Growth Hormone Replacement Therapy in Heart Failure With Reduced Ejection Fraction: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background

Growing evidence suggests that reduced activity of the growth hormone (GH)/insulin-like growth factor (IGF)-1 axis is common and associated with poor clinical status and outcome in heart failure (HF). In addition, preliminary results of growth hormone deficiency (GHD) correction in HF showed an improvement in quality of life, cardiac structure and function, and cardiovascular performance.

Objectives

The aim of the present double-blind, randomized, placebo-controlled trial was to evaluate the cardiovascular effects of 1 year of GH replacement therapy in a cohort of patients with heart failure and reduced ejection fraction (HFrEF).

Methods

Consecutive patients with HFrEF in NYHA functional class I/II/III and concomitant GHD were recruited. GHD patients were randomized to receive GH (0.012 mg/kg every second day ~2.5 IU), or placebo, on top of background therapy. The primary endpoint was peak oxygen consumption (VO_2). Secondary endpoints included hospitalizations, end-systolic left ventricular volumes, N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels, health-related quality of life score, and muscle strength (handgrip).

Results

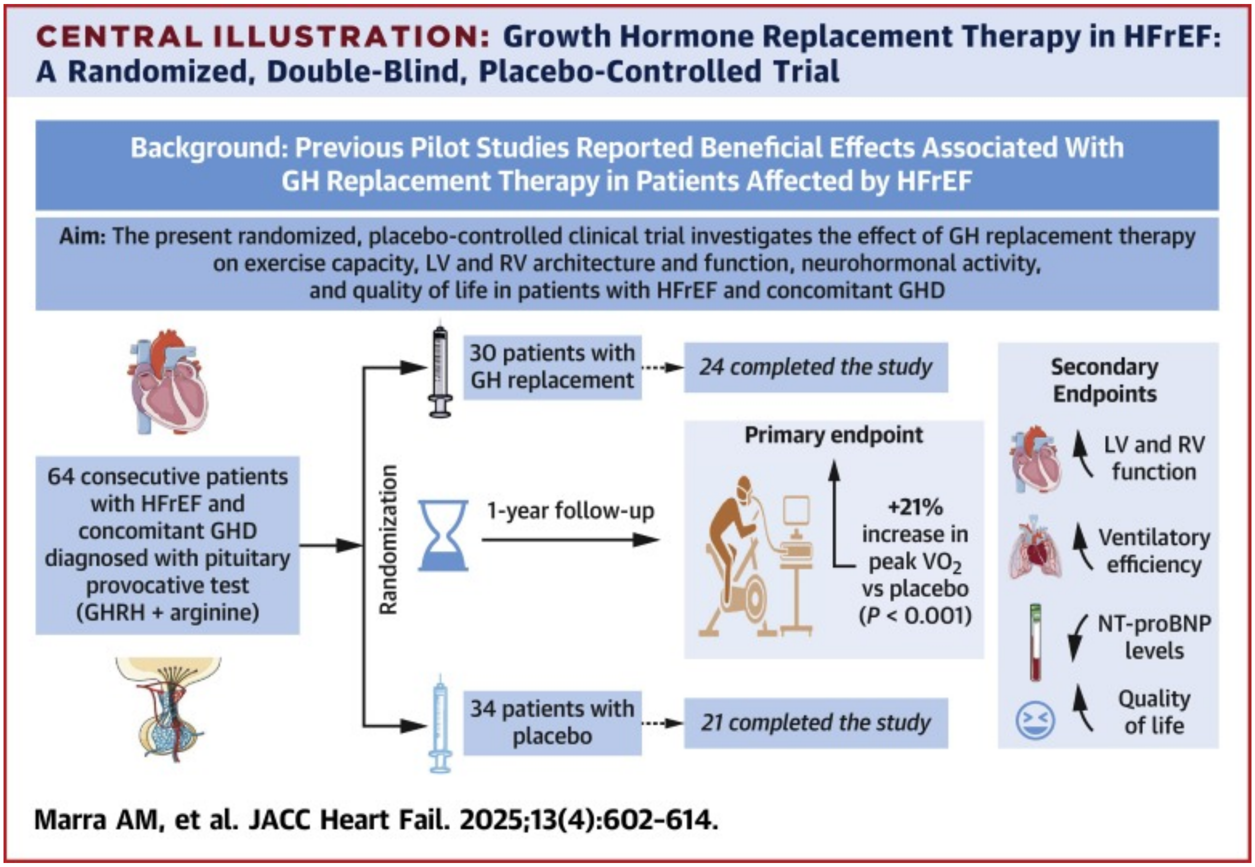
A total of 318 consecutive patients were screened, with 86 (27%) fulfilling the criteria for GHD. Of these, 22 subjects refused to participate in the study. The final study groups consisted of 64 patients, 30 randomized in the active treatment group and 34 in the control group. After 1 year, 45 patients completed the study (21 in the control group and 24 in the active group). A statistically significant improvement of peak VO_2 was reached in the active group (from 12.8 ± 3.4 mL/kg/min to 15.5 ± 3.15 mL/kg/min; $P < 0.01$; delta peak VO_2 between groups: +3.1 vs −1.8; $P < 0.01$). Other cardiopulmonary exercise test parameters (ie, peak workload, VO_2 at the aerobic threshold, O_2 pulse and VE/

VCO_2 slope; $P < 0.05$) also improved, paralleled by an increase in 6-minute walking test distance ($P < 0.05$) and handgrip strength ($P < 0.01$). GH improved right ventricular function (ie, TAPSE and TAPSE/pulmonary artery systolic pressure ratio; $P < 0.01$), leading to an amelioration of clinical status (NYHA functional class; $P < 0.05$) and health-related quality of life (Minnesota Living With Heart Failure Questionnaire; $P < 0.05$). A significant decrease of NT-proBNP was also found ($P < 0.05$).

Conclusions

This randomized, double-blind, placebo-controlled trial demonstrates that GH replacement therapy in HFrEF patients with GHD improves exercise performance, and left ventricular and right ventricular structure and function, leading to an amelioration of clinical status and health-related quality of life. (Treatment of GHD Associated With CHF; NCT03775993)

Central Illustration



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Key Words

cardiac function
cardiopulmonary performance
growth hormone
growth hormone deficiency
heart failure
treatment

Abbreviations and Acronyms

CHF
chronic heart failure

CPET
cardiopulmonary exercise test
GHD
growth hormone deficiency
GHRH
growth hormone releasing hormone
HFpEF
heart failure with preserved ejection fraction
HFrEF
heart failure with reduced ejection fraction
HRQoL
health-related quality of life
IGF
insulin-like growth factor
LVEF
left ventricular ejection fraction
NT-proBNP
N-terminal pro–B-type natriuretic peptide
PASP
pulmonary artery systolic pressure
RV
right ventricular
TAPSE
tricuspid annular plane systolic excursion

Mounting evidence supports the concept that multiple hormonal and metabolic deficiency syndrome is common in chronic heart failure (CHF) and is independently associated with increased all-cause mortality and cardiovascular hospitalization.[1, 2, 3, 4, 5] Among endocrine deficiencies, the impairment of the growth hormone (GH)/insulin-like growth factor (IGF)-1 axis, the most powerful anabolic system, plays a pivotal role.[6,7] Indeed, growth hormone deficiency (GHD) identifies a subgroup of CHF patients characterized by impaired functional capacity, left ventricular (LV) remodeling, and elevated N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels, as well as increased all-cause mortality.[7] We have previously shown that approximately 20% to 25% of CHF patients display GHD (ie, impaired response to a pituitary stimulatory test: growth hormone-releasing hormone [GHRH] + arginine).[7] GHD per se increases cardiovascular mortality in the general population, and low IGF-1 levels predict the development of ischemic heart disease and CHF. GHD modifies cardiac size and function, through a reduction in both myocardial growth and cardiac performance.[8] As a result, GHD patients are characterized by low left ventricular ejection fraction (LVEF) and cardiac output, and high peripheral vascular resistance, resembling the typical phenotype of dilated cardiomyopathy.[9,10] Of note, GH replacement therapy in such patients restores normal LV structure and function,[9,10] demonstrating the continuing ability of IGF-1 to modulate the plasticity of cardiac tissue in adult life. In this regard, this subset of patients affected with both CHF and GHD display worse LV remodeling, exercise performance, and quality of life scores compared with GH-sufficient patients with CHF.[7]

Taken together, there is a scientific background to consider CHF as an appropriate clinical context to screen for GHD and to perform replacement GH therapy in adult patients, also considering the well-known growth-promoting, antiapoptotic, and nitric oxide–mediated vasodilating actions of the GH/IGF-1 axis.

Therefore, we performed a randomized, double-blind, and placebo-controlled trial, aimed at evaluating exercise capacity, neurohormonal parameters, and LV and right ventricular (RV) structure and function in patients with GHD and heart failure with reduced ejection fraction (HFrEF), at baseline and after 1 year of GH replacement therapy. Peak oxygen consumption (VO_2) was the primary endpoint.

Methods

Patients

After a screening period of 36 months involving consecutive patients with stable HFrEF referred to the heart failure (HF) tertiary center of the Department of Translational Medical Sciences, Federico II University (Naples, Italy) eligible patients were recruited and randomized with a permuted block design in a double-blind fashion to receive either placebo or growth hormone (Saizen, Merck KGaA) administration at the dose of 0.012 mg/kg every second day subcutaneously for 12 months, on top of standard medical therapy for HF. Patients randomized to placebo received an identical amount of saline employing the same device used for GH therapy. Drug or placebo were dispensed through the Aluetta system, a high-quality and durable aluminum pen with a dose window for clear visual confirmation of the dosage. Randomization, drug/placebo assignation, and shipment were supported by a professional independent contract manufacturing organization (STM Pharma Pro s.r.l., now Euromed Pharma Services Logistic and Importation), which guaranteed that investigators were totally blinded during all the study. Drug/placebo dispensation was 3 months at a time, to allow clinical monitoring. The full inclusion and exclusion criteria are shown in Table 1.

Table 1. Inclusion and Exclusion Criteria

Inclusion	Exclusion
Patients of either sex affected by stable HF in NYHA functional class I-III	Inability to perform a bicycle exercise test
Age range: 18-85 y	Poorly controlled diabetes mellitus (HbA_{1c} >8.5) and/or active proliferative or severe nonproliferative diabetic retinopathy
Optimal medical therapy for at least 3 mo before randomization	Active and/or history of malignancy
LVEF ≤40%	Unstable angina, or recent myocardial infarction (<6 mo)
Signed informed consent	Severe liver or kidney disease (serum creatinine levels >2.5 mg/dl

Diagnostic Criteria for GHD

Impaired response to a pituitary stimulatory test: GHRH + arginine

- GH peak <9 μg/L for patients ≤30 kg/m^2 BMI
- GH peak <4.1 μg/L for patients with BMI >30 kg/m^2

BMI = body mass index; GH = growth hormone; GHD = growth hormone deficiency; GHRH = growth hormone-releasing hormone; HbA_{1c} = glycosylated hemoglobin; HF = heart failure; LVEF = left ventricular ejection fraction.

The study fully complied with the Declaration of Helsinki. Written informed consent was obtained from each patient, and the study protocol was approved by the Ethics Committee of Federico II University (Prot. N. 290/16). The trial was registered on ClinicalTrials.gov (Treatment of GHD Associated With CHF; NCT03775993).

Study procedures

The present study was a randomized, double-blind, and placebo-controlled trial. Patients were evaluated at baseline and following clinical need, with all the procedures repeated at the end of the study (12 months). Fasting blood samples were taken. A standard 12-lead electrocardiogram was performed to assess heart rhythm and rate, atrioventricular and intraventricular conduction, and repolarization abnormalities. Patients underwent a complete echocardiography exam (including 2 dimensional, color Doppler, and tissue Doppler analysis (VIVID E95, GE HealthCare) and symptom-limited cardiopulmonary exercise test (CPET) (Quark CPET, COSMED). Peak oxygen consumption (VO_2) was measured by breath-to-breath respiratory gas analysis. After a 1-minute warm-up period at 0 W workload, a ramp protocol of 10 W/min was started and continued until limiting symptoms or other indications for exercise termination appeared. Respiratory gas exchange measurements were obtained breath by breath. Peak VO_2 was recorded as the mean VO_2 value over a 20- to 30-second period at maximal effort, after the achievement of a target respiratory exchange ratio (respiratory exchange ratio >1.1).[11] The ventilatory anaerobic threshold was detected by use of the V-slope method. The ventilation per minute (VE) vs carbon dioxide production (VCO_2) relationship (ventilatory efficiency) was measured by plotting ventilation against VCO_2 obtained every 10 seconds of exercise, with slope calculated as a linear regression function including all the phases of the exercise.[11]

Health-related quality of life (HRQoL) was assessed with the MLHFQ (Minnesota Living With Heart Failure Questionnaire).

Muscular strength was evaluated by the handgrip strength with a handheld dynamometer (Lafayette Instrument).

A full work-up was conducted at baseline and at the end of the study. Intermediate visits were scheduled at 3 and 6 months for clinical follow-up, clinical blood sampling, monitoring of therapy, and adverse events. Core laboratories blinded to treatment allocation for all measurements were used (Medical Genetic Department, ASL Napoli 1, Naples, Italy).

Study outcomes

The main objective of the study was to determine whether 1 year of GHD replacement treatment improves peak VO_2.

Secondary endpoints included hospitalizations, end-systolic LV volumes, NT-proBNP levels, HRQoL score, and muscle strength (handgrip).
All the endpoints have been evaluated at 12 months.

Statistical analysis

According to previous observations,[12,13] we set a target increase of peak VO_2 at 3 mL/kg/min at the end of the study in the treated arm (primary endpoint) and an expected decrease of 1 mL/kg/min in the placebo arm. Assuming a significance level of 5%, an 80% study power, and a SD of 4 mL/kg/min for the object variable, a sample of 28 patients in each arm of the study was considered sufficient. In addition, the dropout rate of the recruited patients was expected reasonably low (<15%), based on the documented good tolerability of GH from previous studies in HF.[12,13]
Results were analyzed by a per protocol approach. Data were preliminary tested for normal distribution and homoscedasticity with Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as mean ± SD, whereas continuous data with skewed distributions were expressed as median (Q1-Q3). Categorical variables were expressed as counts and percentages. The 2-sample Student's *t*-test for unpaired data was used to evaluate the treatment effect (delta changes in the GH group vs delta changes in the control group). Statistical analysis was performed using R version 3.0 (R Foundation for Statistical Computing) and SPSS version 25.0 (SPSS Inc). A value of $P < 0.05$ was considered statistically significant.
In addition to internal statisticians, an independent professional statistician (D.B.)—fully blinded to the study procedures and independent from the research group—replicated and verified all the statistical analyses.

Results

Between March 2019 and March 2022, 318 consecutive patients were screened, with 86 (27%) fulfilling the criteria for GHD. Of these, 22 subjects refused to participate in the study for personal reasons. Therefore, the final study groups consisted of 64 patients, 30 randomized in the active treatment group, and 34 patients in the control group.
The patients' characteristics at baseline were similar in the 2 groups (Table 2, Supplemental Table 1). Specifically, more than 50% of patients had ischemic

etiology, were male (about 80%) with a mean age of 65 years, and there were no differences with regard to the main comorbidities (eg, chronic obstructive pulmonary disease, diabetes mellitus, obesity, atrial fibrillation).

