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Effects of human recombinant growth hormone on exercise capacity, cardiac structure, and cardiac function in patients with adult-onset growth hormone deficiency

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Abstract

Objective: Epidemiological studies suggest that adult-onset growth hormone deficiency (AGHD) might increase the risk of death from cardiovascular causes.

Methods: This was a 6-month double-blind, placebo-controlled, randomised, cross-over trial followed by a 6-month open-label phase. Seventeen patients with AGHD received either recombinant human growth hormone (rGH) (0.4 mg injection daily) or placebo for 12 weeks, underwent washout for 2 weeks, and were then crossed over to the alternative treatment for a further 12 weeks. Cardiac magnetic resonance imaging, echocardiography, and cardiopulmonary exercise testing were performed at baseline, 12 weeks, 26 weeks, and the end of the open phase (12 months). The results were compared with those of 16 age- and sex-matched control subjects.

Results: At baseline, patients with AGHD had a significantly higher systolic blood pressure, ejection fraction, and left ventricular mass than the control group, even when corrected for body surface area. Treatment with rGH normalised the insulin-like growth factor 1 concentration without an effect on exercise capacity, cardiac structure, or cardiac function.

Conclusion: Administration of rGH therapy for 6 to 9 months failed to normalise the functional and structural cardiac differences observed in patients with AGHD when compared with a control group.

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Data can be requested from Dr. Sathyapalan, who serves as the custodian of the data.
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Abbreviations

GH, growth hormone; GHD, growth hormone deficiency; AGHD, adult-onset growth hormone deficiency; IGF-1, insulin-like growth factor 1; CMR, cardiac magnetic resonance imaging; LVM, left ventricular mass; rGH, recombinant growth hormone

Introduction

Epidemiological evidence suggests that patients with both hypopituitarism and adult-onset growth hormone deficiency (AGHD) have an increased risk of cardiovascular disease.[1–3] This higher risk of cardiovascular disease may be related to changes in body composition and lipid profiles,[4,5] abnormal vasculature with a carotid intimal thickness greater than that in patients without AGHD, and reduced aortic distensibility.[6–8] In addition, patients with AGHD have a lower exercise capacity than normal sex- and age-matched individuals, and their maximal oxygen uptake is reduced by about 25%.[9,10]

Although several studies have been performed to evaluate the effects of GH replacement on cardiac indices in patients with AGHD,[11–22] whether GH replacement therapy has any direct favourable effects on cardiac function remains unclear. This lack of clarity is mainly due to limitations in trial designs (absence of control groups and small sample sizes) and the use of supraphysiological GH doses.[23] Cardiac magnetic resonance imaging (CMR) has been proposed as the gold standard method with which to minimise the inaccuracy of cardiac imaging obtained by conventional ultrasonic echocardiography,[24–26] which could be an additional confounding factor to consider when a lack of response to GH therapy is encountered. The advantage of CMR versus standard echocardiography is that CMR allows for noninvasive, high-resolution, direct, sensitive, reproducible, and accurate evaluation of the anatomy, ventricular function, myocardial morphology, and tissue damage in a single setting, avoiding geometrical assumptions.[27–29] CMR has been used to investigate a variety of cardiomyopathies, especially hypertrophic cardiomyopathy, in addition to Turner syndrome and Marfan syndrome.[24,30–32] In contrast to echocardiography, CMR is not limited by acoustic windows and has superior inter-study reproducibility, making it valuable for initial assessment and longitudinal follow-up of patients.[27] Arrhythmias and an inability to hold the breath are not contraindications for CMR but can lead to a suboptimal study outcomes. However, implanted defibrillators, pacemakers, and generally any metallic implant are considered absolute contraindications for this technique.

Therefore, the primary endpoint of this study was determination of the difference in left ventricular mass (LVM) between patients with AGHD and controls and elucidation of the change in LVM in patients with AGHD following 6 months of treatment with low-dose of recombinant human growth hormone (rGH). The secondary endpoints were determination of the baseline cardiac function and exercise capacity in controls and patients with AGHD and observation of the changes that occur following treatment.

