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Effect of growth hormone treatment on diastolic function in patients who have developed growth hormone deficiency after definitive treatment of acromegaly

Pouneh K. Fazeli^{1,3}, Jonathan G. Teoh^{2,3}, Eleanor L. Lam^{1,3}, Anu V. Gerweck¹, Tamara L. Wexler^{1,3}, Eliza P. Teo^{2,3}, Brian M. Russell¹, Ronen Durst^{2,3}, David McCarty^{2,3}, Rory B. Weiner^{2,3}, Michael H. Picard^{2,3}, Anne Klibanski^{1,3}, and Karen K. Miller^{1,3}

¹Neuroendocrine Unit, Massachusetts General Hospital, Boston, MA 02114, United States

²Division of Cardiology, Massachusetts General Hospital, Boston, MA 02114, United States

³Harvard Medical School, Boston, MA 02115, United States

Abstract

Objective—Although growth hormone (GH) replacement is prescribed for patients with hypopituitarism due to many etiologies, it is not routinely prescribed for patients with GH deficiency (GHD) after cure of acromegaly (acroGHD). This study was designed to investigate the effect of GH replacement on cardiac parameters in acroGHD.

Design—We prospectively evaluated for 12 months 23 patients with acroGHD: 15 subjects on GH replacement and eight subjects not on GH replacement. Main outcome measures included LV mass corrected for body surface area (LVM/BSA) and measures of diastolic dysfunction (E/A ratio and deceleration time), as assessed by echocardiography.

Results—After 12 months of follow-up, there were no differences between the GH-treated group and the untreated group in LVM/BSA (GH: $74.4 \pm 22.5 \text{ g/m}^2$ vs untreated: $72.9 \pm 21.3 \text{ g/m}^2$, $p=0.89$), E/A ratio (GH: 1.21 ± 0.39 vs untreated: 1.08 ± 0.39 , $p=0.50$) or deceleration time (GH: $224.5 \pm 60.1 \text{ ms}$ vs untreated: $260 \pm 79.8 \text{ ms}$, $p=0.32$). The overall degree of diastolic function was similar between the groups with 42.9% of untreated subjects and 50% of GH-treated subjects ($p=0.76$) classified as having normal diastolic function at follow-up.

Conclusions—There were no significant differences in LVM/BSA or parameters of diastolic function in patients with a history of acromegaly treated for GHD as compared to those who were untreated. These data are reassuring with respect to cardiovascular safety with GH use after treatment for acromegaly, although further longer term study is necessary to evaluate the safety and efficacy of GH treatment in this population.

Corresponding Author: Pouneh K. Fazeli, MD MPH, Neuroendocrine Unit, Bulfinch 457B, Massachusetts General Hospital, Boston, MA 02114, pkfazeli@partners.org, Tel: 617-726-3870, Fax: 617-726-5072.

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The authors declare that they have no conflict of interest.

Keywords

Acromegaly; Growth hormone deficiency; diastolic dysfunction; cardiovascular risk

INTRODUCTION

States of growth hormone (GH) excess, such as acromegaly, and growth hormone deficiency (GHD) are both associated with increased cardiovascular morbidity and mortality [1, 2]. Cardiovascular risk factors such as hypertension, dyslipidemia and insulin resistance are characteristic of untreated acromegaly [3–5] and GHD [6–8] and contribute to the increased risk of cardiovascular morbidity. Treatment of the elevated GH and/or IGF-I levels in acromegaly and of the low GH and IGF-I levels in GHD can result in improvements in many of these cardiovascular risk markers [9–16]; in fact, a reduction in mortality has been demonstrated in patients treated for acromegaly [17, 18] and in men treated for GHD [19].