Table 2. Baseline Characteristics of the Patients Who Completed the Study

Empty Cell	**Control Group (n = 21)**	**Treatment Group (n = 24)**	***P* Value**
Age, y	65.0 ± 9.6	64.0 ± 9.4	ns
Male/female	16/5	22/2	ns
BMI, kg/m^2	30.5 ± 5.2	29.9 ± 5.1	ns
Systolic BP, mm Hg	126.0 ± 17.4	126.2 ± 13.5	ns
Diastolic BP, mm Hg	76.7 ± 11.5	75.2 ± 11.4	ns
NYHA functional class, I-II/III	4/17	1/20	ns
HF etiology, ischemic	11/21 (52)	15/24 (62)	ns
Ejection fraction, %	34.9 ± 5.8	34.7 ± 5.7	ns
NT-proBNP, pg/mL	600 (222-1,613)	710 (179-1,770)	ns
IGF-1, ng/mL	165.0 ± 38.1	142.4 ± 46.4	ns
HgB, g/dL	13.9 ± 1.4	14.1 ± 1.6	ns
eGFR, mL/min/1.73 m^2	85 ± 21	83 ± 22	ns
CRP, mg/dL	0.7 (0.33-2.5)	0.7 (0.3-1.75)	ns
GH peak at the GHRH + arginine provocativ test	3.8 ± 3.3	3.0 ± 2.1	ns
Total cholesterol	136.9 ± 33.0	148.5 ± 40.7	ns
Triglycerides	112.5 ± 41.7	133.5 ± 111.5	ns
Comorbidities			
Atrial fibrillation	3 (15)	5 (20)	ns
COPD	2 (10)	2 (9)	ns
Type 2 diabetes	7 (33)	6 (25)	ns
Dyslipidemia	14 (67)	17 (71)	ns
Medications			
Beta-blockers	20 (95)	21 (88)	ns
Diuretic agents	19 (90)	21 (88)	ns
ACEI/ARBs	4 (19)	4 (17)	ns
MRA	10 (47)	10 (42)	ns

Empty Cell	**Control Group (n = 21)**	**Treatment Group (n = 24)**	***P* Value**
Amiodarone	4 (19)	4 (17)	ns
Antiplatelet agent	10 (47)	14 (57)	ns
Anticoagulant agent	12 (57)	9 (40)	ns
Statins	14 (66)	17 (71)	ns
Antidiabetic agents/insulin	7 (33)	6 (28)	ns
ARNI	15 (71)	18 (75)	ns
SGLT2i	7 (33)	6 (25)	ns
ICD	15 (71)	17 (72)	ns
CRT	2 (10)	2 (8)	ns

Values are mean ± SD, n/n, n/N (%), median (Q1-Q3), or n (%), unless otherwise indicated.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BP = blood pressure; COPD = chronic obstructive pulmonary disease; CRT = cardioverter resynchronization therapy; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; HgB = hemoglobin; ICD = implantable cardioverter-defibrillator; IGF = insulin-like growth factor; MRA = mineralocorticoid receptor antagonist; ns = not significant; NT-proBNP = N-terminal pro–B-type natriuretic peptide; SGLT2i = sodium-glucose cotransporter 2 inhibitor; other abbreviations as in Table 1.

The rate of HF drug prescription was similar in the 2 groups, with about 90% of the patients taking beta-blockers and angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers/angiotensin receptor neprilysin inhibitors, and about 50% of subjects taking mineralocorticoid receptor antagonists. Notably, starting from January 2022, sodium-glucose cotransporter 2 inhibitors (SGLT2is) were available. Therefore, patients enrolled after 2022 were prescribed SGLT2is (about 30%) and waited for 6 months before entering the study. Interestingly, excluding these patients from the analysis did not change the overall results (Supplemental Table 2).

Of the 64 patients, 6 in the treatment group and 13 in the placebo group did not complete the study. Specifically, 1 patient in each group died ($P > 0.05$), and the others (ie, 5 in the active group and 8 in the placebo group) withdrew their consent for personal reasons (eg, impossibility to attend the scheduled visits, change in referral physicians). Finally, 4 patients (all in the placebo group) interrupted the study for trialunrelated clinical causes (ie, laryngeal cancer, recurrent hypotension, recurrent migraine headache, gynecomastia) (Figure 1).

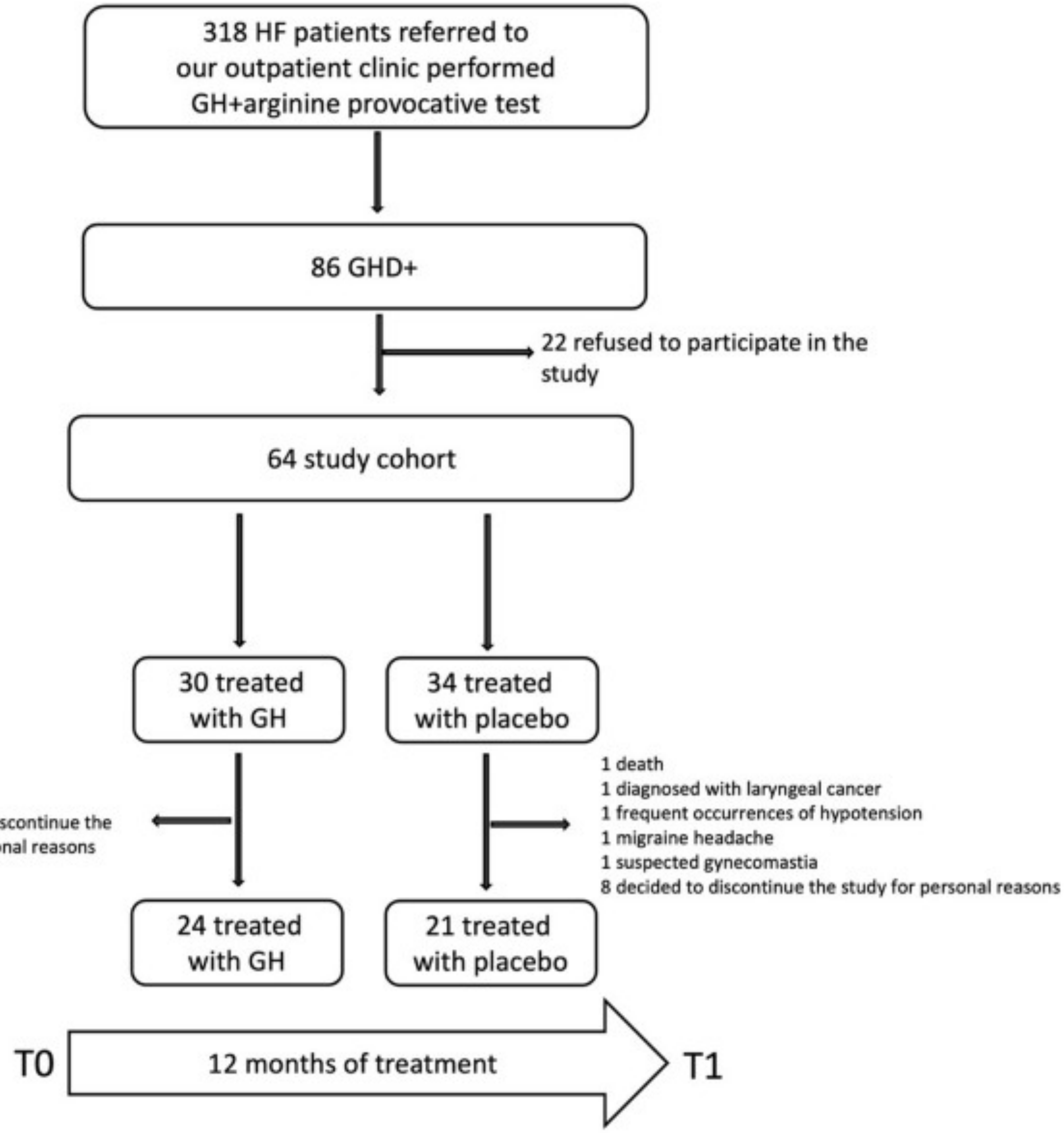

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Figure 1. Flowchart of the Study Protocol

GH = growth hormone; GHD = growth hormone deficiency; GHRH = growth hormone-releasing hormone; HF = heart failure; T0 = baseline; T1 = 1 year.

