Myths and Truths of Growth Hormone and Testosterone in Heart Failure

Cam T. Nguyen, MD, Alistair Aaronson, MD, Ryan P. Morrissey, MD, MeghaAgarwal, MD, Robert D. Willix, MD, Ernst R. Schwarz, MD, PhD

Advanced Heart Failure and Heart Transplantation,
Cedars-Sinai Heart Institute,
Cedars-Sinai Medical Center,
Los Angeles, CA, and Cenegenics Medical Institute, NV, USA

Words: 3,600; References:83

Brief title: Hormone therapy in heart failure

Corresponding author:
Ernst. R. Schwarz, MD, PhD, FACC, FAHA, FESC
Address: 8700 Beverly Bl #6215
          Los Angeles, CA 90048
Phone: 310-423-3851
Fax: 310-423-0127
Email: ernst.schwarz@cshs.org

<u>Abstract</u>

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.

Introduction

Heart failure (HF) is a chronic, complex clinical syndrome of multiple etiologies that results in structuraland 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-edematousweight 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 testosteronehave 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. [6]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[7].IGF-1 circulates bound to protein carriers, IGFBPs; 80% of IGF-1 is bound to IGF-BP3 [8]. The myocardium and the endothelium express receptors of both GH and IGF-1, in addition to producing IGF-1 locally[9, 10]. 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[11]. 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[12].IGF-1 has been shown to promote cell growth and reducecardiomyocyteapoptosis[13].Furthermore, IGF-1 participates in angiogenesis and repair following ischemic events[14].

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 oflow GH/IGF-1 levels in noncacheticpatients withischemic 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 ventricularend-diastolic pressure and peripheral vascular resistance [35].   Duerr et al.demonstratedan 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 shownin ethanol-induced apoptosis of the myocardiumwith 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 massfrom 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

nosignificantchanges 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_{2max}) 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 dihydrotestosterone (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 ischemiaand observed that ratsgiven 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 InterventionTrials

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 showedimprovement 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 beingassociated 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:

1.   Hunt, S.A., et al., *ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society.* Circulation, 2005. **112**(12): p. e154-235.

2.   Remme, W.J. and K. Swedberg, *Guidelines for the diagnosis and treatment of chronic heart failure.* Eur Heart J, 2001. **22**(17): p. 1527-60.

3.   Anker, S.D., et al., *Wasting as independent risk factor for mortality in chronic heart failure.* Lancet, 1997. **349**(9058): p. 1050-3.

4.   von Haehling, S., et al., *Cachexia: a therapeutic approach beyond cytokine antagonism.* Int J Cardiol, 2002. **85**(1): p. 173-83.

5.   Anker, S.D., et al., *Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia.* Circulation, 1997. **96**(2): p. 526-34.

6.   Strobl, J.S. and M.J. Thomas, *Human growth hormone.* Pharmacol Rev, 1994. **46**(1): p. 1-34.

7.   Casanueva, F.F., *Physiology of growth hormone secretion and action.* Endocrinol Metab Clin North Am, 1992. **21**(3): p. 483-517.

8.   Laron, Z., *Insulin-like growth factor 1 (IGF-1): a growth hormone.* Mol Pathol, 2001. **54**(5): p. 311-6.

9.   Colao, A., et al., *Growth hormone and the heart.* Clin Endocrinol (Oxf), 2001. **54**(2): p. 137-54.

10.   Sacca, L., A. Cittadini, and S. Fazio, *Growth hormone and the heart.* Endocr Rev, 1994. **15**(5): p. 555-73.

11.   Cittadini, A., et al., *Insulin-like growth factor-1 but not growth hormone augments mammalian myocardial contractility by sensitizing the myofilament to Ca2+ through a wortmannin-sensitive pathway: studies in rat and ferret isolated muscles.* Circ Res, 1998. **83**(1): p. 50-9.

12.   Tsukahara, H., et al., *Direct demonstration of insulin-like growth factor-I-induced nitric oxide production by endothelial cells.* Kidney Int, 1994. **45**(2): p. 598-604.

13.   Chen, D.B., L. Wang, and P.H. Wang, *Insulin-like growth factor I retards apoptotic signaling induced by ethanol in cardiomyocytes.* Life Sci, 2000. **67**(14): p. 1683-93.

14.   Bayes-Genis, A., C.A. Conover, and R.S. Schwartz, *The insulin-like growth factor axis: A review of atherosclerosis and restenosis.* Circ Res, 2000. **86**(2): p. 125-30.