Whether patients who have received definitive treatment for acromegaly and subsequently develop GHD (acroGHD) are at increased risk of cardiovascular mortality is less established. Similarly, whether treating acroGHD patients with GH results in an increased risk of cardiovascular events is controversial. Recent studies, including a KIMS database study, reported an increased risk of cardiovascular mortality in individuals with acroGHD treated with GH when compared to individuals treated with GH with a history of a non-functioning tumor [20], and a prospective, open-label, two year study found an increased risk of cardiovascular events (one MI and two cerebral infarctions) in the group of 10 individuals with acroGHD being treated with GH as compared to the 10 individuals with a history of a non-functioning adenoma treated for GHD [21]. However, neither of these studies included a control group of patients with acroGHD who did not receive GH replacement. Whether there is an increased risk of cardiac events or changes in cardiac function in individuals with acroGHD treated with GH compared to those with acroGHD who are not treated with GH is unknown.

Characteristic cardiac structural changes are associated with both acromegaly and GHD. In acromegaly, the characteristic cardiomyopathy is a concentric biventricular hypertrophy due to interstitial fibrosis which may be due to a dramatic increase in myocyte apoptosis [22]. Furthermore, the hypertrophy is believed to be independent of the hypertension typical of patients with acromegaly [3, 23]. The hypertrophy has been shown to decrease with treatment of acromegaly [24–29]. In GHD, findings may include reduction in left ventricular (LV) mass and LV systolic function, diastolic dysfunction and decreased ejection fraction [30–33]. These abnormalities have also been shown to improve with growth hormone replacement therapy, even after only six months of treatment [34–36].

Patients who have been treated for acromegaly may develop GHD and therefore may be at risk for the cardiovascular risk associated with a deficiency of GH and IGF-I. We have previously shown that individuals with a history of acromegaly who develop GHD have normal, not reduced, left ventricular mass corrected for body surface area (LVM/BSA) whereas more than 50% of individuals with a history of acromegaly and GH sufficiency have elevated LVM/BSA [37]. Therefore whether treatment with GH is safe in patients with

acroGHD in regard to cardiovascular risk remains largely unknown. We investigated GH administration in patients with GHD after definitive therapy (surgery and/or radiation) for acromegaly compared to those who were untreated to determine its effects on LV mass and diastolic function to help further elucidate its cardiovascular safety profile in this population of patients.

METHODS

Study participants

We studied 23 patients who had been treated for acromegaly and subsequently diagnosed with GHD (acroGHD) for one year. Data from two studies were combined. The first study was an open-label, observational study from which 18 subjects were included — 10 of whom were receiving GH clinically and 8 of whom were not; this study is previously unpublished. The subjects in this study were being treated (or not treated) with GH at the discretion of their clinical endocrinologists. An additional five participants (all on GH) were enrolled as part of a randomized trial investigating the effects of GH treatment on patients with acroGHD as previously published [38]. In total, fifteen subjects were receiving GH treatment during the one-year study and the remaining 8 subjects were not receiving treatment for GHD.

Prior to initiating treatment with GH, all subjects were GH deficient as defined by a peak GH < 5ng/mL in response to GHRH-arginine stimulation, performed as previously described [39], or an IGF-I level more than two standard deviations below the age-specific normal range in subjects who had at least three other anterior pituitary deficiencies documented [40]. Subjects who were using glucocorticoid, thyroid hormone and/or gonadal steroid replacement were on a stable dose for at least three months prior to study enrollment. Seven subjects in the group not receiving GH had a past history of GH use. These subjects were treated with GH for a mean of 10.5 months (range: 1.4 to 30.1 months) and were off of GH treatment for a mean of 42.2 months (range: 4.3 to 61.1 months) prior to study enrollment. Nine of the 15 subjects who received GH for the duration of the study had been receiving GH continuously for a mean of 72.4 months (range: 1.6 to 170.5 months) at the time of the baseline evaluation; the remaining six subjects receiving treatment were started on GH after the baseline visit.

The study was approved by the Partners Healthcare, Inc and Massachusetts Institute of Technology Institutional Review Boards and complied with the Health Insurance Portability and Accountability Act guidelines. Written informed consent was obtained from all subjects.

