Myths and Truths of Growth Hormone and Testosterone in Heart Failure

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Abstract

Heart failure is a chronic clinical syndrome with very poor prognosis. Despite being on optimal medical therapy, many patients still experience debilitating clinical symptoms and have poor quality of life. In recent years, there is great interest in anabolic hormone replacement therapy—namely, growth hormone and testosterone—as an adjunctive therapy in patients with advance heart failure. It has been observed that low levels of growth hormone and testosterone have been associated with increased mortality and morbidity in patients with heart failure. Animal studies and clinical trials have shown promising clinical improvement with hormonal supplementation. Growth hormone has been shown to increase ventricular wall mass, decrease wall stress, increase cardiac contractility, and reduce peripheral vascular resistance, all of which helps to enhance cardiac function resulting in improvement in clinical symptoms. Likewise, testosterone has been shown to improve hemodynamic parameters via reduction in peripheral vascular resistance and increased coronary blood flow through vasodilation thereby improving functional and symptomatic status. To date, growth hormone and testosterone therapy have shown largely positive benefits with minimal adverse effects. However, large, randomized, controlled trials are still needed to assess long-term safety and efficacy.

Keywords
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Growth hormone
Insulin-like growth factor
Testosterone
**Introduction**

Heart failure (HF) is a chronic, complex clinical syndrome of multiple etiologies that results in structural and functional changes whereby the heart needs higher-than-normal filling pressures to maintain cardiac output. The result is symptoms of dyspnea, decreased exercise tolerance, and fluid retention due to pulmonary edema and peripheral edema[1]. Heart failure carries an abysmal prognosis with about 50% of patients dying within four years of diagnosis.[2] Patients with advanced HF can develop cardiac cachexia, defined as non-edematous weight loss of greater than 7.5% of previous normal weight over a 6 month period.[3] Cardiac cachexia is characterized by a tendency towards a catabolic state secondary to the activation of tumor necrosis factor-α (TNF-α), and other proinflammatory cytokines including interleukin-1 (IL-1) and interleukin-6 (IL-6). [4] Patients with cardiac cachexia have considerably worsened prognosis: 50% mortality at 18 months compared to 17% in noncachectic patients. [5]

Patients with heart failure have been observed to have derangements in several neurohormonal systems such as the sympathetic nervous system and the renin-angiotensin-aldosterone system, both of which are the target of excellent medical therapies to abate the maladaptive changes characteristic of heart failure[6]. A new area of interest is hormonal dysregulation in HF. Alterations in the growth hormone/insulin-like growth factor-axis (GH/IGF-1) and deficiencies in other anabolic hormones such as testosterone have prompted an interest in hormonal therapy for HF.

The current perception of hormone therapy is controversial. With the media scrutiny of anabolic steroids use in competitive sports, the potential adverse effects of supratherapeutic levels, and the risk for certain cancers, hormone therapy is generally
approached with caution. Current American College of Cardiology and American Heart Association (ACC/AHA) guidelines recommend against starting hormone therapy in patients with HF, outside of replenishing documented deficiencies. We herein review the evidence behind this recommendation, examining both the efficacy and the safety of GH/IGF and testosterone supplementation in patients with HF.

**GH/IGF-1 Axis**

GH is a single-chain peptide anabolic hormone that is secreted in a pulsatile manner by somatotroph cells of the anterior pituitary gland. GH stimulates the production of insulin-like growth factor 1 (IGF-1) in liver, kidney, and other peripheral tissues. GH acts directly via an endocrine mechanism as well as indirectly via autocrine/paracrine mechanisms mediated by IGF-I. IGF-1 circulates bound to protein carriers, IGFBPs; 80% of IGF-1 is bound to IGF-BP3. The myocardium and the endothelium express receptors of both GH and IGF-1, in addition to producing IGF-1 locally. The relationship between the GH/IGF-1 axis and the cardiovascular system has been studied extensively. The GH/IGF-1 axis directly effects cardiac contractility by enhancing the intracellular calcium availability and regulating expression of contractile proteins. GH/IGF-1 axis stimulates cardiac growth by increasing protein synthesis. IGF-1 modifies systemic vascular resistance by activating the nitric oxide system and regulating nonendothelial-dependent actions. IGF-1 has been shown to promote cell growth and reduce cardiomyocyte apoptosis. Furthermore, IGF-1 participates in angiogenesis and repair following ischemic events.
In patients with GH deficiency, patients were found to have increased total body fat, atherothrombotic and pro-inflammatory abnormalities, dyslipidemia, and insulin-resistance.[15, 16] They were also observed to have increased vessel intima-media thickness, high peripheral vascular resistance and enhanced aorta stiffness.[17, 18] Patients with childhood-onset GH deficiency (GHD) have decreased left ventricular mass and hypokinetic syndrome, a state characterized by low ejection fraction (EF), low cardiac output (CO), and high peripheral vascular resistance. [19-21] Adult-onset GHD did not share features of reduced cardiac mass; however, patients do have impaired cardiac performance and exercise capacity. [22, 23]