Primary endpoint

Patients in the active treatment group showed a statistically significant improvement of the primary endpoint of the study, whereas in the placebo group, a slight, not significant decrease of peak VO_2 was observed, resulting in a statistically significant difference in delta peak VO_2 between the active treatment and the placebo groups (+3.1 vs −1.8 mL/kg/min; $P < 0.01$). Specifically, peak VO_2 rose from 12.8 ± 3.4 mL/kg/min to 15.5 ± 3.15 mL/kg/min after 1 year ($P < 0.01$) in the active group and decreased from 13.1 ± 4.8 mL/kg/min to 11.3 ± 2.5 mL/kg/min (P = ns) in the control group (Figures 2A and 3).

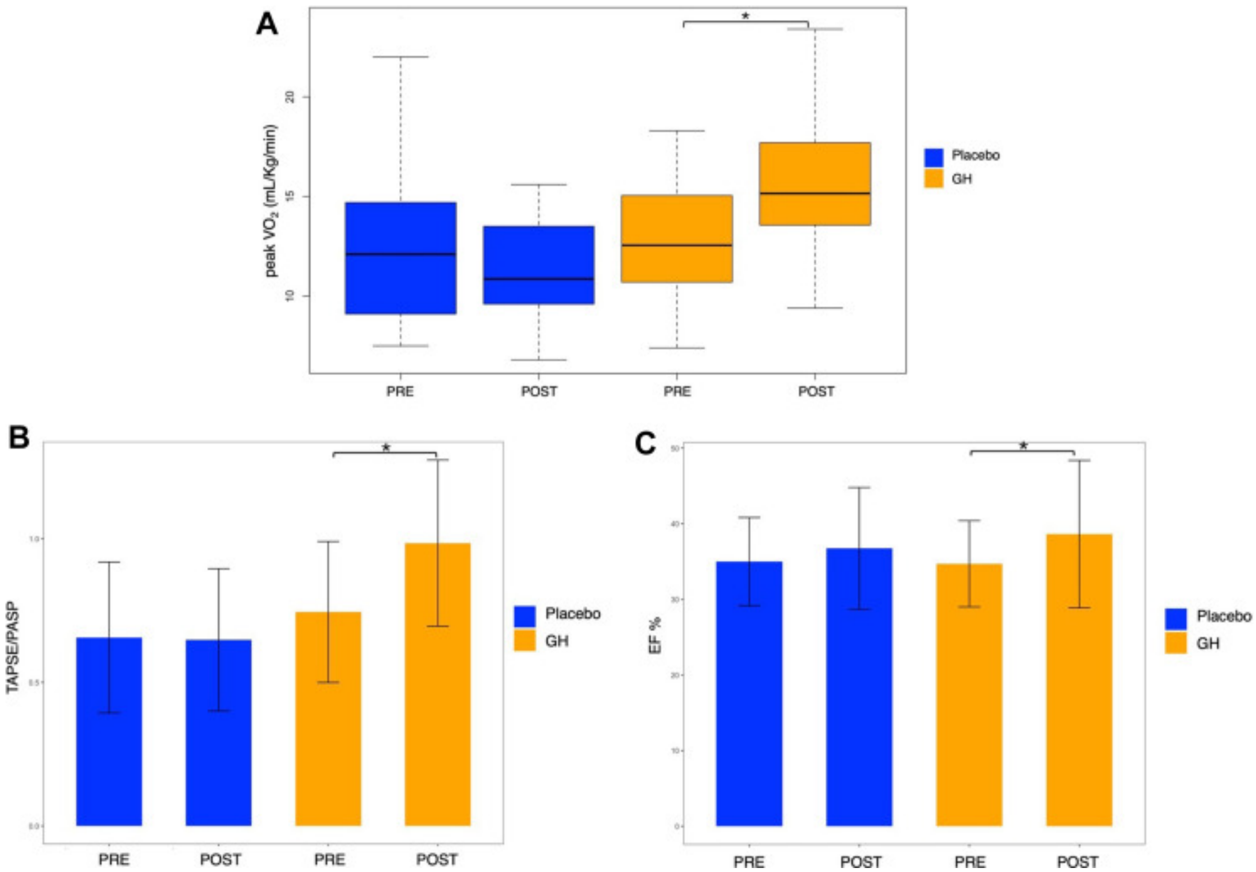

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Figure 2. Principal Endpoints

(A) Peak oxygen consumption (VO_2). (B) Tricuspid annular plane systolic excursion (TAPSE) and pulmonary artery systolic pressure (PASP). (C) Left ventricular ejection fraction (LVEF). EF = ejection fraction; GH = growth hormone.

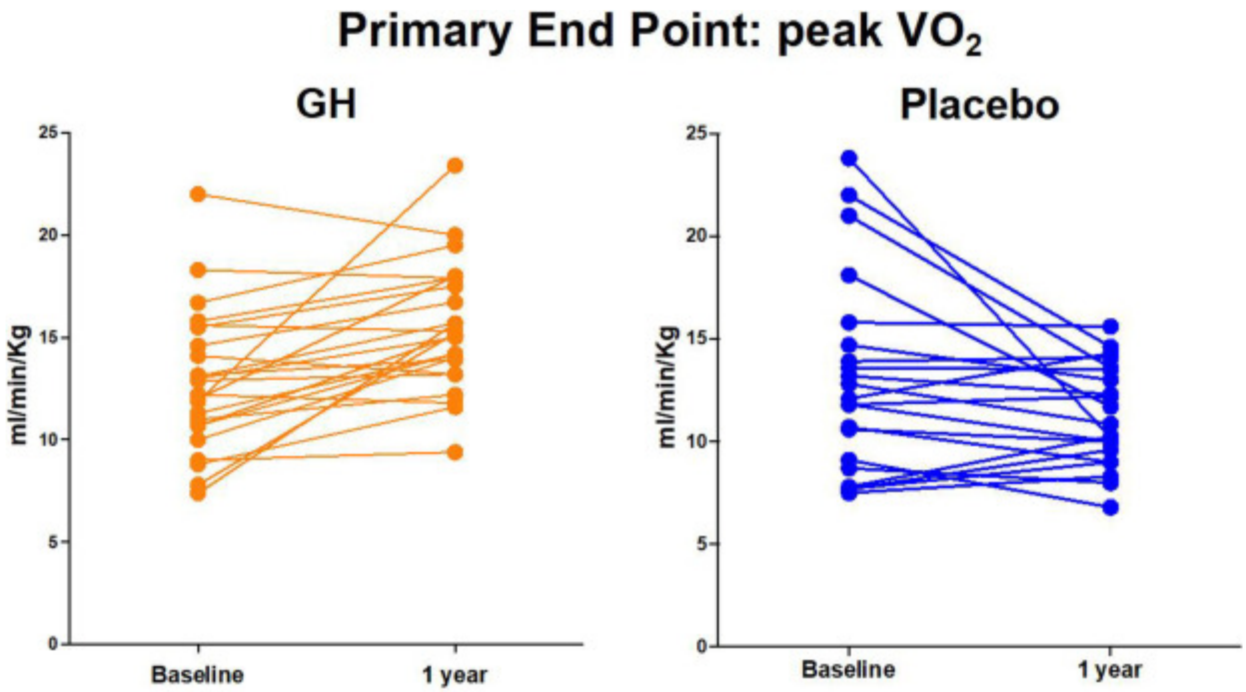

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Figure 3. Spaghetti Plot of the Primary Endpoint

Abbreviations as in Figures 1 and 2.

