

Effects of Hormonal Therapy in Patients with Heart Failure

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Received: April 29, 2014 Revised: September 1, 2014

Accepted: September 2, 2014

Published online: September 19, 2014

Key words: Chronic heart failure; Hormonal deficiencies; Growth hormone; Testosterone

Caminiti G, Fossati C, Battaglia D, Volterrani M. Effects of Hormonal Therapy in Patients with Heart Failure. *Journal of Cardiology and Therapy* 2014; 1(8): 169-175 Available from: URL: <http://www.ghrnet.org/index.php/jct/article/view/862>

ABSTRACT

Chronic heart failure is a multi-etiological disorder with high prevalence and poor prognosis. Several hormonal deficits have been observed in a consistent proportion of patients with this disease. Among them, testosterone deficiency and growth hormone/ insulin-like growth factor-1 axes impairment are highly prevalent and have been associated with a poor prognosis. Several experimental papers have highlighted the positive influence of growth hormone and testosterone in the regulation of heart development and performance. Moreover, many clinical studies have been started to investigate the effect of the administration of these two hormones in heart failure patients; a greater benefit has been evidenced in patients with hormonal deficiencies, by restoring physiological levels with hormonal therapy. These findings are promising, and, although not unanimously, indicate that both testosterone and growth hormone therapy should be considered as adjunctive therapy in advanced heart failure patients. However, larger randomized trials with longer treatment duration are needed to fully elucidate the efficacy and safety of the “hormonal therapy” in this patient population.

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INTRODUCTION

Chronic heart failure (CHF) carries a significantly high morbidity and mortality risk, despite the progressive improvement of medical management obtained in the last decades^[1]. Many patients still experience debilitating symptoms and poor quality of life even if they are on optimal medical therapy. Afterwards, there is a persistent need to discover new therapeutic strategies in order to slow down the progression of the disease, improve clinical symptoms and CHF outcomes.

CHF is a complex syndrome in which several pathophysiological mechanisms, in addition to primary heart disease, are involved^[2]. Multiple hormonal deficiencies are relatively common in CHF; they identify subgroups of patients with higher risk of mortality^[3]. The list of downregulated molecules includes Growth Hormone (GH) and its tissue effector Insulin-Like Growth Factor-1 (IGF-1), thyroid hormone, insulin and testosterone (T)^[4].

Taken together these hormonal disorders can worsen hemodynamic balance of CHF and simultaneously lead to a metabolic shift favoring catabolism and impairment in skeletal muscle bulk and function, the latter being involved not only in development of symptoms but even in the pathophysiology of the CHF syndrome^[5]. Hence, improving the anabolic status of patients with CHF could represent an additional therapeutic target acting on the pathophysiological mechanism that sustains the progression of the disease, possibly affecting survival.

In the last fifteen years several authors have been investigating the GH/IGF-1 axis deficiency and testosterone deficiency. This review discusses the physiological effects of both these natural hormones on

cardiovascular system, their therapeutic effects in heart failure and analyze data from the published studies that used GH or testosterone in patients with CHF.

GH/IGF-1 AXIS

GH is principally involved in the regulation of somatic growth, including cardiac development and function, and exerts its effects either directly or indirectly, by stimulating hepatic production of IGF-1, that mediates GH action on peripheral tissues. GH and IGF-1 are essential for preserving both cardiac morphology and performance in adult life^[6]. Patients with GH and IGF-1 deficiency have impaired cardiac performance, increased peripheral vascular resistance, and reduced exercise capacity. These hemodynamic alterations, that are similar of those observed in heart failure, can be corrected by replacement therapy^[7]. GH/IGF-1 axis has a complex interaction with cardiovascular system: it regulates cardiac growth^[8], stimulates myocardial contractility^[9] and influences vascular tone.

The GH/IGF-1 axis regulates cardiac growth and metabolism, by increasing amino acids uptake, protein synthesis, cardiomyocyte size and muscle-specific gene expression^[10-12]. Ito *et al*^[13] evaluated the effects of IGF-1 administration on cardiac myocytes in rats. After administration of IGF-1, cardiac myocytes were enlarged and expressed increased levels of mRNA of actin, myosin light chain 2 and troponin I. Moreover, IGF-1 prevented myocyte loss by reducing apoptosis of cardiomyocytes^[14].