In GH replacement trials in patients with GHD, GH was shown to have beneficial effects on lean and fat body mass, and improve dyslipidemia. [24] GH replacement also improved LV mass, cardiac performance, diastolic filling and systolic function. [16, 25] However, these changes returned to baseline 6 months to 48 months after GH discontinuation. [25, 26] Despite a few studies that did not report significant changes in cardiac mass and performance[27-29], the majority of trials have shown positive effects on LV mass, wall thickness, LV end-diastolic and end-systolic diameters and cardiac output. [30]

Patients with heart failure have been found to have alterations in the neurohormonal axis. Kontoleon et al. found a significant decrease in growth hormone, insulin-like growth factor I, and testosterone concentrations in patients with chronic heart failure due to idiopathic dilated cardiomyopathy. Growth hormone, insulin-like growth factor I, and free testosterone levels were 0.37+/-0.2 ng/ml, 123.7+/-50 ng/ml and 48.6+/-23.8 pmol/l, respectively in the study group, versus 0.5+/-0.4 ng/ml (P<0.01),
236.3+/−66.4 ng/ml (P<0.001) and 105+/−17 pmol/l (P<0.01), respectively, in the control group.[31] Osterziel et al. observed similar findings of low GH/IGF-1 levels in noncachetic patients with ischemic heart failure compared to age-matched controls[32]. Furthermore, the IGF axis, the ratio of IGF-1 to IGF-binding protein-3 (IGFBP-3), has been shown to be significantly decreased in HF patients compared to control groups, [median(inter-quartile ranges), 0.114 (0.063–0.150) vs. 0.099 (0.052–0.158), P ¼ 0.042].[33] The IGF axis was lower in patients with New York Heart Association (NYHA) functional class III/IV than those with class I/II [0.071 (0.044–0.145) vs. 0.107 (0.068–0.161), P = 0.022]. It was also observed that low IGF axis was associated with increased rates of mortality (P = 0.013), cardiac death (P = 0.035), and both cardiac death and re-hospitalization (P = 0.0085).

**Animal models**

In animal models, GH or IGF-1 has been shown to have beneficial effects on cardiac function, peripheral resistance and survival[34-36]. Yang et al. showed that GH treatment in rats with left ventricular dysfunction enhanced myocardial contractility, cardiac output, and stroke volume. Furthermore, there was a decrease in left ventricular end-diastolic pressure and peripheral vascular resistance [35]. Duerr et al. demonstrated an augmented hypertrophic response of viable myocardium and cardiac function in rats with post-myocardial infarction heart failure given recombinant IGF-1[36]. It was subsequently shown that in the post-infarct rat model that GH prolonged survival, thought to be due to enhanced LV function via marked attenuation of cardiomyocyte apoptosis and pathologic interstitial remodeling in the surviving...
myocardium[37]. A similar retardation of cardiomyocyte apoptosis has been shown in ethanol-induced apoptosis of the myocardium with administration of IGF-1, thus improving cardiac muscle survival[13].

Clinical Intervention trials

Clinical studies have been conducted to evaluate the effects of GH/IGF-1 administration in patients with HF who were already on conventional medical therapy. Fazio et al. was the first group to assess GH therapy in patients with idiopathic dilated cardiomyopathy with moderate to severe heart failure with NYHA functional class with mean of 2.7, AHA Stage C, and LVEF mean of 34% [38]. The open trial study included seven patients who were given 4 IU of recombinant GH (rhGH) every other day over three months. The group observed an increase in left ventricular wall mass from 275±11g to 326±12g (P<0.05), LVEF from 34±1.5 to 47±1.9 (P<0.05), and exercise duration from 6.5±0.5 to 8.9±0.9 (P<0.05), resulting in improvement in hemodynamics, exercise capacity, and myocardial energy metabolism. The patients reported a feeling of well-being and an improved quality of life. Succeeding studies also showed similar results of increased left ventricular mass and hypertrophy with improvement in clinical symptoms[39-41].