Secondary endpoints

Exercise capacity and cardiovascular hemodynamic

Consistent with the observed improvement of the primary endpoint, GH replacement treatment also significantly improved other indexes of cardiopulmonary performance, whereas no effects were observed in the placebo group (Table 3). Specifically, a significant increase in peak workload (from 82.6 W ± 35.6 W to 93.8 W ± 35.1 W; $P < 0.05$) was observed, whereas these parameters remained stable in the control group. Both VO_2 at the aerobic threshold (from 9.1 mL/kg/min ± 4.0 mL/kg/min to 11.6 mL/kg/min ± 2.4 mL/kg/min) and O_2 pulse (from 11.4 mL/beat ± 3.1 mL/beat to 13.6 mL/beat ± 2.8 mL/beat) significantly increased ($P < 0.01$ from baseline and compared with placebo), whereas no significant changes were observed in the placebo group. In addition, VO_2/Work slightly increased in the treated group (from 8.3 ± 2.3 to 9.5 ± 1.8), whereas it slightly decreased in the placebo group (final delta changes between groups: +1.7 and −0.8; $P < 0.01$). The VE/VCO_2 slope, an index of ventilatory efficiency, decreased in the treated group, whereas it slightly increased in the placebo group (from 30.6 ± 3.8 to 29.1 ± 3.1; $P < 0.01$, and from 30.4 ± 5.8 to 35.9 ± 10.8; P = ns, respectively; delta change between groups 1.5 vs 5.5; $P < 0.01$). None of the patients in either group had an exercise oscillatory ventilatory pattern.

Table 3. CPET, 6MWT, and Echocardiographic Parameters

Empty Cell	Control Group (n = 21)				Treatment Group (n = 24)				*P* Value [b]
	Baseline	**12 mo**	**Delta**	***P* Value** [a]	**Baseline**	**12 mo**	**Delta**	***P* Value** [a]	
Baseline heart rate, beats/min	65.0 ± 10.9	66.6 ± 10.2	1.6	ns	66.0 ± 11.9	64.3 ± 9.2	−1.6	ns	0.02
Heart rate at AT, beats/min	96.4 ± 9.8	97.3 ± 12.0	0.9	ns	98 ± 15.9	98.6 ± 14.3	0.6	ns	ns
Peak heart rate, beats/min	112.0 ± 11.4	113.7 ± 13.6	1.7	ns	111.0 ± 16.2	112.7 ± 14.7	1.7	ns	ns
Peak workload, W	75.5 ± 27.1	74.8 ± 23.9	−0.7	ns	82.6 ± 35.6	93.8 ± 35.1	11.2	0.03	0.04
O_2 pulse, mL/beat	9.4 ± 3.5	8.1 ± 2.9	−1.3	ns	11.4 ± 3.1	13.6 ± 2.8	2.2	<0.001	<0.001
VE/VCO_2 slope	30.4 ± 5.8	35.9 ± 10.8	5.5	ns	30.6 ± 3.8	29.1 ± 3.1	−1.5	ns	<0.01
Peak VO_2, mL/kg/min	13.1 ± 4.8	11.3 ± 2.5	−1.8	ns	12.4 ± 2.8	15.5 ± 3.14	3.1	<0.001	<0.01
VO_2 at the AT, mL/kg/min	8.5 ± 4.8	7.1 ± 2.1	−1.42	ns	9.1 ± 4.0	11.6 ± 2.4	2.5	<0.001	<0.01
VO_2/work	8.9 ± 2.1	7.4 ± 1.1	−0.84	ns	8.3 ± 2.3	9.5 ± 1.8	1.8	<0.01	<0.01
Time to AT, min	8.6 ± 1.8	7.3 ± 1.6	−1.6	ns	7.95 ± 2.3	7.98 ± 2.1	0.1	ns	<0.001
RER	1.15 ± 0.02	1.14 ± 0.01	−0.01	ns	1.14 ± 0.01	1.14 ± 0.02	0	ns	ns
6MWT distance, m	405.7 ± 118.7	407.6 ± 136.2	1.9	ns	402.2 ± 117.2	476.7 ± 140.9	34.5	0.04	0.04
Handgrip, kg	22.7 (18.1-26.3)	22.2 (18.1-27.2)	−0.5	ns	20.6 (15.6-32.7)	31.7 (21.5-38.1)	11.1	ns	<0.01
LVMi, g/m^2	122.3 ± 26.8	117.1 ± 41.2	−5.2	ns	126.6 ± 28.7	180.7 ± 222.4	+54.1	0.04	0.04

Empty Cell	Control Group (n = 21)				Treatment Group (n = 24)				*P* Value [b]
	Baseline	**12 mo**	**Delta**	***P* Value [a]**	**Baseline**	**12 mo**	**Delta**	***P* Value [a]**	
LV end-diastolic volume, mL	182.3 ± 48.4	168.5 ± 49.3	−13.8	ns	177.9 ± 59.8	170.4 ± 63.0	−7.5	ns	ns
LV end-systolic volume, mL	120.4 ± 41.7	108.6 ± 42.9	−11.8	ns	118.4 ± 53.3	108.0 ± 55.6	−10.3	0.02	ns
RVEdD, mm	44.6 ± 3.8	41.6 ± 4.2	−3	ns	41.7 ± 8.5	35.6 ± 6.5	−6	ns	ns
RADVi	24.6 ± 4.3	26.7 ± 5.3	2.1	ns	27.1 ± 12.1	29.2 ± 16.5	1.4	ns	ns
Ejection fraction, %	34.9 ± 5.8	36.7 ± 8.0	1.7	ns	34.7 ± 5.7	38.6 ± 9.7	3.9	<0.01	ns
LAVi, mL/m^2	40.0 ± 16.5	46.3 ± 18.8	6.3	ns	38.2 ± 17.7	33.3 ± 12.8	−4.9	ns	0.02
E velocity, cm/s	8.7 ± 3.1	8.0 ± 2.3	−0.67	ns	7.2 ± 1.8	7.9 ± 2.4	0.7	ns	ns
E/e′	10.0 ± 3.9	11.5 ± 5.0	1.5	ns	9.2 ± 2.8	9.1 ± 4.0	−0.1	ns	ns
PASP, mm Hg	35.4 ± 13.1	34.8 ± 10.4	0.7	ns	29.5 ± 6.7	27.6 ± 5.5	−1.7	ns	ns
TAPSE	20.7 ± 4.6	20.5 ± 4.5	−0.2	ns	20.9 ± 4.6	26.0 ± 5.2	5.1	<0.001	<0.01
TAPSE/PASP	0.66 ± 0.26	0.65 ± 0.25	−0.01	ns	0.75 ± 0.25	0.99 ± 0.29	0.24	<0.01	<0.001

Values are mean ± SD, or median (Q1-Q3), unless otherwise indicated.

6MWT = 6-minute walking test; AT = anaerobic threshold; CPET = cardiopulmonary exercise test; E/e′ = E wave and e′ wave on tissue Doppler imaging ratio; LAVi = left atrial volume index; LV = left ventricular; LVMi = left ventricular mass index; ns = not significant; PASP = pulmonary artery systolic pressure; RADVi = right atrial diastolic volume index; RER = respiratory exchange ratio; RVEdD = right ventricular end-diastolic diameter; TAPSE = tricuspid annular plane systolic excursion; VCO_2 = carbon dioxide production slope; VE = ventilation per minute; VO_2 = oxygen consumption.

a

P vs baseline.

b

P vs control group (delta change between-group).

In addition, a significant improvement in the 6-minute walking test distance was observed in the GH group, whereas no effects were observed in the placebo group (from 402.2 ± 117.2 m to 476.7 ± 140.9 m; $P < 0.05$ and from 405.7 ± 118.7 m to 407.6 ± 136.2 m; P = ns, respectively). No changes in blood pressure values were found between baseline and end treatment in either group. On the other hand, a significant decrease in baseline heart rate was observed in the GH replacement therapy group.