The GH/IGF-1 axis enhances intrinsic cardiac contractility by several mechanisms: by modulating myofilament calcium sensitivity^[11,12,15], increasing L-type calcium channel activity^[16] and up-regulating sarcoplasmic reticulum ATPase levels^[17].

On vascular system, the GH/IGF-1 axis exerts its effects by activating the nitric oxide system^[18] and regulating non-endothelial-dependent actions. IGF-1 may cause vasorelaxation both by enhancing Na⁺/K⁺ ATPase activity^[19] and regulating gene expression of K-ATP channel in vascular smooth cells^[20].

Low IGF-1 syndrome in CHF

The GH-IGF-1 neurohormonal axis is frequently abnormal in patients with CHF regardless of the underlying etiology. Kontoleon *et al*^[21] found that patients with CHF due to idiopathic dilated cardiomyopathy have lower levels of circulating GH and IGF-1 compared to healthy controls. Similarly low baseline levels of GH and IGF-1 were found in patients with moderate CHF caused by myocardial ischemia^[22]. In the study of Jankowska *et al*^[23] the estimated prevalence of IGF-1 deficiency in HF, defined as IGF-1 levels below the tenth percentile of healthy peers, was as high as 64%. However, IGF-1 deficiency has been clearly observed in patients with very advanced CHF^[24] and/or cardiac cachexia^[25], conditions in which elevated levels of GH often coexist with low levels of IGF-1, creating a state of ‘growth hormone resistance’. Instead, in the general population of CHF patients, data are more heterogeneous and levels of IGF-1 similar^[25-27] or higher^[28] compared to health controls have also been reported. On the other hand, data from the general population of CHF patients are more heterogeneous, and both^[25-27] similar or higher levels of IGF-1 compared to controls have also been reported.

Whether or not the assessment of IGF-1 levels has a prognostic relevance in CHF is still a debated point with different authors reporting conflicting results. While in a large study in men with CHF low levels of IGF-1 were related to unfavorable outcomes^[23], Andreassen *et al*^[26] did not observe any significant correlation

between IGF-1 levels and patients’ prognosis. Similarly in the study of Petrella *et al*^[24] the IGF-1/GH ratio, but not IGF-1, resulted independently related to survival of CHF subjects in the Cox’s regression analysis. As a consequence of these heterogeneous results, that can be explained by the complexity of GH/IGF-1 axis and its regulatory system involving binding proteins and other regulatory hormones to one side, and by differences on laboratory tests used for evaluating the GH/IGF-1 axis to the other side, there is not agreement on which is the best marker of GH/IGF-1 axis activity. Interestingly, in a population of 142 Japanese CHF patients, Watanabe *et al*^[29] found that the ratio of IGF-1 to IGF-binding protein-3, was associated with increased rates of all-cause mortality, cardiac death, and a composite of cardiac death and re-hospitalization.

The pathophysiology of the reduced activity of GH/IGF-1 axis seems to be multifactorial. Reduced somatotrophic secretion^[30] and peripheral GH resistance^[31] are both involved in the outbreak of low IGF-1 syndrome in HF patients. Other potential explanations include hypothalamic somatostatinergic hyperactivity, drug interference (angiotensin-converting enzyme inhibitors, digoxin, diuretics), nutritional changes caused by CHF, and increased angiotensin II and cytokine production^[32]. Finally GH/IGF-1 axis is markedly deranged in various catabolic conditions in which circulating and tissue levels of inflammatory cytokines are elevated^[33].

Experimental studies

(a) Cardiac effects. Several studies have been performed in rat models with induced myocardial infarction showing anti-remodeling and inotropic effects for GH/IGF-1. Castagnino *et al*^[34] found that a three days administration of GH in rats with experimental myocardial infarction lead to a significant decrease in the incidence of ventricular aneurysms. Amber *et al*^[35] showed that IGF-1 increased cardiac output and reduced histologically-detected myocyte damage in rats with a doxorubicin-induced cardiomyopathy. Duerr *et al*^[36] administered IGF-1 to rats during the onset of experimental post-infarction HF and found a significant increase in the hypertrophic response of viable myocardium and in cardiac performance. Other experimental studies confirmed that GH and/ or IGF-1 attenuates both the early and the late pathologic Left Ventricular (LV) remodelling after myocardial infarction, induces hypertrophy of non-infarcted myocardium, improves LV function and increases cardiac output^[37,38].