In contrast, subsequent randomized, placebo-controlled studies did not observe significant beneficial effects of GH administration[42-45]. In a randomized, placebo-controlled study with 22 patients, Isgaard et al. evaluated the effects of GH in patients with CHF of different etiologies[44]. The group found that GH administration (0.1 IU/kg daily for week 1, 0.25 IU/kg daily for subsequent weeks over 3 months) significantly
increased serum IGF-1 and IGF-1 binding protein 3 (IGF-BP3), which indicated a good response to GH and no obvious GH resistance. However, there were no significant changes in systolic and diastolic function or left ventricular mass. Furthermore, there was no affect on exercise performance, neuroendocrine activation or NYHA classification. Smit et al. found similar findings in their study. The group investigated effects of GH treatment over 6 months on left ventricular function in patients with ischemic cardiac failure. They found no change in LVEF and left ventricular mass. There were also no improvement in left ventricular end diastolic and end-systolic volumes and left ventricular myocardial perfusion[43]. However, they also observed that the increase in IGF-1 in their study group was less than that observed in other studies despite comparable dosage of GH. These findings could be explained by the presence of partial resistance to GH in patients with chronic HF and other chronic illnesses[46]. Consistently, other studies have shown that patients with advanced HF have decreased sensitivity to GH[5, 47].

Furthermore, in a randomized, placebo-controlled study by Acevedo et al., the group evaluated the effects of GH on resting left ventricular ejection fraction, exercise capacity and neurohormonal status in patients with advanced HF. They also observed no significant change in aerobic capacity, resting left ventricular ejection fraction and/or neurohormonal status despite significant improvements in IGF-1 and IGF- binding protein-3 plasma levels[45].

The initial small clinical trials, mentioned above, have shown benefit with GH therapy, however, subsequent larger randomized-controlled trials have shown inconsistent results of improvement in clinical status and cardiac structure and
performance. Tritos et al. performed a meta-analysis of fourteen trial of all types, from uncontrolled to randomized-controlled trials, examining the efficacy and safety of GH therapy in patients with HF secondary to LV systolic dysfunction.[48] They found significant treatment effects (weighted mean difference [95% CI]) for several clinical endpoints including increased exercise duration (1.9 min [1.1-2.7 min], decreased in NYHA class (0.9 [-1.5 to -0.3]) and increased in maximum oxygen consumption (VO$_{2\text{max}}$) by (2.1 mL/kg·min [1.2-3.0 mL/kg·min]). There was also a significant increase in LV mass and wall thickness. Of note, there was a significant association between increase in the serum IGF-1 level and decrease in NYHA class (beta coefficient, -1.97 [-2.72 to -1.23]; P<.001). There was a positive association between increase in serum IGF-1 level and LVEF (beta coefficient, 5.77 [0.39-11.14];P=.035), as well as LV mass (beta coefficient, 32.12 [7.64-56.6]; P=.010).

The variability of response to GH therapy in previous clinical studies led Anker et al. to conduct a study evaluating whether GH resistance is present in patients with HF and whether it may be linked to biochemical response to GH therapy[49]. Acquired GH resistance is a feature of severe catabolism and malnutrition in chronic and critical illnesses [50, 51]. This study found that cachectic patients, but also some noncachectic patients with HF have characteristics of acquired GH resistance, thus preventing response to GH therapy. Cachectic patients showed an increase of total GH and immunologically intact GH and a decrease in IGF-BP3, IGF-1, and GH-BP levels compared with noncachectic patients. There was a 12-fold higher GH/IGF-1 ratio in noncachectic compared to cachectic patients with HF.
**Special populations that may benefit from GH therapy**

Heart failure patients with cachexia have a similar metabolic profile that is comparable to patients with AIDS-associated wasting. These patients also were observed to have biochemical characteristics of GH resistance [52]. Higher dose of GH therapy have been approved by the Food and Drug Administration for treating AIDS-associated wasting. Patients were treated with subcutaneous injections of 4-6 mg/day (12 to 18 IU/day) compared to 7-17 IU/week given in clinical trials with GH therapy in heart failure (one study gave 28 IU/week and another gave 56 IU/week) [48, 52].

Adverse effects observed included increases in tissue turgor complex and musculoskeletal discomfort. Positive effects were observed in two case reports where three cachectic patients with heart failure were given high doses of GH (70 to 98 IU/week for 1 to 3 months) [53, 54]. The patients had significant increase in muscle mass, strength, and exercise capacity. No adverse side effects were reported.