LV structure and function

GH replacement therapy was associated with a significant decrease in LV end-systolic volume, leading to a significant increase of the LVEF in the treated group (from 34.7% ± 5.7% to 38.6% ± 9.7%; $P < 0.05$). However, no differences were found as to EF delta changes between GH and placebo groups (Figure 2B).

A significant decrease in left atrial volume index was observed in the GH treatment arm (from 38.2 ± 17.7 mL/m^2 to 33.3 ± 12.8 mL/m^2; $P < 0.05$), when compared with placebo. No significant differences between groups were found as to measured indexes of diastolic function.

RV structure and function

No significant changes were observed in RV morphology or pulmonary artery systolic pressure (PASP). However, RV longitudinal function significantly improved after 1 year of GH treatment, as seen by the improvement of tricuspid annular plane systolic excursion (TAPSE) (from 20.9 ± 4.6 to 26.0 ± 5.2; $P < 0.01$ from baseline and compared with the control group). As a result, a significant improvement of the TAPSE/PASP ratio (from 0.75 ± 0.25 to 0.99 ± 0.29; $P < 0.01$) was observed (Figure 2C).

Clinical Status and HRQoL

Clinical status improved after GH therapy, as depicted by the significant decrease from the baseline in the NYHA functional class—chi-square test (1, n = 24) 16.5; $P < 0.01$—in the treated group, not paralleled by the same decrease in the control group (from III to I/II: 4 patients vs 0 patients) (Table 4).

Table 4. Clinical Status, Health-Related Quality of Life, and Biochemical Results

Empty Cell	Control Group (n = 21)				Treatment Group (n = 24)				*P* Value [b]
	Baseline	12 mo	Delta	*P* Value [a]	Baseline	12 mo	Delta	*P* Value [a]	
BMI, kg/m²	30.5 ± 5.2	31.0 ± 5.1	0.5	ns	29.9 ± 5.1	30.5 ± 4.6	0.6	ns	ns
Systolic BP, mm Hg	126.0 ± 17.4	124.5 ± 12.2	−1.5	ns	126.25 ± 13.5	125.20 ± 18.0	−1.05	ns	ns
Diastolic BP, mm Hg	76.75 ± 11.5	76.96 ± 9.7	2.9	ns	75.2 ± 11.4	79.6 ± 12.2	4.4	ns	ns
NYHA functional class, I-II/III	4/17	1/20		ns	4/20	18/6		<0.01	<0.01
NT-proBNP, pg/mL	600 (222-1,613)	1,012 (182-1,513)	412	ns	710 (179-1,770)	220 (77-645)	−490	0.02	0.03
IGF-1, ng/mL	165.0 ± 38.1	155.8 ± 50.7	−9.2	ns	142.4 ± 46.4	167.5 ± 62.7	25.1	ns	0.02
HgB, g/dL	13.9 ± 1.4	14.2 ± 1.5	0.23	ns	14.1 ± 1.6	14.7 ± 1.5	0.6	ns	ns
CRP, mg/dL	0.7 (0.33-2.5)	0.35 (0.33-1.0)	−0.3	ns	0.7 (0.33-0.7)	0.4 (0.33-0.7)	−0.3	ns	ns
Total cholesterol, mg/dL	136.9 ± 33.0	132.9 ± 33.9	−4	ns	148.5 ± 40.7	135.6 ± 35.8	−8.7	ns	ns
Triglycerides, mg/dL	112.5 ± 41.7	134.2 ± 64.6	21.7	<0.01	133.5 ± 111.5	114.5 ± 61.1	−23.4	ns	ns
MLHFQ total score	31 ± 20	35 ± 18	+4	ns	35 ± 19	23 ± 10	12	0.01	0.01
Physical domain	15 ± 10	17 ± 8	+2	ns	15 ± 8	10 ± 4	−5	0.04	0.02
Emotional domain	6 ± 5	5 ± 4	−1	ns	8 ± 6	5 ± 4	−3	0.03	0.04

Values are mean ± SD, n/N, or median (Q1-Q3), unless otherwise indicated.

MLHFQ = Minnesota Living With Heart Failure Questionnaire; other abbreviations as in Tables 1 and 2.

a

P vs baseline.

b

P vs control group (delta change between-group).

The HRQoL improved, as testified by the significant decrease in the global MLHFQ score (−12 points vs +3 points; $P < 0.01$, GH vs controls, respectively) with a significant amelioration in both the physical (15 ± 8 vs 10 ± 4; $P < 0.05$) and the emotional (8 ± 6 vs 5 ± 4; $P < 0.05$) domains in the active treatment group, whereas there was a slight nonsignificant worsening of all the scores in the control group (15 ± 10 vs 17 ± 8 and 6 ± 5 vs 5 ± 4 from baseline to 12 months; $P > 0.05$). These delta changes were all statistically significant when the 2 groups were compared.
Handgrip data showed an increase of the strength in the GH group, with a significant difference between the 2 groups at the end of the trial (from 20.6 kg [Q1-Q3: 15.6-32.7 kg] to 31.7 kg [Q1-Q3: 21.5-38.1 kg], delta change +11.1 vs −0.5; $P = 0.04$).

Hormones and biomarkers

At baseline, in both groups, serum IGF-1 levels were comparable between the 2 groups. After treatment, an increase was obtained in the active arm group (from 142.4 ± 46.4 ng/mL to 167.5 ± 62.7 ng/mL, delta changes −9.2 vs +25.1; $P < 0.05$), whereas no differences were found in the placebo group (Table 4).
Furthermore, we observed a significant decrease of NT-proBNP levels in the treated group (from 710 [179-1,770] pg/mL to 220 [77-645] pg/mL) resulting in a significant difference from the placebo group ($P < 0.01$). Other biochemical parameters, including glucose, and creatinine were unaffected by GH therapy. With regard to lipids levels, we did not observe any statistically significant difference in total cholesterol levels; on the other hand, we observed a statistically significant increase in triglyceride levels in the control group, with a not significant decrease in the GH therapy group.

