50]. Improved

insulin sensitivity at muscular level, through an increased availability of glucose as an energy source and through a reduced peripheral sympathetic overactivity, as a result of enhanced nitric oxide availability, might contribute to the reduced fatigability and might also act by promoting peripheral vasodilation resulting in an increase in blood flow and oxygen availability to exercising muscle, with the attendant improvement in muscle strength and effort tolerance. The mechanism by which testosterone would reduce insulin resistance are uncertain. An effect of testosterone on muscle insulin sensitivity has been suggested [51]. Another potential mechanism would be an action of testosterone on visceral adipocytes metabolism [9, 52].

A corollary, but potentially relevant clinical finding, is represented by the effect of testosterone supplementation on neural cardiovascular regulation. In fact, Caminiti et al. [26] reported an improvement in baroreflex sensitivity, a major negative prognostic indicator in CHF [53], in a subgroup of CHF patients after testosterone administration. This effect is likely to be the consequence of an effect of testosterone at central nervous system sites, since androgen receptors have been characterized in brainstem nuclei involved in baroreflex cardiac regulation [54] and a competitive androgen receptors blocking drug which penetrates the blood brain barrier was capable to attenuate BRS [55]. If improvement in baroreflex control of heart rate would also extend to baroreceptor reflex control of muscle sympathetic nerve activity, then, this would have the potential to increase muscle arteriole vasodilation and function. Future studies should include an examination of these possibilities.

Anyway, it does appear that the benefits of testosterone supplementation in CHF do not involve substantial changes in central hemodynamic. In fact, all the studies performed so far on chronic administration of testosterone failed to detect any change in left ventricular function.

As far as side effect of testosterone administration is concerned, skin reactions have been reported in studies using transdermal patches, that were related to the route of administration, whereas no side effects at cardiovascular level have been observed. No side effect requiring discontinuation of testosterone was observed with long-acting intramuscular testosterone, which requires evenly spaced administrations [26].

Conclusions

Low plasma levels of testosterone have been reported in patients with CHF and it has been hypothesized that a relative hypotestosteronaemia could be involved in the pathophysiology and clinical manifestations of HF syndrome.

Growing evidence indicates that testosterone supplementation therapy has the potential to improve muscle strength and power and functional capacity in both male and female patients with CHF. Improvement in insulin sensitivity may contribute to the beneficial effects of testosterone administration.

However, the optimal dose and route of administration is still to be established, as well as the patients who would benefit most by testosterone supplementation. At present, testosterone supplementation should be regarded only as an adjunctive therapy for patients with systolic CHF, inasmuch as no data on the effects of testosterone supplementation are available in patients with CHF and preserved ejection fraction, hypertrophic and other forms of cardiomyopathies. It should be mentioned that animal studies have suggested that testosterone might, indeed, induce hypertrophy, fibrosis, and apoptosis in cardiomyocytes [56, 57]. Contraindications to testosterone administration should be also considered. These include severe liver or kidney diseases, uncontrolled hypertension, significant pulmonary disease, erythrocytosis (hematocrit >50 %), prostate cancer or higher prostate-specific antigen (PSA) levels.

Larger, long-duration studies with clinical outcomes as endpoints, are needed to determine long-term efficacy and safety of such a replacement strategy in patients with CHF of both sexes.

Disclosure None.

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