In the study of Kinugawa *et al*^[39] the acute IGF-1 administration in isolated cardiomyocytes, in both normal and heart failure conditions, exerted a direct positive inotropic effect, due to calcium transient amplitude and calcium availability to the contractile apparatus.

In a rat model, IGF-1 has been shown to improve contractility with an increase in force of contraction by 22% to 24%^[40]. This observed improvement of contractility^[41] is probably due to GH-mediated increase in systolic calcium transients^[42] mediated by a raised activity of the sarcoplasmic reticulum Ca²⁺-adenosine triphosphatase-2^[43].

(b) Peripheral effects. The few data available on peripheral effects suggest that GH/IGF-1 administration can counteract the muscle wasting typically observed during cardiac cachexia. IGF-1 is part of a highly conserved signaling pathway, also involving protein kinase B, that plays a major role in the regulation of skeletal muscle growth^[40]. Della Libera *et al*^[44] evaluated the effects of two different doses of GH on skeletal muscle of rats with HF. Authors demonstrated that the number of apoptotic nuclei, muscle atrophy, and serum levels of Tumour Necrosis Factor α (TNF- α) were decreased with GH compared to controls.

Clinical studies

First evidences of effectiveness of GH replacement therapy in patients with HF has been obtained in small uncontrolled studies. Volterrani *et al.*^[45] observed that a continuous intravenous administration of GH over 24 hours increased cardiac output by more than 50% and decreased pulmonary artery pressures by 25% in 12 patients with CHF due to either ischemic or dilated cardiomyopathy. Fazio *et al.*^[46] treated seven patients with CHF due to dilated cardiomyopathy with recombinant human growth hormone (2 IU rhGH/daily) showing substantial improvements of cardiac function and exercise capacity. Similarly Genth-Zotz *et al.*^[47] administered rhGH for 3 months in patients with ischemic cardiomyopathy. They observed a significant decrease of left-ventricular end-diastolic volume, significant improvement in hemodynamics and exercise tolerance evaluated by cardiopulmonary test.

Based on these promising preliminary results two randomized double-blind placebo-controlled trial were performed. Osterziel *et al.*^[48] randomized 50 patients with CHF secondary to dilated cardiomyopathy to daily 2 IU rhGH or placebo for 12 weeks. Despite an increase in left-ventricular myocardial mass, that was positively related to the IGF-1 levels, left ventricle ejection fraction (LVEF) and left-ventricular end-diastolic volumes were unchanged. Moreover, authors did not find a beneficial effect on NYHA functional class or on the 6 minutes walking distance. In another double-blind placebo-controlled study^[49] twenty two patients with CHF of different aetiologies were randomized to rhGH (0.1 IU/kg per week) or placebo for 3 months. All patients responded with a significant increase in IGF-1 levels. However there was no significant effect on ejection fraction at rest or during exercise and there was no increase in LV mass. These results were confirmed in a smaller study on 19 patients with the administration of GH (0.03 IU/kg rhGH daily) versus placebo. After 8 weeks of treatment, there was no significant effect on LVEF or peak oxygen consumption; however, LV mass appeared to be increased^[50].

These randomized trials were limited by several factors such as small sample size (<50 patients) and short follow-up (3 months). Moreover the administered dose was highly variable. Lastly, all the reported trials were based on the administration of pharmacological doses of GH, independently of the GH/IGF-1 baseline status of the study population. This latter point seems to be of crucial importance in order to predict the therapeutical response to GH therapy. In a randomized single-blinded trial on patients with GH deficiency conducted by Cittadini *et al.*^[51], 56 HF patients were randomized to GH replacement therapy or control. GH replacement therapy was performed for 6 months at the dose of 0.012 mg/kg every second day. Exercise duration, peak workload, and peak VO₂ consumption increased by 14, 15, and 16% respectively. The authors also observed an increased LVEF (from 34.2 to 36.2%; $P=0.01$) and reduced circulating N-terminal pro-brain natriuretic peptide levels only in the active group. These benefits were recently confirmed by the same authors after a 4-years follow up: peak VO₂ improved of 7.1 ± 0.7 mL/kg/min in the GH group versus -1.8 ± 0.5 mL/kg/min in control patients; LVEF increased by $10 \pm 3\%$ in the GH group, whereas it decreased by $2 \pm 5\%$ in control patients^[52].

Moreover, despite the first placebo-controlled trials failed to confirm benefit from GH therapy in patients with HF, as previously observed in uncontrolled studies, results of two recent meta-analyses including 12 and 14 studies respectively^[53,54] suggested that GH treatment can improve several cardiovascular parameters in those patients. Tritos *et al.*^[54] observed a significant increase in exercise duration by 1.9 minutes and in maximal oxygen consumption by 2.1

mL/kg per minute. NYHA class resulted decreased by 0.9.

This discrepancy may also reflect the heterogeneity of IGF-1 increase in response to GH administration. In the study of Fazio *et al.*^[46] patients whose IGF-1 increased by more than the median increase, had an increase of ejection fraction of 7% in comparison to patients with an increase below the median. The presence of a close relationship between change in IGF-1 concentration and GH effects was also confirmed by the meta-analysis of Le Corvoisier^[53].

Recently alternative mechanisms of action have been explored. Adamopoulos *et al.*^[55] investigated the immunomodulatory effects of rhGH administration in CHF. After 12-weeks of treatment authors observed that circulating levels of proinflammatory cytokines, such as TNF- α and interleukin-6 were normalized. The same group subsequently reported that GH reduced the soluble adhesion molecules, the granulocyte-macrophage colony-stimulating factor and the macrophage chemoattractant protein-1^[56].

Side effects: No major adverse events have been reported in the patients who received GH. Frustaci *et al.*^[57] treated 5 patients with dilated cardiomyopathy in a very advanced stage with rhGH, observing an increase of ventricular arrhythmias.

TESTOSTERONE DEFICIENCY IN CHRONIC HEART FAILURE

Androgens are associated with important and multifaceted effects on heart and vascular system in both sexes. In particular T plays an important role in cardiovascular physiology by influencing cardiac function, endothelial function and vascular tone^[58].

T deficiency is a common finding in men with CHF involving about a quarter to a third of subjects with moderate/severe CHF^[21,23]. Serum levels of total and free T in men with CHF were decreased in proportion to CHF severity, while no differences in androgen levels have been found between male patients with CHF of ischemic origin and those with CHF of non-ischemic origin. Androgens deficiency in CHF is not a simple surrogate of disease severity but seems to significantly contribute to worsening the prognosis. Low T levels, together with the depletion of other anabolic hormones, have been identified as independent risk markers for decreased exercise capacity and poor clinical outcome in male patients with HF in several studies^[23,59,60].

Experimental studies

Several studies performed on coronary arteries of rats and swines demonstrated that T has a direct smooth muscle-relaxing, endothelium-independent vasodilatory effect^[61,62]. This effects on arteries seem not to be mediated by androgen receptors^[62]. The vasodilatory effect of T suggest that it directly affects the tunica media of the arteries, possibly by inhibiting L-type and T-type calcium channels^[63]. However some data in favour of a vasoconstrictive effect of T also exist. In isolated and perfused rat hearts, Ceballo *et al.*^[64] showed that T partially inhibits the vasodilatory effect of adenosine by increasing vascular resistance, leading to a decreased flow.

Several observations, obtained in animal models, suggested that T may contribute to the reduction of myocardial infarction size and may exert anti-remodeling effects once heart failure has developed. Liu *et al.*^[65] found that infarct size in the orchietomy group was significantly larger than both the sham and orchietomy plus T groups. Tsang *et al.*^[66] evaluated the infarct size of orchietomized, orchietomized plus T supplementation or controls, occurring as a result of ischemia plus reperfusion: hearts of orchietomized rats had a significantly larger myocardial infarction size than the

orchiectomized plus T supplementation group and control group. Li *et al*^[67] observed that T suppresses ischemia and electrical stimulation induced by norepinephrine release in the isolated rat hearts and that the flutamide could not block this inhibition. There are little informations regarding the mechanisms by which T counteract the ischemic injury of myocardium. It has been recently hypothesized that the beneficial effect of T on cell death may involve the opening of mitochondrial K-ATP channels, allowing K⁺ to more efficiently exit the mitochondria, this resulting in increased stability of the mitochondria^[68].