Patients with GH resistance were observed to have lower levels of IGF-1 thus coadministration of GH and IGF-1 may be beneficial in patients with HF with cachexia and GH resistance. Coadministration of GH and IGF-1 resulted in higher IGF-1 levels compared to administration of IGF-1 alone, which also reduces GH secretion via negative feedback. [55] Combination therapy of GH and IGF-1 also has been shown to reduce incidence of IGF-1 induced hypoglycemias and GH induced insulin resistance. [56]

**Safety**
Most clinical studies with GH administration were safe and did not have major side effects such as increased fluid retention or worsening of arrhythmias. [44] Tritos et al. did not find significant difference in deaths and HF exacerbation between study group compared to control group in fourteen trials (N=212). However, there was an increased risk of occurrence of ventricular arrhythmia among GH treated patients (5.3%) compared with placebo treated patients (0%) [48]. This finding was observed in one small and uncontrolled study that included patients with severely decreased LVEF, therefore, it is uncertain whether GH therapy has proarrhythmic effects. This will have to be addressed in larger studies.

In patients with GH resistance, the therapeutic dose of GH could potentially be increased. However, this may be risky due to the many possible side effects such as diabetes, sympathetic activation or sodium/water retention and carpal tunnel syndrome[57]. A study by Takala et al. used GH doses of 16 IU/day or 24 IU/day in critically ill adults post cardiac surgery, abdominal surgery, multiple traumas or acute respiratory failure[58]. They found that the mortality in the study group was approximately twofold higher than the control group. The majority of the deaths were due to multiple organ failure, septic shock, or uncontrolled infections. However, it was noted that these patients most likely did not have systemic inflammation and neurohormonal activation as a component of their disease [59].

The safety concerns for IGF-1 therapy are hypoglycemia, due to the insulin-like effects of IGF-1, and peripheral edema [57]. High levels of IGF-1 are also associated with increased risk for breast cancer in premenopausal women less than 50 years old [60].
**Testosterone**

Testosterone is a steroid hormone produced primarily in the testes, but also in the adrenal glands, as well as through peripheral conversion from adrostenedione, dehydroepiandrosterone, and dehydroepiandrosterons sulfate (DHEAS). Testosterone can either act in its native form or as 5-alpha dihydrotosterone (DHT), a more potent form when converted by 5-alpha reductase[61]. Both testosterone and DHT act primarily through the intracellular nuclear steroid receptor called androgen receptor (AR)[62]. Like other nuclear receptors, AR contains an N-terminal domain with glutamine repeats, a central DNA-binding domain, and a C-terminal ligand (in this case androgen) binding domain[63]. After testosterone binds the ligand domain of AR, the DNA-binding domain binds the hormone-response elements (HRE) near the regulated gene, and both co-activators and transcription factors stabilize the transcription-initiation complex promoting gene expression[64]. Testosterone has also been recently shown to act via another mechanism, separate from traditional intracellular AR (iAR) binding, which takes time to exert its effect on gene expression. In contrast, several membrane receptors have been identified on vascular smooth muscle cells that have a more rapid response to testosterone stimulation [65].

Testosterone has been shown in vitro to exert a vasodilatory effect on human vasculature[66]. Heart failure involves systemic vasoconstriction and increased vascular resistance, which testosterone have been shown to attenuate. Pugh et al. observed a decrease in vascular resistance and increases in cardiac output via pulmonary artery catheter measurements in patients with heart failure on testosterone therapy [67].
Animal models

Zhang et al. studied male rats with experimental myocardial ischemia and observed that rats given testosterone had significant improvements in LVEF as well as mortality compared to placebo group[68]. They observed that rats with heart failure were observed to have low serum levels of testosterone, elevated TNF-α, and decreased IL-10, a prominent anti-inflammatory factor. When compared to the placebo group, the testosterone group had a greater LVEF (P<0.05), a higher serum IL-10 level (P<0.05), and a lower serum TNF-α level (P<0.05). In addition, Wang et al. investigated the effect of testosterone on cardiac function in rat heart failure models. They demonstrated an improvement of cardiac performance and significant decrease in serum TNF-α level after testosterone administration compared to the untreated group[69].

Clinical Intervention Trials

Lower testosterone levels in heart failure correlate with increased mortality and morbidity. Jankowska et al. demonstrated the 3 year survival in a cohort of heart failure subjects (N=208) with normal levels of testosterone was 83%, but in those who were total testosterone and total testosterone/free testosterone deficient, survival decreased to 74% and 55%, respectively [70]. Furthermore, low testosterone levels have been associated with worsened heart failure symptoms, as documented by increased NYHA class [71, 72]. It has been reported that 26-37% of men with heart failure of any etiology have a testosterone deficiency.[31, 73]
Since low testosterone levels have been shown to correlate with poor HF outcomes, investigators studied testosterone replacement as a potential method to improve outcomes in heart failure. An initial study with 12 patients demonstrated that treating dilated heart failure patients with low dose testosterone resulted in improved cardiac parameters such as decreased left ventricular diameter, decreased left ventricular mass, and decreased natriuretic peptide levels [74]. A more recent, randomized, double-blinded, placebo-controlled parallel trial of testosterone replacement therapy to physiological doses with 76 men with moderate to severe heart failure showed improvement in NYHA class and incremental shuttle walk testing as a test of endurance [73].