Subjects and methods

Seventeen patients (10 male, 7 female; mean age, 48.4 ± 14.6 years; range, 19–74 years) with severe AGHD confirmed by a peak GH concentration of <9 mU/L (3 ng/ml) following an insulin tolerance test were recruited from a tertiary centre. All patients had hypopituitarism secondary to pituitary tumours treated with surgery, radiotherapy, or both. Those who had developed additional pituitary hormone deficiencies underwent appropriate hormone replacement and stabilisation for at least 6 months before being enrolled in the study. The exclusion criteria were previous or current use of rGH therapy, documented ischaemic heart disease, chronic heart failure, a history of atherosclerotic vascular events, and diabetes mellitus. A control group of 16 sex- and age-matched healthy volunteers were recruited by general advertisement. All participants provided written informed consent. The study was performed in accordance with the declaration of Helsinki and was approved by the local ethics committee. The trial registration number is ISRCTN94165486.

The patients were randomised using a random generator table and, using a cross-over design, allocated to either study group A or B. Group A completed a 12-week course of daily subcutaneous injections of rGH at 0.4 mg/day (Humatrope; Eli Lilly and Company, Indianapolis, IN, USA) followed by a 2-week washout period and then received 12 weeks of placebo injections (sterile diluent containing glycerol and m-cresol). Group B began treatment with placebo injections, and following the washout period, initiated rGH injections for the same time period. After the cross-over phase was completed, the patients entered a further 6-month open-label arm in which they were treated with rGH only.

The ejection fraction, stroke volume, cardiac output, end-diastolic volume, end-systolic volume, and LVM were determined using a 1.5-Tesla CMR system (Philips Healthcare, Best, the Netherlands), with subsequent analysis performed using analytical MRI-MASS software (Medis, Leiden, the Netherlands). The LVM was corrected to the body surface area. Echocardiography was also performed simultaneously with routine two-dimensional and Doppler measurements taken according to the American Society of Echocardiography guidelines.

Exercise capacity was evaluated with a modified Bruce treadmill protocol. During the tests, patients wore a tightly fitting facemask connected to a capnograph and a sample tube enabling online measurement of ventilation and metabolic gas exchange (Oxycon Delta system; Jaeger, Hoechberg, Germany). A respiratory exchange ratio of >1, calculated as the peak carbon dioxide production divided by the peak oxygen production, was considered to indicate maximal effort.

The serum concentration of insulin-like growth factor 1 (IGF-1) was measured using a solid-phase enzyme-labelled chemiluminescent immunocentric assay on an Immulite 2000 analytical platform (Siemens/DPC, DPC-UK, Llanberis, Caernarfon, UK.)

All parameters were measured at baseline, 12 weeks, 26 weeks, and the end of the open-label phase. A flow chart of the study design is shown in Appendix 1.

Statistical analysis

Based on a previous study,[33] 13 participants were needed to detect a clinically significant 10-g change in the LVM using CMR. Differences in the measured variables under each of the four conditions (baseline, GH response, control response, and GH response) in the open-label phase response were compared using repeated-measures analysis of variance. The level of significance was set at $P < 0.05$.

Results

The baseline characteristics of the patients are shown in Appendix 1. Seventeen patients were enrolled in the trial, and all completed the GH/placebo arms of the study. Two patients were excluded from the CMR analysis: Patient 16 did not complete the CMR part of the study because he had an intracranial clip, and Patient 8 was excluded because he developed GHD after treatment for acromegaly, which could have made interpretation of any findings impossible due to his previous GH excess. The median time from diagnosis to inclusion in the trial was 22 months. All patients were compliant with the subcutaneous rGH injections and had no significant side effects.

Comparisons between patients and controls are shown in Table 1. Patients with AGHD had significantly higher systolic blood pressure ($P = 0.04$), ejection fraction ($P = 0.009$), stroke volume ($P = 0.05$), LVM ($P = 0.003$), and LVM index ($P = 0.01$) than controls. However, the patients with AGHD exercised for a shorter period of time and had a lower exercise capacity with a lower peak oxygen consumption ($P < 0.001$), anaerobic threshold ($P = 0.001$), and heart rate at peak exercise ($P = 0.006$). The peak respiratory exchange ratio was not significantly different between the two groups, suggesting that similar levels of effort were attained.

The IGF-1 concentration normalised in all treated patients in the active phase

Table 1. Comparison of CMR and cardiopulmonary exercise test measurements between patients with AGHD and age- and sex-matched normal subjects at baseline.

	Controls	AGHD	*P* value
Heart rate (beats/min)	68 (11)	75 (14)	0.18
Systolic BP (mmHg)	131 (13)	143 (18)	0.04*
Diastolic BP (mmHg)	86 (11)	93 (15)	0.14
BSA (m^2)	1.90 (0.17)	2.09 (0.18)	0.005*
EF (%)	67.4 (4.5)	72.3 (5.4)	0.009*
SV (ml)	85.0 (12.4)	98.9 (23.9)	0.05*
CO (L/h)	5758 (967)	6108 (1385)	0.41
ESV (ml)	42.1 (11.7)	35.1 (12.9)	0.11
EDV (ml)	127.2 (23.0)	132.2 (32.9)	0.62
LVM (g)	114.9 (27.4)	144.4 (28.9)	0.003*
LVMI (g/m^2)	59.8 (10.2)	69.1 (10.4)	0.01*
Peak VO_2	40.8 (7.1)	26.3 (6.4)	<0.001*
VE/VCO_2	27.5 (1.9)	27.8 (4.1)	0.79
AT	26.9 (9.5)	15.5 (4.3)	0.001*
Peak RER	1.09 (0.09)	1.11 (0.08)	0.51
Exercise time (s)	982 (312)	702 (279)	0.01*
At maximal exercise			
Pulse (beats/min)	177 (14)	152 (31)	0.006*
Systolic BP (mmHg)	202 (24)	193 (23)	0.29
Diastolic BP (mmHg)	103 (29)	102 (23)	0.91

Values are expressed as mean (standard deviation). The level of significance was calculated using repeated-measures Student's t-test. CMR, cardiac magnetic resonance imaging; AGHD, adult-onset growth hormone deficiency; BP, blood pressure; BSA, body surface area; EF, ejection fraction; SV, stroke volume; CO, cardiac output; ESV, end-systolic volume; EDV, end-diastolic volume; LVM, left ventricular mass; LVMI, left ventricular mass index; VO_2, peak oxygen consumption; VE/VCO_2, slope of the relation between ventilation and carbon dioxide production; AT, anaerobic threshold; RER, respiratory exchange ratio.

($P = 0.005$). Treatment with rGH had no effect on any of the CMR or exercise variables during the cross-over phase, and further changes were not observed during the 6-month open-label extension phase in which the patients continued with rGH therapy. No modification in the left ventricular dimensions was observed on echocardiography. Doppler echocardiography studies revealed a prolonged mitral E wave deceleration time and isovolumic relaxation time (Table 2).

Discussion

This study has shown that patients with AGHD have a lower exercise capacity than controls but normal left ventricular function. Exercise capacity was not corrected by a low dose of GH replacement, suggesting that longer treatment is required for GH to contribute to cardiac functional remodelling.

The association between AGHD and cardiovascular changes is controversial. Our baseline observations that patients with AGHD had lower exercise capacity without left ventricular systolic dysfunction are in accordance with previous studies.[13,34–37] Conversely, other researchers have reported a decreased LVM[14,16,17,20,38] and reduced ejection fraction on echocardiography[38,39] or radionuclide angiography[20] in patients with GHD. However, when CMR is used, 1 year of GH treatment did not influence cardiac mass or contractility.[34,40] Similarly, in the present study, untreated AGHD was not associated with reduced systolic function or reduced LVM at baseline compared with controls. This could explain the absence of the increase in systolic function with GH treatment.

GH was originally thought to only regulate somatic growth, but it has profound effects on several physiological processes that can be affected by GHD. It is involved in the maintenance of skeletal muscle mass and strength, body composition, and fuel metabolism.[41] Animal studies have shown that GH affects the development and maintenance of the heart both directly and indirectly (via IGF-1)[42]; thus, cardiac health could be affected by GHD. GH increases myocardial muscle mass and converts the contractile protein myosin to a more forceful phenotype (low adenosine triphosphate V3 isoform).[43] Myocytes treated with GH express increased levels of sarcoplasmic reticulum calcium adenosine triphosphate 2 (SERCA2) mRNA and protein.[44]

Several trials examining the effects of GH treatment on cardiac structure and function in patients with GHD have been published. In a meta-analysis of 16 trials (9 blinded, 7 open) conducted in 2003, 468 patients underwent echocardiography for assessment of the left ventricle.[45] The authors concluded that GH administration resulted in an increase in the left ventricular dimensions (septum, posterior wall, and left ventricular diastolic dimension), mass, and stroke volume. Since the publication of this meta-analysis, however, conflicting results have been reported.[11–17,34,38,46–49] Factors such as the severity and age of onset of GHD, timing of the initiation of GH treatment, concomitant use of replacement therapy or other medications, and cardiovascular risk factors could account for these discrepancies. Because of the high sensitivity of CMR, studies based on these techniques should have sufficient statistical power to detect clinically significant changes with fewer patients.[26,33,50] In contrast, the limitations of echocardiography mean that a minimum of 132 patients is required to accurately measure the same change with echocardiography.[51]

Exercise capacity is consistently lower than normal in patients with AGHD.[9,10,52,53] In some controlled trials, the peak oxygen consumption increased with GH replacement,[9,52,10,53] although the effect disappeared in one patient when the peak oxygen consumption was corrected for

Table 2. Comparison of CMR and cardiopulmonary exercise test measurements between patients with AGHD and age- and sex-matched normal subjects at baseline, after 3 months of placebo or 3 months of growth hormone therapy, and after 6 months of open-label growth hormone therapy.

	Baseline	Placebo	Active	12 months	*P* value
Heart rate (beats/min)	75 (14)	83 (11)	84 (15)	83 (14)	0.28
Systolic BP (mmHg)	143 (19)	143 (18)	141 (18)	135 (15)	0.49
Diastolic BP (mmHg)	93 (15)	90 (12)	88 (13)	86 (11)	0.39
IGF-1 (μg/L)	114.6 (47.4)	122.8 (53.4)	185.2 (72.8)	154.2 (45.2)	<0.001
CMR					
EF (%)	72.3 (5.4)	70 (5.6)	69.2 (6.1)	70.5 (7.1)	0.59
SV (ml)	98.9 (23.9)	93.1 (22.7)	90.6 (20.7)	95.4 (19.5)	0.85
CO (L/h)	6108 (1385)	6071 (1152)	6117 (1422)	6010 (1082)	0.99
ESV (ml)	35.1 (12.9)	39.9 (14.6)	41.0 (11.3)	41.3 (16.7)	0.6
EDV (ml)	132.2 (32.9)	129.6 (37.4)	130.2 (31.4)	132.9 (33.5)	0.99
LVM (g)	144.4 (22.9)	144.0 (28.9)	138.2 (22.6)	138.6 (30.6)	0.87
LVM/BSA (g/m^2)	69.1 (10.4)	68.5 (12.5)	65.4 (8.3)	66.2 (12.7)	0.77
Cardiopulmonary exercise test					
Peak VO_2	26.3 (6.4)	24.1 (7.9)	23.5 (7.4)	22.7 (5.1)	0.48
VE/VCO_2	27.8 (4.0)	27.2 (4.5)	28.5 (5.8)	27.3 (6.9)	0.9
AT	15.5 (4.2)	15.3 (4.9)	15.4 (5.9)	15.9 (5.1)	0.99
Peak RER	1.11 (0.08)	1.08 (0.14)	1.06 (0.15)	1.19 (0.20)	0.11
Exercise time (s)	702 (279)	734 (254)	653 (244)	732 (238)	0.78
Heart rate at max exercise (beats/min)	152 (31)	151 (30)	147 (26)	151 (22)	0.95
Systolic BP (mmHg) at max exercise	193 (23)	195 (29)	183 (29)	182 (28)	0.42
Diastolic BP (mmHg) at max exercise	102 (23)	106 (25)	102 (19)	87 (16)	0.06
Echocardiogram					
Ao (cm)	3.0 (0.4)	2.8 (0.3)	2.9 (0.4)	3.0 (0.3)	0.64
LA (cm)	3.4 (0.7)	3.3 (0.6)	3.7 (0.8)	3.8 (0.6)	0.14
LVDd (cm)	5.1 (0.5)	4.8 (0.8)	5.1 (0.6)	4.9 (0.7)	0.33
LVDs (cm)	3.4 (0.9)	3.3 (1.0)	3.4 (1.1)	3.3 (1.0)	0.99
IVS (cm)	1.0 (0.2)	1.1 (0.2)	1.1 (0.3)	1.1 (0.3)	0.96
PW (cm)	1.3 (0.3)	1.1 (0.4)	1.1 (0.3)	0.9 (0.2)	0.21
EF (%)	65 (9)	58 (7)	63 (10)	61 (7)	0.05*
MVe (m/s)	0.8 (0.1)	0.7 (0.2)	0.7 (0.1)	0.7 (0.2)	0.04*
MVa (m/s)	0.7 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6
E/A	1.2 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	0.94
DT (ms)	211 (40)	270 (58)	222 (56)	255 (64)	0.02*
IVRT (ms)	89 (11)	91 (21)	86 (25)	119 (20)	<0.001*

Values are expressed as mean (standard deviation). The level of significance was calculated using a repeated-measures analysis of variance *F*-test (sphericity assumed). CMR, cardiac magnetic resonance imaging; AGHD, adult-onset growth hormone deficiency; BP, blood pressure; IGF-1, insulin-like growth factor 1; SV, stroke volume; CO, cardiac output; ESV, end-systolic volume; EDV, end-diastolic volume; LVM, left ventricular mass; VO_2, peak oxygen consumption; VE/VCO_2, slope of the relation between ventilation and carbon dioxide production; AT, anaerobic threshold; RER, respiratory exchange ratio; Ao, aorta; LA, left atrium; LVDd, left ventricular dimension in diastole; LVDs, left ventricular dimension in systole; IVS, interventricular septal dimension in diastole; PW, posterior wall of left ventricular dimension in diastole; EF, ejection fraction of left ventricle; MVe, mitral valve E wave; MVa, mitral valve A wave; E/A, ratio of mitral E wave over A wave; DT, mitral E wave deceleration time; IVRT, isovolumic relaxation time.

body mass.[10] Other similarly designed studies have not shown any such effect on exercise performance.[51,54–56]

We found changes in exercise capacity and cardiac structure and function similar to those in previous studies. However, we found no change in cardiac structure or function using the gold standard method of assessment (CMR) and no change in exercise capacity as assessed by cardiopulmonary exercise testing after GH replacement. This occurred despite achieving physiological GH replacement as shown by normalisation of IGF-1. However, we did observe some minor changes in diastolic function with prolongation of the mitral E wave deceleration time and isovolumic relaxation time, suggesting mild left ventricular diastolic impairment.

In this study, systolic function was normal in patients with AGHD, and their LVM was greater than in normal subjects. This observation persisted when the left ventricular mass was corrected for the body surface area. The explanation for this difference may be the higher blood pressure in the patients with AGHD than in the normal subjects. Further differences between our study and others were caused by the lack of effect of GH therapy despite a significant increase in the IGF-1 concentration. Our observations on exercise capacity are in agreement with those of other groups who showed little change with GH therapy.[54]

It is possible that our patients differed from those of previous study populations. The patients were heterogeneous with respect to the duration of untreated AGHD and underlying diseases. The duration of AGHD may have been insufficient for the development of systolic dysfunction. Considering that the half-life of rGH is around 4 hours, the wash-out period for the study was set at 2 weeks. However, it is possible that the effects of GH could have lasted longer and thus affected the results. Ideally, GH therapy should be titrated based on the IGF-1 response to optimise the outcome; however, we had to use a fixed dose of GH because titration of GH would have resulted in unblinding of the study. All but one of our patients presented with GHD as adults, and previous groups have reported differences between patients who develop GHD in childhood and those who develop it in adulthood. Those with GHD as children have a lower left ventricular wall thickness and mass.[57,58] Several effects of GH might influence long-term cardiovascular outcomes,[59,60] but these were not explored in the present study. Our study supports the need for long-term GH treatment to manage the functional cardiac abnormalities that may occur in patients with severe GHD.