Conflicting data exist regarding the relation between testosterone supplementation (TS) and cardiomyocytes apoptosis. TS and testosterone plus estrogen supplementation in cardiomyocytes of ovariectomized rats reduced apoptosis occurring as a result of ischemia plus reperfusion; nevertheless high doses of T have been linked to significant myocardial hypertrophy, myocardial fibrosis and activation of apoptosis^[69]. The anti-remodelling effect of T in heart failure seems to be related to its cytokines modulation restoring the balance between pro-inflammatory and anti-inflammatory cytokines that is altered in heart failure^[70]. In particular, T suppresses the macrophage production of TNF α ^[71], while increases CD4+T-lymphocytes production of interleukin-10 (IL-10)^[72]. Zhang *et al*^[73] treated rats with heart failure with T or placebo. TS increased IL-10 levels, decreased TNF α , suppressed ventricular remodeling and improved cardiac function compared to placebo. Moreover, rats undergoing TS showed a lower mortality rate than placebo (31.8% vs 68.2%).

Clinical studies

Haemodynamic effects. Given its vasodilatory proprieties, T may be beneficial to patients with CHF who have a maladaptive chronic vasoconstriction, by decreasing afterload and improving coronary artery blood flow. In the study of Pugh *et al*^[74] subjects were given T 60 mg via oral route and central haemodynamics were monitored over 2 days. The acute administration of T determined a 10.3% increase of cardiac output and a 17.4% decrease in systemic vascular resistance. Improvement of electrocardiographic signs of ischaemia during exercise stress testing, as a result of coronary vasodilation, has been observed in hypogonadal patients after TS^[75,76].

Clinical effects: (a) functional capacity: In a first double blind, placebo controlled, pilot study, significant improvements in exercise capacity and symptoms in men with CHF following treatment with T compared to placebo were observed^[77]. This was a small study, conducted on twenty ambulatory male patients (median age 62 years), with a short, 12-weeks, follow up. T was administered by intramuscular injection every two weeks and exercise tolerance was evaluated by 6 Minutes Walking Test (6MWT). This preliminary result was confirmed in a larger, double-blind randomized placebo controlled trial, with a 12 months follow up conducted in a similar population of stable CHF patients. Malkin *et al*^[78] enrolled 76 men with CHF (LVEF 32.5 \pm 11%) over a maximum follow up period of 12 months. In this study T was supplied as an adhesive skin patch (Androderm 5 mg). The primary outcome was change on functional capacity assessed by the Incremental Shuttle Walk test at 12 months; changes on quality of life, mood and depressive symptoms were also assessed. Subjects on TS had a 25% increase of functional capacity compared to placebo at 12 weeks. NYHA class also improved by at least one functional class in 35% patients in T group compared with 8% in placebo group ($p=0.01$). Instead, no between groups differences in Minnesota Living with Heart

Failure or Beck Depression Inventory were found. Moreover, there were no changes in cardiac morphology or LVEF. In this study 19 patients withdrew due to skin reactions and 55% experienced minor skin reactions.

Our group made the most objective evaluation of changes in functional capacity after TS^[79]. Seventy elderly patients with stable CHF, median age 70 years, LVEF 31.8 \pm 7%, were randomly assigned to receive T (intramuscular injection every 6 weeks) or placebo for 12 weeks. The primary outcome was change on functional capacity assessed by cardiopulmonary test; muscle strength, glucose metabolism, baroreflex sensitivity were also evaluated. The study demonstrated a clear improvement of performance at cardiopulmonary test after T replacement: peak VO₂ (2.9 \pm 0.8 vs 0.3 \pm 0.07) significantly increased, and VE/VCO₂ slope (-4.4 \pm 1.0 vs -1.5 \pm 0.4) significantly decreased in patients receiving T compared to placebo. Also 6MWT distance, NYHA class, muscle strength and baroreflex sensitivity significantly improved in T compared to placebo group. Again in this study no significant change in LVEF or other echocardiography parameters were detected in either group. Interestingly the increase in peak VO₂ and muscular strength were related to the increase in plasma levels of testosterone and not related to changes in left ventricular function suggesting that T exerts direct effect on skeletal muscles without affecting myocardial function. The improvement of several prognostic indicators observed in this trial suggests that TS can impact the outcome of CHF subjects.

The recent metanalysis of Toma *et al*^[80] confirmed that TS in patients with CHF is associated with an improvement in exercise capacity by 54 m using the 6MWT. Trials results suggest that TS acts through peripheral mechanisms. This is confirmed by the finding that the improvement in exercise capacity in these studies occurred in the absence of any change on myocardial structure or function such as LVEF. It is possible that TS determines a peripheral vasodilation leading to an increase of cardiac output; this in turn improves oxygen delivery to skeletal muscles that secondarily delay transfer to anaerobic metabolism.