Study protocol

Subjects presented for a baseline evaluation which consisted of a history/physical exam, including a height and weight, blood draw and echocardiographic assessment (see *Echocardiography* below). Subjects then presented again 12 months later for a repeat history/physical exam and echocardiogram.

Echocardiography

Echocardiographic and Doppler images were acquired using a 2.5–5 MHz transducer on a Vivid-7 or Vivid-I cardiac ultrasound system (GE Healthcare, Milwaukee, Wisconsin). Transthoracic echocardiographic images were acquired from parasternal and apical windows with the patient in the left lateral semi-recumbent position. At least four cardiac cycles were recorded during each acquisition. Parasternal long axis and short axis views of the left and right ventricles, and apical four chamber, two chamber and long axis views were recorded.

Left ventricular dimensions were measured according to the American Society of Echocardiography guidelines [41]. Left ventricular dimensions and 2D tracings of the endocardial and epicardial walls of the mid-ventricle were used to calculate mass (LVM) using the Area-Length method. Normal gender-specific values for LVM were based on American Society of Echocardiography guidelines [41]. LVM was corrected for body surface area (BSA) using the Mosteller calculation: $[(\text{height (cm)} \times \text{weight (kg)})/3600]^{1/2}$ [42].

LV volumes and ejection fraction were measured from the apical four and two chamber views by the biplane method of discs. Pulsed wave Doppler was performed at the level of the mitral leaflet tips to obtain parameters of LV diastolic filling [peak early filling (E) and atrial contraction (A) velocities, E/A ratio, E wave deceleration time]. Pulsed wave Doppler was performed 0.5cm into the right upper pulmonary vein in the apical four chamber to obtain peak systolic (S) velocity, peak antegrade diastolic (D) velocity, and the S/D ratio. Tissue Doppler was performed to obtain tissue velocities at the septal and lateral mitral annulus. The peak myocardial systolic (s'), early (e'), and late (a') diastolic velocities were measured, and the E/e' ratio calculated using the average of the septal and lateral annular e' measurements. These diastolic parameters were used to categorize LV diastolic function as normal, delayed relaxation or restrictive [43].

Biochemical assessment

IGF-1 levels were measured using the Immulite 2000 automated immunoanalyzer (Siemens Healthcare Diagnostics Inc, Tarrytown, NY) – a solid-phase, enzyme-labeled chemiluminescent immunometric assay with an intra-assay coefficient of variation ranging from 2.3–3.9%.

Statistical analysis

Statistical analysis was performed using JMP PRO 11 (SAS Institute, Inc., Cary, NC) software. Means and standard deviations, or if the data were non-normally distributed, medians [interquartile ranges] were reported. The means were compared using the Student's t-test and the Wilcoxon test was used to compare non-normally distributed data. To compare categorical variables, the Pearson's chi-squared test was used. A p-value of < 0.05 on a two-tailed test was used to indicate significance.

RESULTS

Clinical characteristics

Baseline characteristics of study subjects are listed in Table 1. Subjects were a mean of 54.2 ± 13.4 (SD) years at baseline. Fifteen subjects (mean age $\pm$ SD: 50.8 ± 13.8 years) were receiving GH treatment during the course of the study and 8 subjects (60.5 ± 10.4 years) were not being treated during the 12-month study. The group of subjects receiving GH had a median BMI that was lower than the group not receiving treatment (27.5 kg/m^2 vs 38.6 kg/m^2 ; $p=0.02$). There were no significant differences between the groups with respect to duration of disease (mean of 20 years for all study participants), history of pituitary surgery, history of radiation treatment. Although more individuals in the untreated group had a history of hypertension (GH: 6.7% vs untreated: 62.5%, $p=0.004$), there was no significant difference in mean arterial pressure between the groups at baseline (GH: $84.1 \text{ mm Hg} \pm 7.9$ vs untreated: $86.1 \text{ mm Hg} \pm 5.6$, $p=0.49$).