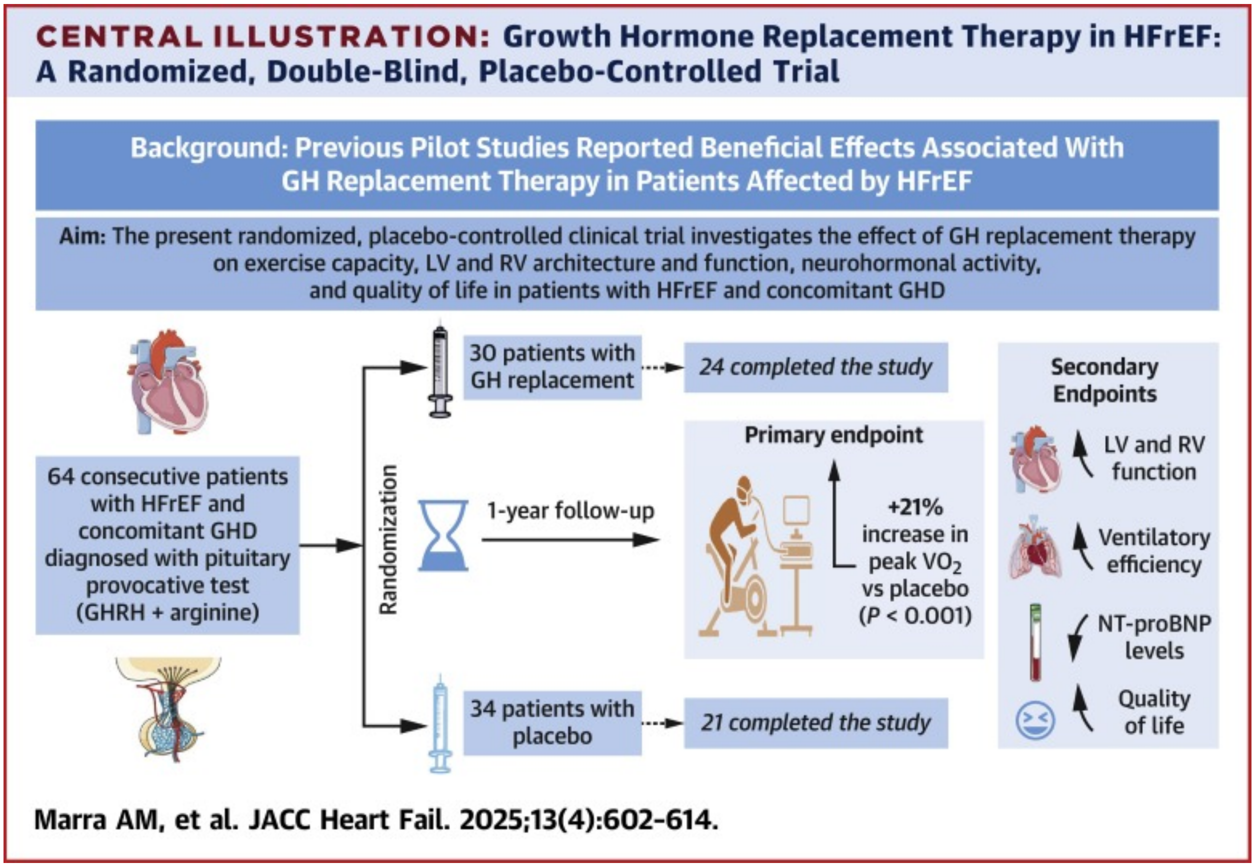
Safety and Tolerability

All patients were periodically clinically evaluated, and clinical investigators were available at patients' request or at clinical need. Of course, not all the procedures (eg, CPET, quality of life questionnaires, echocardiography) were performed during these clinical evaluations. During GH replacement therapy, we observed 3 major events in the active group (1 death and 2 hospitalizations) and 6 events in the placebo arm (1 death and 5 hospitalizations) (P = ns). Patients experiencing hospitalization were not withheld from ongoing treatment (GH or placebo). In addition, 4 patients in the placebo

group interrupted the study for the following reasons: laryngeal cancer, hypotension, migraine headache, and gynecomastia. Even if GH may cause fluid retention, no differences in the need of diuretic adjustment were found between the groups. Despite the well-known counterregulatory role of GH in glucose homeostasis, serum fasting glucose did not increase but slightly decreased after GH therapy. electrocardiogram and Holter monitoring revealed no changes in ventricular or supraventricular arrhythmias after GH therapy.
Between the well-known side effects of GH therapy, no patients reported arthralgia, whereas 2 patients reported transient headache (1 in the GH group and 1 in the placebo group; *P* = ns), and 3 patients experienced muscle/joint pain (1 in the GH group and 2 in the placebo group; *P* = ns).

Discussion

For the first time, the beneficial effects of GH replacement therapy in patients with HFrEF and coexisting GHD are demonstrated in a double-blind, randomized, placebo-controlled trial, with significant improvement in physical performance, cardiac morphology and function, neurohormonal profile, and quality of life (Central Illustration). The primary prespecified endpoint (peak VO_2) significantly improved by 22% in the active treatment group. The study also shows that GH replacement therapy was safe and well-tolerated by the patients. Of note, the beneficial effects of GH correction were obtained on top of new-generation guideline-directed medical therapy. Finally, the study confirms the relatively high prevalence (27%) of GHD in patients with HFrEF.



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Central Illustration. Growth Hormone Replacement Therapy in HFrEF: A Randomized, Double-Blind, Placebo-Controlled Trial

GH = growth hormone; GHD = growth hormone deficiency; GHRH = growth hormone-releasing hormone; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; NT-proBNP = N-terminal pro–B-type natriuretic peptide; RV = right ventricular; VO_2 = oxygen consumption.

Effects of GH replacement treatment

Exercise Performance

HF represents a typical condition of maladaptive response, leading to an impairment of the physiological delivery of oxygen to the mitochondria.[11] Thus, HF patients display a reduction of the maximal VO_2 because of the reduction in muscle O_2 supply, which no longer fulfils the increasing demand for O_2.[11]

The present investigation shows an improvement in cardiopulmonary performance and exercise capacity in the active treatment group, as testified by a significant increase in the total distance at the 6-minute walking test and a significant improvement in the VO_2 max and a decrease of the VE/VCO_2 slope at the CPET from baseline and compared with the placebo group. These findings are congruent with those reported by Le Corvoisier et al,[14] who described an increase in exercise duration and VO_2 max in several previous studies. These data were later confirmed by the randomized controlled single-blind trial performed by Cittadini et al[12,13] at 6 months and 48 months after GH treatment.

From a pathophysiological point of view, the improvement of exercise capacity is likely due to the combined effects of GH treatment on the heart, pulmonary and peripheral vascular tissues, and skeletal muscles. The increase in the O_2 pulse (ie, the ratio of VO_2 to heart rate, reflecting the amount of O_2 extracted per heartbeat) represents a good estimation of the LV stroke-volume changes during exercise,[11] in line with the improvement of LVEF. Further supporting a positive cardiac effect from the GH treatment, the patients in the active group experienced an increase in the VO_2/Work (ie, an improvement of the extent of the aerobically regenerated adenosine triphosphate),[11] with a significant delta change when compared with control subjects.

In addition, the observed improvement in RV function is likely to result in better respiratory efficiency as evidenced by the reduction associated with GH replacement in the VE/VCO_2 slope, a robust index of ventilatory efficiency,[15] with a growing body of evidence showing a possible role in prognosis beyond the peak VO_2.[11] The VE/VCO_2 slope reflects the amount of CO_2 produced, the ratio between the physiological dead space and the tidal volume, and the arterial CO_2 partial pressure, with its impairment due to early occurrence of decompensated acidosis, increased waste ventilation, and impairment of metabolic-reflex and/or chemoreflex control.[11]

Finally, with regard to the peripheral effects of the GH, the improvement in the time to AT observed in the treatment group suggests an increase in aerobic metabolism during exercise, leading to the ability to perform aerobic exercise for a longer time in the active group.

Taken together, patients with concomitant HFrEF and GHD under GH replacement therapy experienced an improvement in respiratory efficiency, and a better O_2 extraction and maximal performance, resulting in amelioration of exercise capacity.

Clinical status, HRQoL, and psychological health

GH replacement treatment led to a significant improvement in HRQoL, as testified by a significant decrease in the total MLHFQ score. The MLHFQ is a well-validated questionnaire aimed to identify, through 21 6-point Likert scale questions, the physical, emotional, and socioeconomic effects on patients' life caused by HF. In our study, GH replacement treatment significantly improves from the baseline in both the physical and emotional domains, with a significant difference with the placebo for the physical domain. The HRQoL of HF patients represents a priority in HF management, reflecting the disease's impact on patients' daily lives.[16] Notably, it has been showed that HF patients prioritize improvements in HR-QoL and independence over increasing life expectancy.[17]

LV structure and function

The present study showed a significant increase from the baseline of LVEF in the active treatment group, mostly driven by a significant decrease in the LV end-systolic volume. Notably, the same effect was not observed in the control group. This is congruent with the overall effect described in the meta-analysis by Le Corvoisier et al,[14] which reported an increase in LV wall thickness (intraventricular septum and posterior wall), and a decrease in LV end-diastolic and end-systolic diameters, resulting in a reduced LV end-systolic stress wall and an increase in LVEF of about 5%, later confirmed by Cittadini et al,[12,13] in a recent randomized, controlled, single-blind trial.

From a pathophysiological point of view, it is well-known that GH treatment attenuates LV pathologic remodeling and improves LV function, as shown in the preclinical model of large myocardial infarction[8] and several studies have proven the typical pattern elicited by GH/IGF-1, characterized by myocardial growth with preserved capillary density, the absence of fibrosis, and direct stimulation of anti-apoptotic pathways.[18] Findings from the present trial are in line with these proposed mechanisms, leading to an improvement in cardiopulmonary performance. However, no differences were found between the groups at the end of the study, limiting the interpretation of the present finding about the role of GH on LV.

