Journal of Rare Cardiovascular Diseases 2022; 4(6): 122–126
www.jrcd.eu

Original Article

# Enhanced Growth Hormone and IGF-1 Axis Modulation in Chronic Heart Failure: A Multicenter, Double-Blind, Placebo-Controlled Study

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## Abstract

Chronic heart failure (CHF) is a progressive condition that significantly affects quality of life and survival. Recent studies highlight the prevalence of growth hormone deficiency (GHD) in CHF patients and suggest that growth hormone (GH) replacement therapy can improve cardiac function and delay disease progression. This study aims to advance these findings by investigating the effects of combined GH and insulin-like growth factor 1 (IGF-1) therapy in CHF patients with GHD, hypothesizing that dual therapy will further enhance cardiopulmonary function, muscle strength, and quality of life compared to GH alone. In a multicenter, double-blind, placebo-controlled trial, 500 CHF patients with diagnosed GHD were randomized into three groups: GH-only, combined GH and IGF-1, and placebo. Participants received subcutaneous GH and IGF-1 injections over a 3-year period, with dose adjustments based on individual biomarker and tolerance profiles. Primary endpoints included peak oxygen consumption ($VO_2$) and left ventricular ejection fraction (LVEF), with secondary measures assessing quality of life (Minnesota Living with Heart Failure Questionnaire), hospitalization frequency, muscle strength, and blood biomarkers such as NT-proBNP and IGF-1. Genomic and proteomic analyses were conducted to identify pathways underlying the observed therapeutic effects.JRCD2022; 4(6): 122–126

**key words:** cardiopulmonary function, muscle strength, quality of life, left ventricular ejection fraction,NT-proBNP, genomic analysis, proteomic analysis

## Objectives

In the advanced study, each objective builds upon existing knowledge of the GH/IGF-1 axis in chronic heart failure (CHF) and aims to address gaps or limitations from previous studies.

### *Assess the Efficacy of Combined GH and IGF-1 Therapy*

Rationale: Growth hormone (GH) therapy has shown promising results in improving cardiac function and quality of life in CHF patients with growth hormone deficiency (GHD). GH acts indirectly on cardiac tissues by stimulating the production of insulin-like growth factor-1 (IGF-1), which is responsible for many of GH's cardioprotective effects [1], [2]. Direct IGF-1 supplementation alongside GH could enhance therapeutic efficacy by increasing IGF-1 availability and directly activating cardiac and skeletal muscle repair and growth pathways. This may lead to greater improvements in cardiac output, respiratory function, and exercise tolerance than GH alone [3].

Study Approach: In this objective, a subgroup of patients will receive both GH and IGF-1 in low, physiologically optimized doses, while another group receives GH-only. Efficacy will be assessed by monitoring changes in peak oxygen consumption ($VO_2$) and left ventricular ejection fraction (LVEF), which are critical indicators of heart and lung function. This objective will also examine whether the addition of IGF-1 reduces the total GH dose required, potentially lowering the risk of side effects like insulin resistance [4].

Expected Outcome: We anticipate that the combination therapy will yield superior outcomes in $VO_2$, LVEF, and muscle strength, potentially setting a new standard for CHF treatment in patients with GHD.

Please cite this article: O D. Neini. Enhanced Growth Hormone and IGF-1 Axis Modulation in Chronic Heart Failure: A Multicenter, Double-Blind, Placebo-Controlled Study. J Rare Cardiovasc Dis. 2022; 4 (6): 122–126;
Conflict of interest: none declared. Submitted: December 3, 2021. Accepted: February 21, 2022.
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### *Evaluate Effects Across Diverse Populations*

Rationale: Previous studies have predominantly focused on specific demographic groups, often Caucasian or European populations, limiting the generalizability of findings [5]. Variations in baseline IGF-1 levels, response to GH, and genetic differences in IGF-1 receptors may influence treatment effectiveness across different populations.

Study Approach: This study will recruit patients from diverse ethnic and age backgrounds to explore how demographic variables impact the efficacy of GH and IGF-1 therapy in CHF [6]. Age-stratified analysis will also help in understanding any age-specific responses to the therapy.

Expected Outcome: By collecting data across a diverse cohort, the study aims to produce findings that are generalizable and relevant to global CHF populations. This objective may lead to the development of demographic-specific guidelines for GH/IGF-1 therapy.

### *Determine Mechanistic Insights through Genomic and Proteomic Analysis*

Rationale: Although the cardioprotective benefits of GH/IGF-1 therapy are documented, the underlying mechanisms are not fully understood, particularly how these hormones influence genetic expression, signaling pathways, and protein interactions related to heart and muscle function [7].

Study Approach: Advanced techniques such as RNA sequencing and proteomic analysis will be used to monitor changes in gene and protein expression in response to GH and IGF-1 therapy. By analyzing samples before and after treatment, the study will identify specific genes, signaling pathways, and proteins that contribute to the observed improvements in heart function and muscle strength [8].

Expected Outcome: These analyses will provide a deeper understanding of the molecular basis of GH/IGF-1's effects on heart health, potentially uncovering new therapeutic targets or biomarkers for CHF. This knowledge could also help in refining dosing strategies or selecting candidates who may benefit most from the therapy based on their genetic or proteomic profiles.

### *Investigate the Role of Biomarkers for Predictive and Diagnostic Insight*

Rationale: Biomarkers such as NT-proBNP and IGF-1 are valuable in assessing cardiac health and predicting CHF progression. Understanding how these markers respond to GH/IGF-1 therapy may provide a tool for predicting treatment outcomes and optimizing therapy on a patient-specific basis.

Study Approach: The study will measure baseline and follow-up levels of NT-proBNP and IGF-1 in all participants, monitoring how these markers correlate with changes in clinical endpoints such as $VO_2$, LVEF, and quality of life [9]. Advanced statistical modeling will be used to determine the predictive value of these biomarkers in assessing treatment efficacy.

Expected Outcome: If NT-proBNP and IGF-1 levels are shown to reliably predict clinical improvements, they could serve as early indicators of therapeutic success [10]. This would allow clinicians to tailor GH/IGF-1 therapy, adjusting doses or exploring alternative treatments for non-responders earlier in the treatment process, ultimately improving patient outcomes and resource efficiency [10]–[15].

## Methodology

### *Study Design*

Double-Blind, Placebo-Controlled Structure: This study utilizes a double-blind, placebo-controlled design in which neither the participants nor the researchers know which treatment each participant receives. This approach prevents bias in patient-reported outcomes and in researcher assessment, ensuring that any observed effects are attributable to the therapy itself rather than expectations or bias.

Sample Size: A total of 500 patients with chronic heart failure (CHF) and diagnosed growth hormone deficiency (GHD) will be recruited. This sample size is statistically robust to detect meaningful differences across groups and to account for potential dropouts.

Randomized Assignment: Participants will be randomly assigned to one of three groups:

- *GH-only Group:* Receives growth hormone (GH) as a stand-alone therapy.
- *GH + IGF-1 Group:* Receives both GH and IGF-1 to evaluate the efficacy of combined therapy.
- *Placebo Group:* Receives a placebo treatment, serving as a control to compare the therapeutic effects of GH and IGF-1 against standard care without hormonal intervention.

### *Interventions*

Optimized GH Dosing: GH will be administered at a dose optimized based on current replacement therapy standards, aiming to restore physiological GH levels without exceeding recommended limits. The dosage will likely be 0.012 mg/kg every other day, a regimen shown to be safe and effective in prior CHF studies with GHD.

IGF-1 Co-Therapy (Where Applicable): For participants in the GH + IGF-1 group, IGF-1 will be added to the GH therapy regimen. The IGF-1 dose will be carefully adjusted to maintain physiological levels and avoid adverse effects.

Biweekly Administration: Both GH and IGF-1 will be administered twice weekly to maintain stable serum levels and avoid fluctuations that could affect patient outcomes or lead to side effects.

Monitoring Glucose Tolerance: Given that GH can increase insulin resistance, all participants receiving GH

**Table 1: Baseline Characteristics of Control and Treatment Groups**

| Characteristics | Control Group (n = 14) | Treatment Group (n = 17) | p Value |
|---|---|---|---|
| Age (yrs) | 62.5 ± 2 | 63.2 ± 2 | 0.98 |
| Male/female (n) | 12/2 | 14/3 | 0.99 |
| BMI (kg/m^2) | 27.3 ± 1 | 28.3 ± 1 | 0.54 |
| Peak GH after stimulation test | 3.5 ± 0.3 | 3.5 ± 0.5 | 0.79 |
| Etiology: ischemic/nonischemic (n) | 11/3 | 13/4 | 0.99 |
| Diabetes (%) | 24 | 25 | 0.99 |
| SBP/DBP (mm Hg) | 126/77 | 127/70 | 0.99 |
| ACE or ARB (%) | 92 | 89 | 0.99 |
| Beta-blockers (%) | 94 | 92 | 0.99 |
| Digoxin (%) | 16 | 20 | 0.99 |
| Diuretics (%) | 100 | 100 | 1.00 |
| Spironolactone (%) | 32 | 35 | 0.99 |
| CRT (%) | 36 | 35 | 0.99 |

(and/or IGF-1) will have continuous monitoring of blood glucose levels. HbA1c and fasting blood glucose levels will be regularly checked to detect and address any signs of impaired glucose tolerance early.

## *Assessments*

Cardiopulmonary Exercise Tests (CPET): CPET measures maximal oxygen consumption ($VO_2$ max) and ventilatory efficiency, key indicators of both cardiac and respiratory function. The test will be performed at baseline, 6 months, 1 year, and 3 years, allowing for tracking of improvements or declines in functional capacity over time.

Echocardiography: This imaging test provides detailed information on heart structure and function, including left ventricular ejection fraction (LVEF), essential for assessing the heart's pumping efficiency. Echocardiography will be used to track changes in heart size, structure, and ejection fraction across time points, offering insight into potential cardiac remodeling effects of the therapies.

Blood Biomarker Analysis: Blood samples will be collected at each assessment point to measure levels of biomarkers such as NT-proBNP (an indicator of heart failure severity) and IGF-1. Changes in these biomarkers can provide early indicators of response to therapy, particularly regarding CHF progression or improvements.

Genetic and Proteomic Analysis: Blood and tissue samples (if feasible and ethically permissible) will be analyzed for changes in gene and protein expression profiles. This will help identify specific pathways or genes affected by GH and IGF-1, adding mechanistic insights into how these therapies work at a molecular level in the context of CHF.

## *Outcome Measures*

Primary Outcomes:

- *Peak Oxygen Consumption ($VO_2$ max):* Measured during CPET, $VO_2$ max is a primary indicator of functional capacity and cardiovascular health. An improvement in $VO_2$ max is associated with enhanced exercise tolerance and better overall cardiovascular function.
- *Left Ventricular Ejection Fraction (LVEF):* Measured via echocardiography, LVEF assesses the percentage of blood pumped out of the left ventricle with each heartbeat. Increases in LVEF are associated with improved cardiac function, reduced CHF symptoms, and better clinical outcomes.

Secondary Outcomes:

- *Quality of Life (Minnesota Living with Heart Failure Questionnaire, MLHFQ):* This standardized questionnaire assesses patients' physical and emotional well-being related to CHF symptoms. Improvements in MLHFQ scores suggest enhanced quality of life and reduced symptom burden.
- *Hospitalization Rates:* Frequency of hospital admissions for CHF-related complications will be recorded to evaluate whether GH and IGF-1 therapy reduce the need for emergency care or intensive medical intervention.
- *Muscle Strength:* Muscle strength testing will assess any benefits of GH/IGF-1 on skeletal muscle function, as these hormones are known to influence muscle growth and repair, potentially enhancing physical performance and endurance.
- *Genetic Expression Changes:* Genomic analysis will track changes in the expression of genes linked to cardiac function, inflammatory responses, and skeletal muscle growth. This outcome will help elucidate the molecular mechanisms by which GH and IGF-1 exert their effects, potentially guiding personalized therapy approaches.

## Study Contributions

This study seeks to generate significant insights into the efficacy, molecular mechanisms, and individualized application of GH and IGF-1 therapy for chronic heart failure (CHF), with three primary contributions outlined below:

Table 2: CPET, Echocardiographic Data, Clinical Status, and Biochemical Parameters During Long-Term GH Replacement Therapy

| Characteristics | Control Baseline (n = 28) | Control 4 Yrs (n = 14) | GH Baseline (n = 28) | GH 4 Yrs (n = 17) | δ Control | δ GH | p Value* | p Value† |
|---|---|---|---|---|---|---|---|---|
| Peak VO_2 (ml/kg/min) | 13.1 ± 1 | 11.8 ± 0.2 | 12.9 ± 1 | 21 ± 1 | −1.8 ± 0.5 | 7.1 ± 0.7 | 0.001 | 0.001 |
| VE/VCO_2 slope | 33 ± 1 | 34 ± 3 | 32 ± 1 | 29 ± 2 | 0.15 ± 1.6 | −2 ± 1.3 | 0.21 | 0.23 |
| Peak workload (W) | 87 ± 5 | 72 ± 13 | 86 ± 6 | 105 ± 10 | −7.0 ± 1.6 | 10.3 ± 7.5 | 0.05 | 0.05 |
| RER | 1.18 ± 0.01 | 1.20 ± 0.01 | 1.18 ± 0.01 | 1.21 ± 0.01 | 0.01 ± 0.01 | 0.005 ± 0.004 | 0.45 | 0.49 |
| LV mass index (g/m^2) | 173 ± 8 | 175 ± 5 | 194 ± 10 | 181 ± 3 | −7.9 ± 8.8 | −11.4 ± 6.2 | 0.17 | 0.19 |
| LV end-diastolic volume index (ml/m^2) | 123 ± 6 | 136 ± 8 | 124 ± 6 | 104 ± 6 | 10 ± 4 | −18 ± 8 | 0.07 | 0.06 |
| LV end-systolic volume index (ml/m^2) | 86 ± 6 | 95 ± 11 | 85 ± 5 | 60 ± 4^§ | 8 ± 3 | −22 ± 6 | 0.005 | 0.001 |
| End-systolic stress (kdynes/cm^2) | 409 ± 8 | 484 ± 11 | 398 ± 34 | 259 ± 11 | 7,518 | −13, 221 | 0.01 | 0.01 |
| Ejection fraction (%) | 31 ± 2 | 29 ± 5 | 32 ± 2 | 42 ± 2 | −2 ± 5 | 10 ± 3 | 0.001 | 0.001 |
| NYHA functional class | 2.7 ± 0.2 | 3.1 ± 0.3 | 2.6 ± 0.1 | 1.6 ± 0.2^‡ | 0.42 ± 0.17 | −0.38 ± 0.14 | 0.001 | 0.002 |
| MLWHFQ | 47 ± 7 | 46 ± 3 | 46 ± 4 | 34 ± 8^D | 1.4 ± 0.8 | −9.8 ± 1.2 | 0.001 | 0.001 |
| IGF-1 (ng/ml) | 97 ± 11 | 82 ± 12 | 94 ± 8 | 166 ± 12 | −29.9 ± 9.6 | 73.7 ± 13 | 0.001 | 0.001 |
| NT-proBNP (pg/ml) | 3,940 ± 1,050 | 4,909 ± 432 | 3,201 ± 900 | 2,794 ± 432 | 1,239 ± 121 | −289 ± 123 | 0.001 | 0.001 |

*Values are mean ± SEM.*

Abbreviations: CPET = cardiopulmonary exercise test; IGF = insulin-like growth factor; LV = left ventricular; MLWHHQ = Minnesota Living With Heart Failure Questionnaire; RER = respiratory exchange rate; SEM = standard error of the mean; $VCO_2$ = carbon dioxide production; VE = ventilation per min; $VO_2$ = oxygen consumption.

* Significance of the Δ changes between-group from baseline to 4 years.

† Adjusted significance of the Δ changes between-group from baseline to 4 years, after sensitivity analysis.

‡ $p < 0.001$ from baseline.

§ $p < 0.01$ from baseline.

. $p < 0.05$ from baseline.

## *Comprehensive Efficacy Data: A Broader Understanding of GH/IGF-1 Therapy's Role in CHF Across Demographics*

Objective: This study aims to produce extensive data on the effectiveness of GH and IGF-1 therapy in a large, diverse population of CHF patients. Previous studies on GH therapy in CHF have often been limited in sample size and demographic diversity, focusing primarily on specific populations, which restricts generalizability.

Approach: By including 500 patients with varied ethnic backgrounds, age ranges, and comorbidities, the study will address whether responses to GH/IGF-1 therapy vary based on demographic or clinical characteristics. Primary outcomes ($VO_2$ max, LVEF) and secondary outcomes (hospitalization rates, quality of life) will be analyzed across demographic subgroups.

Expected Findings: This study will provide a broader understanding of how factors such as age, ethnicity, and genetic background influence the efficacy of GH/IGF-1 therapy. For instance, older patients may have different responses or tolerances compared to younger patients, and specific ethnic groups may exhibit variations in baseline GH/IGF-1 levels or receptor sensitivity. Identifying these demographic-specific patterns will help clarify whether certain groups benefit more from GH/IGF-1 therapy or if unique risks are associated.

Impact: The data collected will support informed treatment decisions that consider individual demographic factors, potentially leading to targeted recommendations for GH/IGF-1 therapy and ensuring the therapy is applied in the most effective and safe way for diverse populations.

## *Mechanistic Pathway Insights: Identification of Specific Pathways Associated with GH/IGF-1 Therapy's Cardioprotective Effects*

Objective: While GH and IGF-1 are known to impact cardiac health, the specific molecular pathways involved in their cardioprotective effects are not fully understood. Identifying these pathways is crucial for optimizing GH/IGF-1 therapy in CHF, as it may reveal new therapeutic targets for enhanced or refined treatments.

Approach: The study will use genomic and proteomic analyses to investigate gene expression and protein changes associated with GH/IGF-1 therapy. By comparing pre- and post-treatment samples, researchers will identify molecular changes associated with improvements in cardiac function and muscle strength.

Expected Findings: Mechanistic insights are expected to reveal specific genes and proteins involved in heart muscle repair, inflammation reduction, or vascular function improvement. For example, GH/IGF-1 may influence pathways related to calcium handling in heart muscle cells, endothelial function, or anti-apoptotic effects in cardiac tissues.

Impact: Pinpointing these pathways will validate GH/IGF-1's effectiveness in cardiac protection and guide the development of future drugs targeting these mechanisms. Additionally, understanding these pathways could help identify biomarkers to predict a patient's likelihood of benefiting from GH/IGF-1 therapy, allowing for more precise patient selection in clinical practice.

### *Clinical Guidelines: New Insights for Individualized Therapy Protocols Based on Demographic and Genomic Profiles*

Objective: Personalized medicine aims to tailor treatments to individual patient profiles, including demographic information and genetic characteristics. This study aims to create detailed guidelines for applying GH/IGF-1 therapy in CHF patients based on these unique profiles.

Approach: By analyzing demographic and genomic data alongside treatment outcomes, the study will identify patterns that correlate specific patient characteristics with successful responses to GH/IGF-1 therapy. For example, certain genetic markers may predict favorable responses or higher side effect risks.

Expected Findings: Evidence may support adjusting GH/IGF-1 doses based on genetic variations in GH/IGF-1 receptors, baseline IGF-1 levels, or insulin sensitivity profiles. Guidelines could be developed to indicate optimal doses, preferred patient populations, and specific adjustments for those with comorbidities or genetic predispositions for insulin resistance.

Impact: These insights will enable the development of individualized therapy protocols, minimizing trial-and-error and reducing adverse effects. Personalized guidelines will enhance GH/IGF-1 therapy's clinical application, ensuring that patients receive precisely the right dose and duration for their profiles. Such guidelines will also inform clinicians on when to avoid GH/IGF-1 therapy in patients unlikely to benefit, improving both safety and cost-effectiveness in CHF treatment.

## *Summary*

Together, these contributions will advance the understanding and application of GH/IGF-1 therapy in CHF. Comprehensive efficacy data will clarify which patients benefit most from the therapy, mechanistic insights will deepen knowledge of how the therapy functions at a cellular level, and personalized clinical guidelines will enhance safety and effectiveness, moving towards precision medicine in managing CHF.

## Conflict of interest

The authors declare no conflict of interests. All authors read and approved final version of the paper.

## Authors Contribution

All authors contributed equally in this paper.

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