Subsequent trials using physiologic doses of testosterone in patients with HF resulted in similar cardiac benefits as shown in previous trials. Caminiti et al. concluded that heart failure patients treated with adjunctive testosterone showed improvement in the mean peak oxygen consumption (16.3±1.7, P<0.05), mean 6-minute walk test (6MWT) (472.8±138.4 m, P<0.05), and mean quadriceps maximal voluntary contraction (SD 135.6±21.2 Nm, P<0.05) when compared with placebo (14.1±3.6), (428.2±2112.0), and (119±.726.3) respectively [75]. It was observed that increase in testosterone levels was significantly related to improvement in peak oxygen consumption, and maximal voluntary contraction. Interestingly, there was no significant changes in LV function either in testosterone or placebo [72]. Additionally, Iellamo et al. conducted a double-blind, randomized, placebo-controlled trial in which 36 elderly women with stable heart failure (average ejection fraction 33%) with normal total testosterone levels were treated with a testosterone patch versus placebo in addition to maximal medical therapy. The
results of this study were consistent to the results in previous studies in which there was significant improvement in 6MWT (357.2±43, P<0.05) as well as peak oxygen consumption (13.2±1.8, P<0.05) compared to the placebo group (291.3±39, P<0.05) and (10.1±1.3, P<0.05), respectively [76]. The increase in 6MWT related to increase in free testosterone levels. This study concluded that the increase in functional capacity was associated to the increase in plasma levels of testosterone and not associated to LV function.

**Safety Concerns with Testosterone Replacement**

Testosterone therapy has been linked to an exacerbation of prostate cancer [77] and increase in hematocrit [78], as well as being associated with atherosclerosis, unfavorable lipid profiles, ventricular hypertrophy, and cardiac dysfunction [79]. However, these adverse side effects where observed when testosterone was administered at supraphysiological levels, namely in anabolic steroid users. When administered at physiological levels, there is reported decrease in ventricular mass and an increase in cardiac index [67, 73, 80].

The Endocrine Society Task Force recommends testosterone therapy in symptomatic androgen deficient men (low morning total testosterone level). Testosterone therapy aims to initiate and preserve secondary sex characteristics, improve sexual function and sense of well-being, increase muscle mass and strength, and enhance bone mineral density. The goal testosterone levels should be within normal to mid-normal physiologic levels. Testosterone treatment is contraindicated in patients with breast or prostate cancer, a palpable prostate nodule, PSA > 4ng/mL or
3ng/mL in men at high risk for prostate cancer, hematocrit > 50%, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms with International Prostate Symptom Score above 19, or uncontrolled or poorly controlled heart failure[81].

Basaria et al. reported an increase in adverse cardiovascular-related events in the testosterone treatment group compared to placebo, which led to an early cessation of the study at the recommendation of the data and safety monitoring board[82]. The most common “cardiovascular-related event” in the testosterone group was peripheral edema. No echocardiographic nor catheterization findings were able to link this edema to a clear cardiac etiology. Furthermore, the testosterone group had at its baseline a higher incidence of hyperlipidemia and pre-existing cardiovascular disease compared to the control group, and with lipid profile being most consistently documented link to atherosclerosis among other risk factors [83], thus if there truly were an increase in “cardiovascular events,” they have been due to pre-existing cardiovascular disease rather than solely testosterone administration. It was also observed that the testosterone group received supraphysiological levels, which has already been documented to be potentially unsafe [79].

**Recommendations**

GH and testosterone therapy have been shown to have promising therapeutic effects in patients with HF, despite numerous small, short term clinical trials showing mixed results. Particular groups may benefit from supplementation in addition to conventional therapy, such as patients with hormonal deficiency or in the low normal range. Patients with GH resistance may warrant a pretreatment screening prior to
supplementation to adjust dosing and possible direct IGF-1 administration in addition to GH.

Testosterone treatment has been observed to have beneficial effects in both men and women with HF with few adverse effects. In our patients with advanced heart failure and other co-morbid conditions such as cachexia and depression, we routinely screen for and treat testosterone deficiency with successful increases in markers of nutritional status as well as improved functionality and sense of well-being. Despite the promising role of hormonal supplementation in HF, larger, long-term trials with hard clinical endpoints are warranted to assess efficacy and safety
References:


