1. Introduction

Heart failure is a complex progressive multisystem disease state with significant morbidity and mortality. There has been significant improvement in the survival...
The GH–IGF axis is pivotal not only to the growth of a child into adulthood, but also to cardiac structure and function [13]. Favorably expressed in areas of the heart exposed to increased mechanical stress [14], both GH and IGF have receptors on cardiac myocytes [15-17]. Through an autocrine/paracrine mechanism, IGF facilitates cell hypertrophy, delays myocyte apoptosis, and affects myocardial contractility by increasing intracellular calcium and myofilament calcium sensitivity [18-20]. IGF receptors are also present on endothelial cells and stimulate production of nitric oxide, an endogenous vasodilator [21]. In addition, IGF participates in angiogenesis and repair following ischemic events [22]. Finally, IGF affects physical and functional capacity by maintaining muscle mass, strength and body composition and regulating nutrient metabolism [11].

2.1 GH–IGF axis physiology in heart failure

Heart failure is a chronic, multi-etiologic disease of high prevalence and poor prognosis [11]. It is a disease of the myocardium manifested by left ventricular dysfunction that produces secondary changes in other organs resulting in symptoms of dyspnea, muscular fatigue and exercise intolerance. Adaptation of the circulatory system in heart failure: changes in heart rate, blood pressure and cardiac output are regulated through direct hemodynamic as well as indirect neurohormonal mechanisms [9,11]. The GH–IGF axis is a highly prevalent abnormal neurohormonal axis in patients with heart failure [23]. Kountoleon et al. found that patients with idiopathic dilated cardiomyopathy (DCM) who present with heart failure have lower levels of circulating GH and IGF compared with healthy controls [9]. Similar low baseline levels of GH and IGF were found in patients with moderate heart failure caused by myocardial ischemia [24]. Interestingly, Anker et al. unveiled contradictory results: elevated levels of GH in patients with heart failure [25]. The elevated levels of GH coexist with low levels of IGF, creating a state of ‘growth hormone resistance’ [25]. This phenomenon occurs primarily in heart failure patients with coexistent cardiac cachexia [25-27]. In fact, cardiac cachexia, a negative predictive factor in heart failure [28,29], is a state of anabolic/catabolic mismatch associated with severe heart failure. Osterziel et al. showed that GH resistance is directly proportional to the severity of heart failure [30]. This association is primarily mediated through low levels of IGF as opposed to the concentration of GH, lending to the term ‘low IGF-1 syndrome’ [31].

2.2 GH therapy in heart failure

While there is no large prospective randomized control trial (RCT) that examines GH therapy in patients with heart failure, there are several smaller studies. These studies show a wide variability in results. Owing in part to heterogeneity in type and severity of heart failure as well as dosing regimen and variation in outcome measurements, we describe many of the key studies evaluating GH therapy in heart failure.

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**Article highlights.**

- Hypogonadism in heart failure has been associated with worse New York Heart Association functional class and prognosis.
- Testosterone supplementation in heart failure results in improved hemodynamics, decreased left ventricular remodeling and improved strength.
- The ‘low IGF syndrome’ (low insulin-like growth factor irrespective of growth hormone levels) is the mechanism behind ‘growth hormone resistance’, which is directly associated with heart failure severity.
- Improved survival has been observed with growth hormone therapy in patients with heart failure.
- Both growth hormone and testosterone show significant promise as new therapeutic agents in heart failure therapy, but large, randomized, controlled trials are needed to confirm their effectiveness.

This box summarizes key points contained in the article.