Mean IGF-1 levels at the baseline visit were higher in the GH treated group ($157.7 \pm 75.1 \text{ ng/ml}$) as compared to the non-treated group ($103.3 \pm 54.3 \text{ ng/ml}$), due to the fact that the majority of subjects in the GH group were already being treated with GH (for a mean of 72.4 months) prior to the baseline visit. At 12 months, the mean GH dose in the GH-treated group was $0.51 \pm 0.30 \text{ mg/day}$.

Echocardiographic characteristics

Baseline LV mass—At baseline, the mean LV mass corrected for BSA (LVM/BSA) was similar in both the GH group ($77.8 \text{ g/m}^2 \pm 18.2$) and the untreated group ($79.1 \text{ g/m}^2 \pm 25$; $p=0.90$), even after controlling for age ($p=0.68$) and for history of hypertension ($p=0.21$). There was also no difference in LVM/BSA when comparing all of the subjects who were receiving GH at the time of the baseline visit ($n=9$) as compared to all of the subjects who were not being treated at baseline ($n=14$): GH-treated subjects: 71.3 g/m^2 [67.8, 79.0] vs not treated subjects: 77.2 g/m^2 [57.7, 107.2]; $p=0.59$ ($p=0.44$ when controlling for age; $p=0.70$ when controlling for history of hypertension).

Baseline diastolic function—Diastolic function was graded on a 3-point scale as normal, delayed relaxation or restrictive. At baseline, in the GH group, ten subjects (66.7%) had normal diastolic function and five (33.3%) were classified as having delayed relaxation. In the untreated group, six subjects (75%) had normal diastolic function and 2 subjects (25%) had delayed relaxation; this difference was not statistically significant ($p=0.68$). When comparing subjects who were already on GH at the time of the baseline visit to subjects not treated with GH at baseline, there was similarly no statistically significant difference in the percentage of normally classified subjects in each group (GH-treated: 55.6% vs not treated: 78.6%, $p=0.24$). Baseline data on the E/A ratio – a ratio of early to late ventricular filling velocities and a marker of how effectively the left ventricle fills between contractions -- and baseline deceleration time – another marker of diastolic function are listed in Table 2.

Twelve month follow-up

Two subjects did not complete the study. One subject in the GH group, a 54yo man who had been on GH replacement for 6 years prior to enrollment in the study, passed away a few months after his baseline visit after the development of severe flu-like symptoms. The second subject, a 53yo man who was not being treated with GH during the study dropped out after the baseline visit due to the inability to schedule a follow-up visit. A third patient, a 56yo woman who was not on GH treatment during the study and had no prior history of treatment with GH passed away of unexpectedly of unknown causes approximately three months after completing the study.

At the 12-month follow-up visit, mean BMI increased in both groups. The increase in BMI was less in the GH-treated group ($0.1 \text{ kg/m}^2 \pm 1.5$) as compared to the untreated group ($0.3 \text{ kg/m}^2 \pm 1.9$) but this difference was not statistically significant ($p=0.86$). Mean arterial pressure was similar in both groups at 12 months (GH: $85.3 \text{ mm Hg} \pm 7.2$ vs $88.2 \text{ mm Hg} \pm 8.2$, $p=0.45$).

Twelve-month echocardiographic parameters

Twelve-month LV Mass: At the 12-month follow-up visit, mean LVM/BSA was similar in both the GH group and the non-treated group (GH: $74.4 \pm 22.5 \text{ g/m}^2$ vs untreated: $72.9 \pm 21.3 \text{ g/m}^2$, $p=0.89$; $p=0.28$ when controlling for age; $p=0.89$ when controlling for history of hypertension). The mean change in LVM/BSA over the 12-month period was $-5.1\% \pm 18.3$ in the GH group as compared to $-0.8\% \pm 24.2$ in the untreated group; this difference was not statistically significant ($p=0.69$; $p=0.74$ when controlling for age; $p=0.08$ when controlling for history of hypertension).