15.   McCallum, R.W., et al., *Growth hormone deficiency and vascular risk.* Clin Endocrinol (Oxf), 2002. **57**(1): p. 11-24.

16.   Colao, A., et al., *Beginning to end: cardiovascular implications of growth hormone (GH) deficiency and GH therapy.* Growth Horm IGF Res, 2006. **16 Suppl A**: p. S41-8.

17.   Cuneo, R.C., et al., *The growth hormone deficiency syndrome in adults.* Clin Endocrinol (Oxf), 1992. **37**(5): p. 387-97.

18.   Capaldo, B., et al., *Increased arterial intima-media thickness in childhood-onset growth hormone deficiency.* J Clin Endocrinol Metab, 1997. **82**(5): p. 1378-81.

19.   Longobardi, S., et al., *Left ventricular function in young adults with childhood and adulthood onset growth hormone deficiency.* Clin Endocrinol (Oxf), 1998. **48**(2): p. 137-43.

20.   Thuesen, L., et al., *Short and long-term cardiovascular effects of growth hormone therapy in growth hormone deficient adults.* Clin Endocrinol (Oxf), 1994. **41**(5): p. 615-20.

21.   Valcavi, R., et al., *Cardiac performance and mass in adults with hypopituitarism: effects of one year of growth hormone treatment.* J Clin Endocrinol Metab, 1995. **80**(2): p. 659-66.

22.   Colao, A., et al., *Impaired cardiac performance in elderly patients with growth hormone deficiency.* J Clin Endocrinol Metab, 1999. **84**(11): p. 3950-5.

23.   Colao, A., et al., *The severity of growth hormone deficiency correlates with the severity of cardiac impairment in 100 adult patients with hypopituitarism: an observational, case-control study.* J Clin Endocrinol Metab, 2004. **89**(12): p. 5998-6004.

24.   Maison, P., et al., *Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a Metaanalysis of Blinded, Randomized, Placebo-Controlled Trials.* J Clin Endocrinol Metab, 2004. **89**(5): p. 2192-9.

25. Amato, G., et al., *Body composition, bone metabolism, and heart structure and function in growth hormone (GH)-deficient adults before and after GH replacement therapy at low doses.* J Clin Endocrinol Metab, 1993. **77**(6): p. 1671-6.

26. ter Maaten, J.C., et al., *Long-term effects of growth hormone (GH) replacement in men with childhood-onset GH deficiency.* J Clin Endocrinol Metab, 1999. **84**(7): p. 2373-80.

27. Gillberg, P., et al., *Commencing growth hormone replacement in adults with a fixed low dose. Effects on serum lipoproteins, glucose metabolism, body composition, and cardiovascular function.* Growth Horm IGF Res, 2001. **11**(5): p. 273-81.

28. Gibney, J., et al., *The effects of 10 years of recombinant human growth hormone (GH) in adult GH-deficient patients.* J Clin Endocrinol Metab, 1999. **84**(8): p. 2596-602.

29. Nass, R., et al., *Effect of growth hormone (hGH) replacement therapy on physical work capacity and cardiac and pulmonary function in patients with hGH deficiency acquired in adulthood.* J Clin Endocrinol Metab, 1995. **80**(2): p. 552-7.

30. Colao, A., *The GH-IGF-I axis and the cardiovascular system: clinical implications.* Clin Endocrinol (Oxf), 2008. **69**(3): p. 347-58.

31. Kontoleon, P.E., et al., *Hormonal profile in patients with congestive heart failure.* Int J Cardiol, 2003. **87**(2-3): p. 179-83.

32. Osterziel, K.J., et al., *The severity of chronic heart failure due to coronary artery disease predicts the endocrine effects of short-term growth hormone administration.* J Clin Endocrinol Metab, 2000. **85**(4): p. 1533-9.

33. Watanabe, S., et al., *Insulin-like growth factor axis (insulin-like growth factor-I/insulin-like growth factor-binding protein-3) as a prognostic predictor of heart failure: association with adiponectin.* Eur J Heart Fail, 2010. **12**(11): p. 1214-22.

34. Cittadini, A., et al., *Growth hormone attenuates early left ventricular remodeling and improves cardiac function in rats with large myocardial infarction.* J Am Coll Cardiol, 1997. **29**(5): p. 1109-16.

35. Yang, R., et al., *Growth hormone improves cardiac performance in experimental heart failure.* Circulation, 1995. **92**(2): p. 262-7.

36. Duerr, R.L., et al., *Cardiovascular effects of insulin-like growth factor-1 and growth hormone in chronic left ventricular failure in the rat.* Circulation, 1996. **93**(12): p. 2188-96.

37. Cittadini, A., et al., *Growth hormone prolongs survival in experimental postinfarction heart failure.* J Am Coll Cardiol, 2003. **41**(12): p. 2154-63.

38. Fazio, S., et al., *A preliminary study of growth hormone in the treatment of dilated cardiomyopathy.* N Engl J Med, 1996. **334**(13): p. 809-14.

39. Genth-Zotz, S., et al., *Recombinant growth hormone therapy in patients with ischemic cardiomyopathy : effects on hemodynamics, left ventricular function, and cardiopulmonary exercise capacity.* Circulation, 1999. **99**(1): p. 18-21.

40.   Osterziel, K.J., et al., *Randomised, double-blind, placebo-controlled trial of human recombinant growth hormone in patients with chronic heart failure due to dilated cardiomyopathy.* Lancet, 1998. **351**(9111): p. 1233-7.

41.   Jose, V.J., et al., *Growth hormone therapy in patients with dilated cardiomyopathy: preliminary observations of a pilot study.* Indian Heart J, 1999. **51**(2): p. 183-5.

42.   van Thiel, S.W., et al., *Six-months of recombinant human GH therapy in patients with ischemic cardiac failure.* Int J Cardiovasc Imaging, 2004. **20**(1): p. 53-60.

43.   Smit, J.W., et al., *Six months of recombinant human GH therapy in patients with ischemic cardiac failure does not influence left ventricular function and mass.* J Clin Endocrinol Metab, 2001. **86**(10): p. 4638-43.

44.   Isgaard, J., et al., *A placebo-controlled study of growth hormone in patients with congestive heart failure.* Eur Heart J, 1998. **19**(11): p. 1704-11.

45.   Acevedo, M., et al., *Administration of growth hormone to patients with advanced cardiac heart failure: effects upon left ventricular function, exercise capacity, and neurohormonal status.* Int J Cardiol, 2003. **87**(2-3): p. 185-91.

46.   Van den Berghe, G., et al., *Growth hormone-releasing peptide-2 infusion synchronizes growth hormone, thyrotrophin and prolactin release in prolonged critical illness.* Eur J Endocrinol, 1999. **140**(1): p. 17-22.

47.   Niebauer, J., et al., *Deficient insulin-like growth factor I in chronic heart failure predicts altered body composition, anabolic deficiency, cytokine and neurohormonal activation.* J Am Coll Cardiol, 1998. **32**(2): p. 393-7.

48.   Tritos, N.A. and P.G. Danias, *Growth hormone therapy in congestive heart failure due to left ventricular systolic dysfunction: a meta-analysis.* Endocr Pract, 2008. **14**(1): p. 40-9.

49.   Anker, S.D., et al., *Acquired growth hormone resistance in patients with chronic heart failure: implications for therapy with growth hormone.* J Am Coll Cardiol, 2001. **38**(2): p. 443-52.

50.   Bentham, J., J. Rodriguez-Arnao, and R.J. Ross, *Acquired growth hormone resistance in patients with hypercatabolism.* Horm Res, 1993. **40**(1-3): p. 87-91.

51.   Ross, R.J. and S.L. Chew, *Acquired growth hormone resistance.* Eur J Endocrinol, 1995. **132**(6): p. 655-60.

52.   Windisch, P.A., F.J. Papatheofanis, and K.A. Matuszewski, *Recombinant human growth hormone for AIDS-associated wasting.* Ann Pharmacother, 1998. **32**(4): p. 437-45.

53.   Cuneo, R.C., et al., *Cardiac failure responding to growth hormone.* Lancet, 1989. **1**(8642): p. 838-9.

54.   O'Driscoll, J.G., et al., *Treatment of end-stage cardiac failure with growth hormone.* Lancet, 1997. **349**(9058): p. 1068.

55.   Kupfer, S.R., et al., *Enhancement of the anabolic effects of growth hormone and insulin-like growth factor I by use of both agents simultaneously.* J Clin Invest, 1993. **91**(2): p. 391-6.

56.   Bondy, C.A., et al., *Clinical uses of insulin-like growth factor I.* Ann Intern Med, 1994. **120**(7): p. 593-601.

57.   Moxley, R.T., 3rd, *Potential for growth factor treatment of muscle disease.* Curr Opin Neurol, 1994. **7**(5): p. 427-34.

58.   Takala, J., et al., *Increased mortality associated with growth hormone treatment in critically ill adults.* N Engl J Med, 1999. **341**(11): p. 785-92.