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of patients diagnosed with heart failure over the recent years with much being owed to medical therapy advances and a deeper knowledge of the neurohormonal contribution to this condition [1,2]. The unique clinical picture of heart failure is not solely defined by pathology of the cardiovascular system but is also influenced by peripheral cytokine, hormonal and musculoskeletal dysfunction. The milieu of cytokines and hormones in heart failure is a maladaptive response that tends to a proinflammatory state, tipping the metabolic balance towards catabolism in this subset of already weakened individuals. Individuals with heart failure have demonstrated diminished growth hormone secretion and insulin sensitivity, increased TNF-α levels and increased levels of interleukin-1 (IL-1) and interleukin-6 (IL-6) [3-8]. In addition to this proinflammatory cytokine, hormonal and paracrine mechanism, IGF facilitates cell hypertrophy, delays myocyte apoptosis, and affects myocardial contractility by increasing intracellular calcium and myofilament calcium sensitivity [18-20]. IGF receptors are also present on endothelial cells and stimulate production of nitric oxide, an endogenous vasodilator [21]. In addition, IGF participates in angiogenesis and repair following ischemic events [22]. Finally, IGF affects physical and functional capacity by maintaining muscle mass, strength and body composition and regulating nutrient metabolism [11].

2. GH–IGF axis

Growth hormone (GH) is an anabolic hormone released from the anterior pituitary that regulates somatic growth. GH is secreted in a pulsatile manner, with periods of quiescence [11]. Its biological effects are transmitted directly through specific transmembrane receptors expressed in almost all types of cells [11]. Indirectly, and clinically most significant, GH stimulates the production of insulin-like growth factor (IGF) in the liver (endocrine action) and in peripheral tissue [11]. Together, these two neurohormonal mediators make up the GH–IGF axis [12].

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2.2.1 Idiopathic dilated cardiomyopathy

Cardiomyopathies are diseases of heart muscle classified by the underlying etiology and pathophysiology \[32,33\]. Dilated and hypertrophic forms are the most prevalent and lead to significant morbidity and mortality \[34\]. Systolic dysfunction is characteristic of dilated cardiomyopathy but can also occur in patients with hypertrophic cardiomyopathy who develop left ventricular dilatation. With systolic dysfunction, myocardial contractility is impaired, resulting in poor ejection fraction and increased left ventricular end diastolic volume, which results in increased wall stress \[35\]. The heart normally compensates with hypertrophy, but when this mechanism is exhausted or deficient, clinical symptoms of heart failure occur \[36\]. GH is a hormonal mediator of hypertrophy, hence the association of its deficiency with clinical symptoms of heart failure point to the need for further study \[9,24,37\].

Fazio \textit{et al.} treated idiopathic DCM patients with GH with the expectation that hemodynamic abnormalities would improve \[36\]. The relatively small group of seven patients showed an increase in left ventricular mass, improved hemodynamic parameters and improved exercise capacity that was associated with clinical improvements \[36\]. Similarly, increased left ventricular mass and evidence of hypertrophy were found in subsequent studies by Jose \textit{et al.}, Perrot \textit{et al.} and Osterzeil \textit{et al.} \[10,38,39\].

Owing to the deficiency of hypertrophy in DCM, the increase in left ventricular mass that occurs with GH leads to increased wall thickness, which reduces the chamber size. Wall stress is indirectly proportional to wall thickness; therefore, hypertrophied myocardium results in decreased systolic wall stress, a major determinant of oxygen consumption \[40\]. The heart then uses less energy and pumps more effectively, improving ejection fraction \[36,41\]. In addition, there is a reduction in systemic vascular resistance (SVR), which further increases cardiac output, particularly during exercise \[11,36,41-45\]. Finally, cardiac output may be enhanced due to the direct effect of GH increasing myocardial contractility by enhancing sarcolemmal affinity to calcium, without increased energy requirements \[11,20,46-48\].

2.2.2 Ischemic cardiomyopathy

DCM can be caused by a wide variety of diseases, but ischemic disease is the most common \[49,50\]. After myocardial infarction, ventricular remodeling leads to progressive left ventricular dilatation, wall thinning and resultant systolic dysfunction \[49,51,52\]. Since patients with idiopathic DCM have similar left ventricular dysfunction and favorably respond to GH therapy, patients with ischemic cardiomyopathy were evaluated. In mice with myocardial infarction, Jayasankar \textit{et al.} demonstrated that local GH expression by adenoviral-mediated gene transfer in infarcted tissue did preserve left ventricular size and increase wall thickness \[51\]. Genth-Zotz \textit{et al.} conducted human studies in post-myocardial infarction patients and found similar increases in left ventricular wall thickness and improvement in hemodynamic parameters and functional status \[53\]. As described above, left ventricular wall thickness is inversely proportional to wall stress, hence hypertrophy reduces wall stress, a determinant of oxygen consumption \[40\]. The heart uses less energy and, assisted by the peripheral effects of GH, which reduces SVR, the heart pumps more efficiently to improve stroke volume, therefore, increasing cardiac output \[36,41,51,53\].

In addition, improved survival has been observed after GH therapy, which has been associated with decreased systemic inflammation \[54-56\]. Reduction of proinflammatory markers and oxidant stress prevents cardiomyocyte apoptosis and therefore may prevent enlargement of infarct size \[54-59\]. This preserves myocardial function, which may help preserve ejection fraction. In addition, inhibition of growth factors such as collagen and fibronectin prevents pathologic ventricular remodeling, fibrosis and the development of a stiff myocardium, which might progress to diastolic dysfunction and, subsequently, diastolic heart failure \[55,56,58\].

2.2.3 Response variability in GH therapy for chronic heart failure

Some studies on idiopathic and ischemic dilated cardiomyopathy have failed to show clinical improvement, hemodynamic improvement, change in exercise capacity or beneficial changes on left ventricular structure and function \[10,39,60-65\]. The variability in outcomes might be due to variations of study design: different and usually relatively small sample sizes, the absence of double-blinding, lack of placebo groups, and gender bias, among other parameters \[41\]. Even though the underlying etiology of heart failure (e.g., ischemic vs non-ischemic) may play a role on outcomes, GH dosing is the most influential variable in predicting a beneficial study outcome.

Several studies in patients with idiopathic DCM showed improvement of hemodynamic parameters and clinical status if GH was administered on an alternate-day dosing regimen \[23,36,38,45,54,55,58,59,64,65\]. This approach would reflect more the human body’s physiologic secretion of GH, which is pulsatile with periods of secretory quiescence \[11\]. In addition, there was a significant variation in dose, with patients receiving higher doses conferring greater success \[55\], even if administered daily \[24,47,66,67\]. On the other hand, higher doses of GH were associated with more pronounced cardiac fibrosis \[57\], diabetes and hypertension \[68\].

As described above, increased severity of heart failure was associated with GH resistance: high serum levels with low IGF levels \[25,27\]. In these patients, administering additional GH may not elicit the same rise in serum IGF compared with patients with low serum GH levels \[24\]. In fact, after GH administration, improvement in ejection fraction and left ventricular mass was dependent of the degree of improvement in IGF \[10,41\]. Therefore, failure to use GH doses high enough to overcome GH resistance may account for the lack...
of efficacy in some studies [25,41] and the presence of efficacy in studies that used a higher dose [11,24,47,66,67].

2.3 Other beneficial effects of GH therapy on the heart
A small, 10-patient study with coronary artery disease-induced heart failure and daily GH therapy showed no beneficial effect in left ventricular parameters but did show lower serum triglycerides and adipose body tissue as well as increased concentrations of high-density lipoprotein (HDL) in patients who received GH therapy [62].

2.4 Adverse effects of GH therapy
The main side effects noted in various studies are fluid retention, gynecomastia and orthostatic hypotension [69].

3. Testosterone

As many as 26 – 37% of men affected with chronic heart failure have been found to be deficient in testosterone [70-72]. It is noteworthy that men without heart failure but androgen deficiency often report similar symptoms such as shortness of breath, fatigue and deterioration of muscle mass [73]. Testosterone levels have been shown to correlate inversely with New York Heart Association (NYHA) heart failure class levels as well as prognosis [5,74]. The effect of testosterone deficiency in heart failure and its potential role for supplementation remains understudied, yet preliminary studies indicate that testosterone may have multiple roles in modifying the symptoms and cardiovascular function in patients with heart failure.