In the GH group, two subjects with an elevated LVM/BSA at baseline had normal values at follow-up (Figures 1A and B). One of these subjects started GH for the study and therefore had been treated with GH for 12 months at the time of the follow-up evaluation and the other subject had been on GH for 182 months continuously at the time of the 12-month visit. One subject treated with GH went from a slightly elevated baseline LVM/BSA to a more elevated LVM/BSA at follow-up and a second subject treated with GH progressed from a normal LVM/BSA at baseline to a slightly elevated LVM/BSA at follow-up (Figures 1A and B). Both of these subjects started GH for the study and were therefore on 12 months of GH at the time of follow-up. Two subjects, one in the GH group and one in the untreated group went from a normal LVM/BSA at baseline to a low value at the 12-month follow-up visit (Figures 1A).

Twelve-month diastolic function: The degree of diastolic function was again classified in the two groups at the 12-month visit. Seven subjects (50%) were characterized as having normal diastolic function in the GH group and seven subjects (50%) had delayed relaxation. Three subjects (42.9%) of the non-treated group had normal diastolic function and four subjects (57.1%) had delayed relaxation. The difference between the groups was not statistically significant ($p=0.76$).

In the GH group, four subjects (28.6%) who were classified as having normal diastolic function at baseline were classified as having delayed relaxation at the 12-month visit (Table 3). All four of these subjects had been on GH prior to the baseline visit for a range of 33 to 154 months. Two subjects (28.6%) in the non-treated group were similarly classified as normal at baseline and were found to have delayed relaxation at the 12-month visit. One subject (7.1%) in the GH group was classified as having delayed relaxation at baseline and had normal diastolic function at the 12-month visit. The remainder of subjects in both groups remained stable over the 12-month period. These changes in diastolic function were not significantly different between the groups ($p=0.90$). Twelve month data on the E/A ratio and deceleration time – two components of diastolic function – are listed in Table 2 and graphically represented in Figures 2 and 3.

DISCUSSION

Both acromegaly and GHD are associated with characteristic cardiac structural changes as well as increased cardiovascular mortality. We have shown that in individuals treated for acromegaly who subsequently develop GHD, there were no significant differences in LV mass corrected for body surface area or diastolic function when comparing those treated with GH replacement for a range of 12–182 months to those not receiving treatment for GHD. These data are reassuring as to the effects of GH replacement therapy on LV mass and diastolic function in patients who, though currently GH-deficient, have a history of prolonged cardiac exposure to supraphysiologic circulating GH and IGF-1 and therefore, unlike the majority of individuals with GHD who have decreased LVM/BSA, these individuals have been shown to have a normal LVM/BSA which makes the cardiovascular risk of treatment with GH in this population unclear.

GHD may affect up to 60% of individuals in remission after treatment for acromegaly [44]. In patients with a history of acromegaly and subsequent GHD, visceral adipose tissue of the abdomen and total body fat levels are higher as compared to individuals treated for acromegaly with subsequent GH sufficiency [45] and quality of life scores are impaired [46]. Individuals with GHD who are treated with GH replacement experience reductions in body weight and body fat as well as increases in lean mass [47] and reductions in the waist-to-hip ratio and hs-CRP levels [48]. Importantly, most studies also demonstrate an effect of improvement in quality of life in individuals treated for GHD [47] and therefore investigating the effects of GH replacement in acroGHD is of great importance.

Short-term GH replacement has been studied in acroGHD patients. In a 6-month randomized, placebo-controlled study of GH treatment in 30 subjects, treatment with GH decreased total fat mass, visceral fat and led to a decline in mean hsCRP levels as compared to the placebo group [38]. Importantly, quality of life has also been shown to improve in acroGHD patients treated with GH [38, 49]. A one-year, non-randomized study evaluated the effects of GH treatment on 16 individuals and did not find significant changes with respect to body composition, cardiac parameters or quality of life after one-year of treatment but the baseline IGF-1 SDS score in this study [50] was significantly higher than the mean IGF-1 SDS score in the randomized study (-0.4 vs -1.98) [38] and therefore the baseline degree of GH deficiency was significantly less, making it less likely that significant

differences would be observed in a small group of subjects. Longer-term studies involving treatment of acroGHD patients with GH for up to 3 years also demonstrate sustained improvements in quality of life and cardiovascular risk markers [21, 51].

Studies using large data bases including the KIMS database [20, 52] and the Dutch National Registry of Growth Hormone Treatment [53] have also demonstrated improvements in lipid levels [20, 53] and quality of life in individuals with acroGHD but an increase in cardiovascular mortality was demonstrated in the individuals with acroGHD treated with GH in the KIMS database compared to those treated for GHD with a history of a non-functioning pituitary adenoma. An increased risk of cardiovascular events was also appreciated in a smaller open-label study comparing GH-replaced patients with a history of acromegaly to GH replaced patients with a history of a non-functioning pituitary adenoma [21]. Importantly, the cardiovascular risk of acroGHD individuals who are not treated with GH is not known and therefore whether there is an increased risk of cardiovascular death in individuals treated with GH compared to the untreated group is simply not known.

Given the improvements in quality of life and the improvements in cardiometabolic risk factors, an important question is whether treatment with GH replacement will negatively impact cardiac structure or function in individuals with a history of acromegaly. Although our study was only one year in duration, given our study design, we are able to evaluate the long-term effects of GH replacement in this population. Nine out of the 15 subjects in the GH group had been receiving GH prior to enrollment in the study and therefore were not GH-naïve prior to study initiation. While this was a limitation of our study, as it did not give us a clear picture of the echocardiographic parameters of the GHD subjects at baseline, it was also its greatest strength, as it allowed us to evaluate patients who had been treated for a mean of 72 months with GH replacement at the time of the baseline visit. Of the eight subjects on whom we have 12-month follow-up data in the group receiving GH replacement prior to initiation of the study, all 8 had normal LVM/BSA at 12-months. Therefore, quite reassuringly, there were no significant differences with respect to LVM/BSA or diastolic function in these two groups. An additional limitation of our study is the fact that we did not perform an *a priori* power calculation. A power calculation based on the standard deviation of LVM/BSA of our 23 subjects demonstrated that to detect a 5 g/m² difference in LVM/BSA between the groups, we would have needed over 500 subjects and therefore would have made this study impossible to complete. Nevertheless, we are reassured by the fact that a majority of the GH-treated group had been on GH for a mean of 72 months prior to enrolling in the study and there were no significant differences in LVM/BSA or diastolic function between the groups at baseline or after 12 months. While there were two deaths in the study, one was in a subject on GH and one in a subject not treated with GH. Although further study is needed to evaluate the cardiovascular risk of treatment with GH in acroGHD patients, our data suggest that long-term GH use does not adversely affect cardiac structure or function in patients with GHD after treatment for acromegaly.

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Highlights

- Patients with GHD after cure from acromegaly are rarely treated with GH due to safety concerns
- We followed 23 patients with a history of acromegaly and current GHD for 1 year
- We measured echocardiographic parameters including diastolic function
- At 1 year, overall degree of diastolic function was similar in patients treated with GH and those not treated with GH

Figure 1. Left ventricular mass corrected for body surface area (LVM/BSA) in women (Panel A) and men (Panel B) at baseline and follow-up

The horizontal lines encompass the normal range for LVM/BSA and the vertical line separates the GH groups from the untreated group.

Panel A: At baseline two female subjects (both on GH) had elevated LVM/BSA values and one normalized at follow-up. Two additional female patients had normal LVM/BSA at baseline which dropped to below normal range at follow-up. One of these subjects was on

GH and one was untreated. Subjects 1, 2 and 10 were not on GH at the time of the baseline visit.