59.   Demling, R., *Growth hormone therapy in critically ill patients.* N Engl J Med, 1999. **341**(11): p. 837-9.

60.   Hankinson, S.E., et al., *Circulating concentrations of insulin-like growth factor-I and risk of breast cancer.* Lancet, 1998. **351**(9113): p. 1393-6.

61.   Ding, V.D., et al., *Sex hormone-binding globulin mediates prostate androgen receptor action via a novel signaling pathway.* Endocrinology, 1998. **139**(1): p. 213-8.

62.   Brown, C.J., et al., *Androgen receptor locus on the human X chromosome: regional localization to Xq11-12 and description of a DNA polymorphism.* Am J Hum Genet, 1989. **44**(2): p. 264-9.

63.   Jenster, G., et al., *Domains of the human androgen receptor involved in steroid binding, transcriptional activation, and subcellular localization.* Mol Endocrinol, 1991. **5**(10): p. 1396-404.

64.   Shibata, H., et al., *Role of co-activators and co-repressors in the mechanism of steroid/thyroid receptor action.* Recent Prog Horm Res, 1997. **52**: p. 141-64; discussion 164-5.

65.   Ma, R., et al., *[Membrane testosterone receptors in cultured vascular smooth muscle cells].* Zhonghua Nan Ke Xue, 2010. **16**(5): p. 428-32.

66. Jones, R.D., et al., *The vasodilatory action of testosterone: a potassium-channel opening or a calcium antagonistic action?* Br J Pharmacol, 2003. **138**(5): p. 733-44.

67. Pugh, P.J., T.H. Jones, and K.S. Channer, *Acute haemodynamic effects of testosterone in men with chronic heart failure.* Eur Heart J, 2003. **24**(10): p. 909-15.

68. Zhang, Y.Z., et al., *Effects of testosterone on cytokines and left ventricular remodeling following heart failure.* Cell Physiol Biochem, 2007. **20**(6): p. 847-52.

69. Li, Z.B., et al., *[Testosterone therapy improves cardiac function of male rats with right heart failure].* Zhonghua Nan Ke Xue, 2009. **15**(11): p. 994-1000.

70. Jankowska, E.A., et al., *Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival.* Circulation, 2006. **114**(17): p. 1829-37.

71. Chaggar, P.S., et al., *Neuroendocrine effects on the heart and targets for therapeutic manipulation in heart failure.* Cardiovasc Ther, 2009. **27**(3): p. 187-93.

72. Guder, G., et al., *Low circulating androgens and mortality risk in heart failure.* Heart, 2010. **96**(7): p. 504-9.

73. Malkin, C.J., et al., *Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial.* Eur Heart J, 2006. **27**(1): p. 57-64.

74. Tomoda, H., *Effect of oxymetholone on left ventricular dimensions in heart failure secondary to idiopathic dilated cardiomyopathy or to mitral or aortic regurgitation.* Am J Cardiol, 1999. **83**(1): p. 123-5, A9.

75. Caminiti, G., et al., *Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study.* J Am Coll Cardiol, 2009. **54**(10): p. 919-27.

76. Iellamo, F., et al., *Testosterone therapy in women with chronic heart failure: a pilot double-blind, randomized, placebo-controlled study.* J Am Coll Cardiol, 2010. **56**(16): p. 1310-6.

77. Brand, T.C., E. Canby-Hagino, and I.M. Thompson, *Testosterone replacement therapy and prostate cancer: a word of caution.* Curr Urol Rep, 2007. **8**(3): p. 185-9.

78. Gruenewald, D.A. and A.M. Matsumoto, *Testosterone supplementation therapy for older men: potential benefits and risks.* J Am Geriatr Soc, 2003. **51**(1): p. 101-15; discussion 115.

79. Sullivan, M.L., et al., *The cardiac toxicity of anabolic steroids.* Prog Cardiovasc Dis, 1998. **41**(1): p. 1-15.

80. Pugh, P.J., et al., *Testosterone treatment for men with chronic heart failure.* Heart, 2004. **90**(4): p. 446-7.

81.   Bhasin, S., et al., *Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline.* J Clin Endocrinol Metab, 2010. **95**(6): p. 2536-59.

82.   Basaria, S., et al., *Adverse events associated with testosterone administration.* N Engl J Med, 2010. **363**(2): p. 109-22.

83.   Neaton, J.D. and D. Wentworth, *Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group.* Arch Intern Med, 1992. **152**(1): p. 56-64.