3.1 Normal physiology of testosterone
Testosterone is an anabolic steroid hormone secreted by the Leydig cells of the testes in response to luteinizing hormone stimulation. The free level of this hormone is influenced by sex hormone-binding globulin and 5-alpha reductase, which converts testosterone to dihydrotestosterone [75]. The receptors for testosterone are found throughout multiple systems. Intracellular nuclear transcription factors respond to testosterone by regulating gene expression and cellular metabolism [76]. Several new membrane-bound receptors have been identified in reproductive, cardiovascular, immune and musculoskeletal tissues which are more rapid in their response to testosterone stimulation [77].

3.2 Testosterone physiology in heart failure
Testosterone plays an important role in cardiovascular physiology. The cardiovascular system in heart failure has been shown to respond to testosterone in vitro, ex vivo and in vivo through several controlled trials. In vitro studies have identified testosterone-sensitive L-type calcium ion channels, which respond to stimulation by causing vasodilatation in the human vascular system [78,79]. This has also been shown by Malkin et al. through an ex vivo study. Using isolated subcutaneous blood vessels from patients diagnosed with heart failure, patients with androgen deficiency and healthy controls, his group showed that testosterone augmented vascular tone and reactivity [80]. An in vivo study found a similar vasodilatory effect of testosterone by measuring acute hemodynamics via cardiac catheterization in patients with heart failure [81]. These patients were treated with 60 mg of buccal testosterone and monitored via pulmonary artery catheter over 2 days. The patients were noted to have a 10.3 ± 4.6% increase in cardiac output and a 17.4 ± 9.6% decrease in systemic vascular resistance from baseline measurements. Heart failure is a condition of increased sympathetic tone, decreased cardiac output and maladaptive vasoconstriction. The peripheral vasodilatory effects of testosterone may prove beneficial to patients with heart failure who are subject to a maladaptive chronic vasoconstriction.

In addition to effectively reducing systemic vascular resistance through vasodilation, testosterone significantly improves coronary blood flow through vasodilation. Patients with heart failure often have chronic anginal symptoms despite optimal medical therapy. In this subset of affected patients, these symptoms can have a devastating effect on patients’ quality of life. Testosterone therapy has been shown in vitro and in vivo to improve coronary artery blood flow and ischemic threshold [82-84]. Webb et al. showed that coronary vessel diameter and blood flow increased in response to physiologic doses of intracoronary testosterone. Both Malkin et al. and English et al. have shown a significant improvement in time to electrocardiographic ST segment depression during exercise stress testing in hypogonadal patients with heart failure when treated with testosterone replacement therapy. A recent study recorded electrocardiographic significant ischemic events in ambulatory patients over a period of 3 months in patients with coronary artery disease who were treated with testosterone or placebo. Patients treated with testosterone had a significant decrease in the number of symptomatic and silent ischemic episodes, whereas those given placebo experienced no benefit [85]. These studies demonstrate the efficacy of testosterone supplementation in altering the hemodynamic compromise as well as ischemic symptoms seen in patients with chronic heart failure. Of interest, the greatest effect of testosterone treatment was seen in patients with the lowest baseline serum levels of testosterone, although patients with normal baseline levels also derived benefit. So far, no studies have been performed specifically to evaluate differences in hemodynamic response to testosterone between nonischemic and ischemic cardiomyopathy.

3.3 Testosterone therapy in chronic heart failure
Clinically, testosterone supplementation has been shown to improve functional status in patients with heart failure. Recently, several controlled trials have been conducted that point to effective functional and symptomatic status improvement in patients with heart failure treated with androgen supplementation. Tomoda et al. first provided quantitative pharmacological data supporting the potential for androgen...
supplementation to provide clinical efficacy [86]. His group showed that patients with dilated heart failure treated with small doses of the androgen oxymetholone had a significant decrease in left ventricular diameter, left ventricular mass and serum natriuretic peptide concentrations. These clinical data reflected improvement in cardiac function as described by previous hemodynamic evaluation [81]. To prove further the clinical utility of testosterone therapy, a few randomized prospective trials were done. Pugh et al. randomized 20 patients with heart failure to receive either intramuscular testosterone or a placebo injection [87]. The patients were followed and were assessed for mood, endurance (based on the incremental shuttle walk test; ISWT) and a physician-determined symptom score. The group treated with testosterone had a clearly significant improvement in all three of these measures. The ISWT is a well-validated correlate to measurement of peripheral oxygen consumption (peak VO2), a prognostic indicator assessed in heart failure patients [88,89]. Patients treated with intramuscular testosterone had on average an improvement of 91 m in the ISWT compared with 26 m in the placebo group. Heart failure symptom scores, which were assessed by physicians, significantly improved in patients treated with testosterone compared with placebo-treated individuals. These first studies provided controlled data to validate the utility of testosterone therapy for both symptom management and as a prognostic indicator in patients with chronic heart failure.

A follow-up study by Malkin et al. validated the efficacy of testosterone in the treatment of patients with chronic heart failure. In this double-blinded, placebo-controlled, prospective study 76 men with moderate to severe heart failure were treated with either transdermal testosterone or placebo. Subjects were followed over a period of 12 months and assessed for exercise tolerance via the ISWT as well as NYHA class, handgrip strength and left ventricular function by two-dimensional transthoracic echocardiography. The authors found a significant improvement in ISWT (ISWT improved by 25 ± 15 m) and NYHA class in patients treated with testosterone compared with patients receiving placebo. In addition, there was a significant improvement in dominant handgrip strength and increase in left ventricular cavity length in patients treated with testosterone.

Interestingly, patients treated with intramuscular testosterone in the primary pilot study experienced more improvement in functional status than those who used a transdermal route. As the testosterone doses given in these intramuscularly treated patients were higher, it was suggested that there is a significant dose-response relationship. Of note, serum concentrations of testosterone correlated significantly with level of functional improvement, confirming the dose-response relationship in testosterone therapy.

The most recent trial using testosterone as therapy for heart failure was conducted by Caminiti et al. and objectively measured changes in functional status, biochemical measures as well as prognostic indicators [90]. In this study, 70 men with heart failure were randomized to long-acting intramuscular testosterone or placebo. Baseline measurements of cardiopulmonary testing, left ventricular function, 6-min walk test (6MWT), quadriceps maximal contraction (MVC) and peak torque, insulin sensitivity and baroreflex sensitivity (BRS) were obtained and repeated after 3 months of intramuscular testosterone or placebo given every 6 weeks. Those treated with testosterone saw a significant increase in peak VO2, decrease in ventilation/carbon dioxide output (VE/VCO2) slope and increase in BRS, all of which have been validated as prognostic indicators in patients with heart failure [88,90-93]. Functionally, patients treated with intramuscular testosterone showed a significant improvement in NYHA class and an increase of 86.2 ± 14.5 m on the 6MWT compared with 37.3 ± 8.7 meters seen in placebo-treated patients. Quadriceps MVC and torque were also significantly improved by testosterone therapy. In addition, insulin resistance was improved in those treated with testosterone, while placebo had no effect. Once again, improved MVC and 6MWT correlated with serum testosterone concentrations. These studies indicate that patients with heart failure show significant improvements in functional, biochemical and prognostic cardiopulmonary status when treated with testosterone supplementation.

3.4 Adverse effects of testosterone therapy

The main adverse effects of testosterone therapy include local inflammation and rash at the site of administration. Other side effects most commonly occur when testosterone levels become supraphysiologic and include hirsutism, gynecomastia, elevated hematocrit and the possibility of prostate or breast malignancy exacerbation. Precaution should be taken in screening patients for these malignancies, obstructive sleep apnea, polycythemia and prolactinemia. In addition, testosterone levels should be measured routinely and therapy adjusted to maintain physiologic serum levels [94,95].

4. Hormone deficiency in the elderly

As life expectancy continues to rise, the growing elderly population experiences an age-related decline in naturally occurring hormones such as testosterone and GH [96]. Low levels of these hormones lead to fatigue, decreased libido, decreased muscle and bone mass and anemia [73,96], as well as its pivotal role in heart failure, as described above.

5. Conclusion

Anabolic hormone deficiencies, GH and testosterone, are common in heart failure and are associated with greater morbidity and mortality. GH is a pituitary hormone that contributes to ventricular muscle mass, which decreases wall stress in the dilated ventricles of patients with systolic heart failure. In addition, it increases cardiac contractility, behaves as an antioxidant and decreases inflammation, which can prevent
cardiac remodeling and reduce infarct size, and has even been shown to improve lipid profiles. Data are variable. However, studies that use a more physiologic, alternative dosing regimen or high enough doses to overcome GH resistance show favorable results. Testosterone is an anabolic steroid hormone secreted by the testes that also acts to decrease left ventricular wall stress by hypertrophy. Studies on testosterone have shown improvement in hemodynamic parameters, a result of its decrease in SVR, as well as improvement in functional capability. Unfortunately, used in excess, testosterone therapy can have harmful side effects and can also potentiate undiagnosed malignancies such as prostate or breast cancer. While eliciting these effects is largely dependent on proper dose, frequency and route of the hormone as well as clinical and laboratory follow-up evaluations, more large randomized, controlled trials need to be conducted on these agents and their potential role in heart failure therapy. For symptom improvement, however, an optimized hormonal balance with normal or even high-normal levels might be beneficial outside direct hemodynamic effects, especially for elderly men with heart failure.

6. Expert clinical pharmacotherapy opinion

Our present understanding of the role that testosterone plays in modifying the condition of heart failure is relatively preliminary. Multiple studies confirm that testosterone levels are lower in patients with heart failure and that these levels do correlate with both functional status and prognosis. In spite of this, the ability of testosterone replacement to achieve long-term improvement in these measures as well as the ability for supplementation to affect hard outcomes remains uncertain. The studies at hand are encouraging as it seems that at least functional status and quality of life can be improved with supplementation in hypogonadal patients with heart failure. On the other hand, the studies have been conducted with relatively short follow-up periods, and long-term efficacy and safety should be measured before committing a patient to life-long testosterone supplementation. Long-term studies should be conducted in this patient population to ascertain not only the safety and efficacy of testosterone therapy, but also the meaningfulness of supplementation in terms of outcomes on hospitalization rates and mortality. At present, several institutions including our own are actively pursuing trials to confirm the findings of these preliminary studies and add more data in the form of the outcomes mentioned above.

Similarly, GH therapy can become an important therapeutic intervention in heart failure patients. The hormone compensates for lack of an anabolic response in a disease state that is pro-catabolic. This benefit is evident only in trials that simulate physiologic release of the hormone, a methodology that lacks consistency in most trials in this field. In addition, there is an absence of large, randomized, control trials on this topic, which leaves interpretation of the benefits of this hormone inconclusive. Data more recently points towards IGF as opposed to GH being the more significant mediator in altering cardiac morphology; therefore, future research should focus on IGF, eliciting the nature of the relationship of the GH-IGF axis during replacement therapy, and whether it is more useful to administer IGF or GH in replacement therapy. Also, much work is yet to be done regarding the risk of toxicity of these hormones and the doses required to avoid complications but still obtain maximal results.

With the cost of healthcare on the rise and reimbursements for rehospitalizations for heart failure decreasing, it is becoming increasingly important to find the correct pharmacologic regimen for advanced heart failure patients. Maximized on current approved therapies, patients, doctors and pharmaceutical companies will need to increasingly shift their attention towards newer, safer agents for use in this chronic debilitating disease.

Declaration of interest

ER Schwarz is a consultant for the Cenegenics Research Foundation.
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