RV structure and function

Right heart dysfunction measured by TAPSE has been previously reported in patients with HFrEF and concomitant GH deficiency.[7] The present trial shows a considerable increase in right heart contractility with an improvement in TAPSE of almost 25% in the active treatment group, without any recorded change in the placebo arm. Considering the results of seminal studies reporting that peak VO_2 is driven predominantly by the RV function,[19,20] the improvement observed in RV function associated with GH replacement therapy is likely to play a role also in the recorded improvement of the primary endpoint.

Accordingly, patients in the active treatment group showed an increase in the TAPSE/PASP index, which is a surrogate for RV arterial coupling with an excellent correlation with RV arterial coupling measured invasively by pressure-volume loops,[21,22] and a powerful and independent predictor of mortality in HFrEF.[23] The lack of effect on pulmonary pressures can be traced to the presence of pulmonary pressures still within normal ranges, which implies a probable absence of pulmonary vascular remodeling. Hence, being pulmonary vascular resistances assumedly stable during the study course, with a parallel increased contractility, it is expected to have no changes in pulmonary pressures.[24]

The positive effect on exercise capacity exerted by GH replacement therapy in the present trial may also be due to a remarkable improvement in right heart function. As previously discussed, the significant improvement in ventilator efficiency (ie, VE/VCO_2 slope) observed after the GH therapy further supports the role of the right heart.

Comparison with Previous Studies of GH Therapy in CHF

To date, 16 studies have investigated the role of GH in HF, with conflicting results. However, in 2007, Le Corvoisier et al,[14] in a meta-analysis including all the studies, reported the global effect size by outcomes of all the 12 studies available (4 open studies, and 8 blinded, randomized, placebo-controlled trials), including a total of 195 patients. As a result, GH treatment leads to an increase in LV wall thickness (intraventricular septum and posterior wall), a decrease in LV end-diastolic and end-systolic diameters, resulting in a reduced LV end-systolic stress wall, with an increase in LVEF. In addition, a reduction of systemic vascular resistance and an improvement in cardiovascular performance, as testified by an increase in peak VO_2 and exercise duration were reported. After the publication of this metanalysis, 4 other studies were subsequently published.[12,13,25,26] All these studies[12,13,25] but 1[26] reported an increase in LVEF. In addition, when the effects of 48 months of treatment were evaluated in the longest study available in the published reports, a significant improvement in cardiovascular performance (ie, peak VO_2) was observed.[13] Taken together, the inconsistencies of GH trials in HF appear mainly due to the lack of evaluation of baseline GH status in candidate patients, with GH replacement therapy associated with beneficial effects in the subset of patients with documented GHD.

GH Deficiency in HF

Adult GHD affects about 200 to 300 patients per millions of inhabitants with an estimated prevalence of approximately 100,000 patients.[9] GHD per se is associated with metabolic (increased insulin resistance and fat mass, and decreased lean body mass, dyslipidemia, and bone mineral density) and cardiovascular (cardiac dysfunction, decreased fibrinolysis, and premature atherosclerosis) disarrangement, leading to a lower exercise capacity, impaired quality of life, and increased mortality.[10] In addition, GHD is associated with increased levels of biomarkers associated with worse cardiovascular risk, such as increased serum levels of C-reactive protein, proinflammatory cytokines, adipokines, oxidative stress, coagulation system, and endothelial dysfunction.[10] The present investigation confirms previous reports, showing a prevalence of GHD in our cohort of HF subjects of about 30%.[7,12,13,27] With regard to the etiology and the pathophysiology of the reduced activity of the GH/IGF-1 axis in HF, in none of our patients, the most frequent causes of GHD (ie, a nonfunctioning pituitary adenoma or other pituitary mass lesions)[9] were found, as well as none had a positive anamnesis of previous cranial irradiation, traumatic brain injury, or vascular diseases. This is of great interest because all our patients fall in the category of idiopathic GHD, usually accounting only for 8% of causes of GHD in the general population,[9] further suggesting that HF could be a specific clinical context[28] in which a GHD should be screened, as recommended by the 2016 AHA (American Heart Association) guidelines for the diagnosis and treatment of cardiomyopathies[29] and the 2019 ESC (European Society of Cardiology) guidelines for the diagnosis and treatment of heart failure with preserved ejection fraction (HFpEF).[30] In addition, no correlations were found about GH levels in response to the GHRH + arginine test and the clinical variables.

There are several possible explanations for the GHD in HF patients, classically grouped into 3 categories:[31] 1) local hypoperfusion of the hypothalamic–pituitary axis (leading to a reduction in the somatotropic secretion); 2) alterations related to the chronic disease, inflammation, and liver congestion (leading to a peripheral GH resistance, a hypothalamic somatostatinergic hyperactivity—further caused by nutritional changes caused by HF, and increased angiotensin and cytokine production); and 3) effects of CHF therapy of GH/IGF-1 axis (eg, drug interference: angiotensin-converting enzyme inhibitors, digoxin, diuretic agents). Further studies are needed to elucidate the proper mechanism of the GHD in HF.

Clinical implications

The present trial demonstrates for the first time with the robust design of the randomized, double-blind, placebo-controlled trial that correction of GH deficiency in the context of HFrEF is associated with a significant improvement of exercise performance (ie, VO_2 max, VE/VCO_2 slope, O_2 pulse, and walking distance), and cardiac pathologic remodeling, leading to an overall amelioration of clinical status (ie, NYHA functional class) and heart-related quality of life (ie, MLHFQ). Of note, these results were observed on top of guideline-directed medical therapy with a considerable proportion of patients taking new-generation drugs (angiotensin receptor neprilysin inhibitor, SGLT2i). Consequently, if confirmed by larger studies, our results suggest that HFrEF represents an appropriate clinical context in which GHD should be screened, being a common and treatable condition with an available safe and effective replacement therapy. On the other hand, the same approach is routinely employed for other HF-associated deficiencies, such as iron deficiency.

Study limitations

This was a single-center study. However, all measurements were fully blinded, and many parameters were objective and not easy to be biased by subjectivity. In addition, the overall dropout rate was higher than expected (about 30%); however, it was mostly driven by personal reasons of patients, and strongly caused by the impact of COVID-19 lockdown on patients' behaviors and attitude to attending hospitals, rather than from evidence of side effects. In addition, the discontinuation rate was higher in the control group. Notably, even if the numerosity of the group of patients able to complete the study was lower than the calculated sample size, the recruited patients were enough to reach the prespecified primary endpoint and most of the secondary endpoints. Finally, from a statistical point of view, due to the lack of control for multiple comparisons, the final results of the present study should be interpreted with caution; we hope that this study will be used as a hypothesis-generating for future investigations involving a higher number of patients.

Conclusions

The present randomized, double-blind, and placebo-controlled trial demonstrates that GH replacement therapy in HFrEF improves exercise performance, improves LV and RV function, leading to an amelioration of clinical status, and of health-related quality of life.

Perspectives

COMPETENCY IN MEDICAL KNOWLEDGE: Approximately 30% of patients with HFrEF fulfil the criteria of GH deficiency, which has been associated with poor cardiovascular performance, quality of life, and prognosis. GH replacement therapy has been associated with an improvement in these aspects; however, to date, there is not a clear indication for GH replacement therapy.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The present study investigates the beneficial effects of replacement treatment of GH deficiency in patients with HFrEF in terms of quality of life and cardiovascular performance.

TRANSLATIONAL OUTLOOK: Although this randomized, double-blind, placebo-controlled trial includes a small cohort of patients, it demonstrates a beneficial effect of GH replacement therapy in heart failure with GH deficiency, suggesting a possible role for this treatment.

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Appendix

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Supplemental Table 1 and 2.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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