Conclusion

This study confirms that patients with AGHD have a lower exercise capacity, greater LVM, and normal systolic function compared with controls. While GH therapy normalised the IGF-1 concentration in patients with AGHD, there was no change in the exercise capacity, cardiac structure, or cardiac systolic function during the 9 months of GH treatment.

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Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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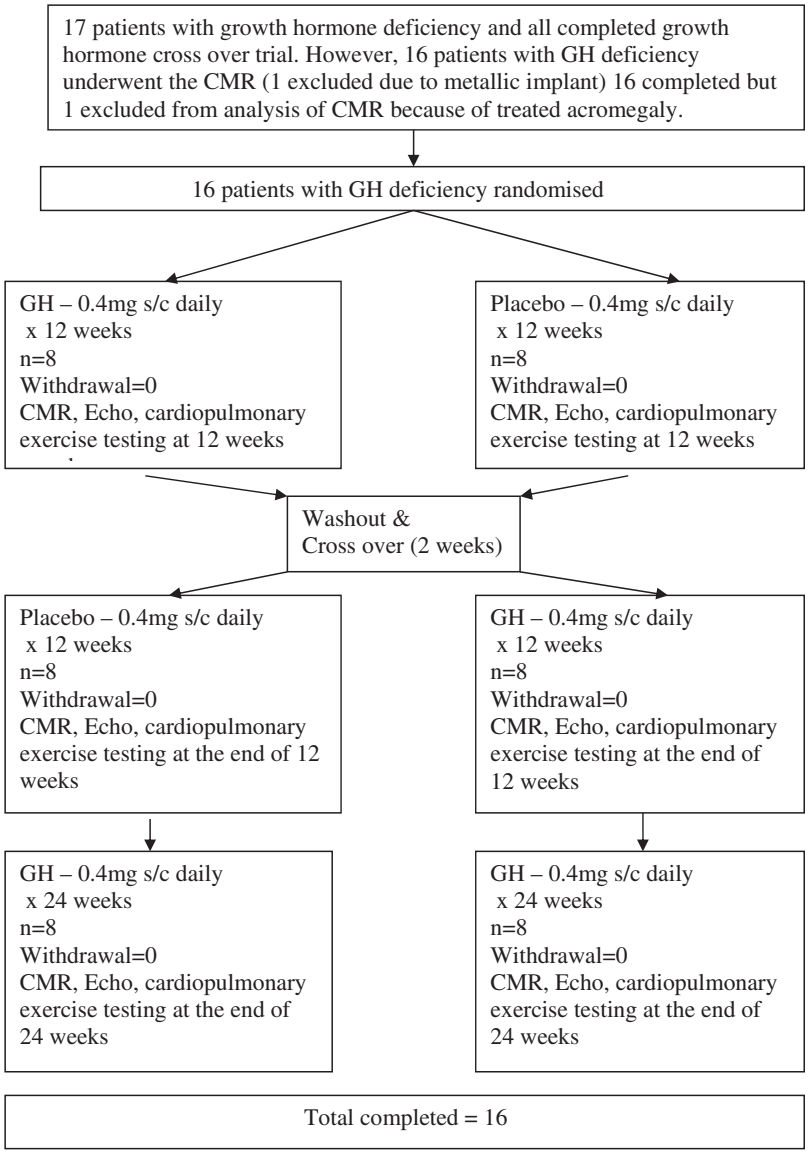
Appendix 1. Flow chart of patient progression through the trial and those who underwent CMR: 15 patients with AGHD compared with 16 age- and sex-matched controls



CMR, cardiac magnetic resonance imaging; AGHD, adult-onset growth hormone deficiency; GH, growth hormone.