An important issue that need clarification is which should be the target population of TS. At first it is not clear whether TS represents a potential therapy only for male subjects or it can be effective also in females. Results of the only trial carried out on women with CHF secondary to coronary artery disease show that TS exerts similar effects in women than in men^[81]. In this study thirty-six female patients with stable CHF (LVEF 32.9 \pm 6) were randomly allocated in a 2:1 ratio to receive testosterone transdermal patch or placebo for 24 weeks. At the end of the study there was a significant increase of peak VO₂ and a significant decrease of VE/VCO₂ slope only in the TS group. 6MWT distance, NYHA class, muscle strength, and insulin sensitivity significantly improved in testosterone compared to placebo group. On the other hand, no significant changes in LVEF, heart rate, or systolic and diastolic blood pressure were detected in either group.

Another point that remains to be clarified is to determine if TS can benefit all CHF subjects or only those with reduced testosterone levels. This point is difficult to establish because most studies did not used baseline testosterone levels as inclusion or exclusion criteria. We observed that the improvement in peakVO₂ and muscle strength were greater in male patients with lower baseline testosterone levels; while the improvements in ventilatory efficiency, 6MWT, dynamic muscular performance and insulin sensitivity did not differ significantly between male with low and normal testosterone levels^[79]. Interestingly, also in women, the improvement in 6MWT distance in the treated group was greater in patients with low T levels

than in patients with normal baseline T levels^[81].

Given its prevalent peripheral effects TS could enhance the effects of exercise training determining greater symptoms relieve. In a double blind randomized controlled trial, Stout *et al.*^[82] studied forty-one elderly male patients with CHF and low T status which were randomly allocated to exercise with T or exercise with placebo groups. They observed similar improvements in the Shuttle Walk Test (18% vs 19%), body mass (-1.3 kg vs -1.0 kg), and hand grip strength (2.1 kg vs 2.5 kg) from baseline in the two groups. However, the exercise with T group showed significant improvements from baseline in peak oxygen uptake, Beck Depression Inventory, leg strength, and several quality of life domains of Medical Outcomes Study Short-Form; none of these results were found in the exercise with placebo group.

Other effects: Some small clinical studies suggest alternative mechanisms by which TS could improve clinical conditions of CHF patients. Thirteen patients with moderate to severe HF received either TS or placebo for 4 weeks. TS significantly improved insulin resistance (1.9 ± 0.8 HOMA units; $p=0.03$), and the response was inversely correlated with the increase in bioavailable T^[83]. Similar results were observed in other studies conducted in both males and females, in which insulin resistance was a secondary endpoint^[79,81].

Although anti-inflammatory effects of T have been suggested by experimental studies^[73] and clinical trials in subjects with coronary artery disease^[84], in men with CHF serum levels of TNF- α were similar before and after treatment with T or placebo, irrespective of the length of study or route of administration^[85]. Similarly Stout *et al.*^[82] found that inflammatory markers were unchanged after TS.

Side effects: The meta-analysis of Toma *et al.*^[77] showed no safety concerns in any of the trials. The main adverse effects of TS included local inflammation and rash at the site of administration. In particular, there was a high drop out rate in the study of Malkin *et al.*^[75] due to skin reactions, but it was the only study with a long term follow up. No trial showed significant increase of prostate specific antigen in men. However, in order to rule out any possible important side effect, a long-term surveillance in larger numbers of patients is required.

CONCLUSION

Available data support the idea that treatment with GH and T effectively impact clinical conditions of CHF patients with significant benefits that appear to be greater in those with hormonal deficiency. Given its impact on strong prognostic factors, its broad spectrum of positive effects and its safety, the “hormonal” therapy provides a potential future therapeutical option in CHF. However, up to the present, it cannot be recommended because of the scarcity of long term studies. If clinical benefits will translate into an improvement of the patients’ outcome remains to be established. To this purpose, larger randomized trials with longer treatment duration are needed to fully elucidate the efficacy and safety of rhGH and T therapy in CHF.

Interestingly, though both GH and T improve exercise tolerance, one of the leading symptoms of CHF, they seem to act through complementary mechanisms. Indeed, while treatment with rhGH has been mostly associated with improvement of several “central” cardiac parameters, treatment with testosterone demonstrated almost exclusively “peripheral” effects. Therefore it is possible that GH and T could have additive effects. Unfortunately no data are available on their simultaneous administration in CHF patients with multiple hormonal deficit.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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