Panel B: At baseline, five of the male patients had an elevated LVM/BSA (two in the GH group and three in the untreated group) and of these one in the GH group and two in the untreated group had normal values at follow-up. One male subject in the GH group with a normal baseline LVM/BSA had an elevated value at follow-up. Subjects 1,2 and 3 were not on GH at the time of the baseline visit.

Figure 2. E/A ratio in the untreated subjects (Panel A) and the GH treated subjects (Panel B) at baseline and after 12 months follow-up

The horizontal lines encompass the normal range for the E/A ratio. A low E/A ratio is suggestive of impaired relaxation and an elevated ratio suggests restrictive filling.

Panel A: In the untreated group, six subjects had an abnormal E/A ratio at baseline and one normalized at the time of the follow-up visit.

Panel B: In the GH group, seven subjects had an abnormal E/A ratio at baseline and four of these subjects (#1,3,4 and 15) were not on GH at the time of the baseline visit. Two subjects

who started GH after the baseline visit had normalization of their E/A ratio at follow-up (# 1 and 3). Two subjects with a normal E/A ratio at baseline had an elevated value – suggestive of restrictive filling -- at follow-up (subjects 5 and 9) and one subject had a normal E/A ratio at baseline and had a low value – suggestive of impaired relaxation -- at follow-up (subject 14); this subject had been on GH for 166 months at the time of the follow-up visit. Subjects 1–5 and 15 were not on GH at the time of the baseline visit.

Figure 3. Deceleration times in the untreated subjects (Panel A) and the GH treated subjects (Panel B) at baseline and after 12 months follow-up

The horizontal lines encompass the normal range for the deceleration time. A low deceleration time is suggestive of restrictive filling and an elevated time suggests impaired relaxation.

Panel A: In the untreated group, two subjects had elevated deceleration times at baseline which remained elevated at follow-up and an additional two had baseline normal

deceleration times and elevated times at follow-up; 57% of subjects had an abnormal deceleration time at follow-up.

Panel B: In the GH group, four subjects had an abnormal deceleration time at baseline and three of these subjects (# 1, 5 and 15) were not on GH at the time of their baseline visit and the fourth subject (#10) had only been on GH for 1.6 months at the time of the baseline visit. Two of these subjects (#1 and 15) had normalization of their deceleration time at follow-up, whereas the other two had elevated times at follow-up. One subject (# 2) had a normal deceleration time at baseline and a low time – suggestive of restrictive filling -- at follow-up and an additional four subjects had normal deceleration times at baseline and elevated times at follow-up; 50% of subjects in the GH group had an abnormal deceleration time at follow-up. Subjects 1–5 and 15 were not on GH at the time of the baseline visit.

Table 1

Baseline characteristics of study subjects

	Group receiving GH (n=15)	Untreated group (n=8)	p-value
Age (years)	50.8 ± 13.8	60.5 ± 10.4	0.07
Male/Female	5/10	5/3	0.18
BMI (kg/m ²)	27.5 [24.7, 35.3]	38.6 [32.9, 45.5]	0.02
History of hypertension, number (%)	1 (6.7%)	5 (62.5%)	0.004
Mean arterial pressure (mm Hg)	84.1 ± 7.9	86.1 ± 5.6	0.49
Duration of disease (months)	212 ± 106	294 ± 187	0.28
History of surgery, number (%)	13 (86.7%)	7 (87.5%)	0.95
Time since surgery (months)	192 ± 106	204 ± 106	0.81
History of radiation, number (%)	11 (73.3%)	6 (75%)	0.93
History of somatostatin analogue therapy, number (%)	4 (26.7%)	1 (12.5%)	0.43
ACTH deficiency, number (%)	9 (60%)	4 (50%)	0.65
TSH deficiency, number (%)	12 (80%)	5 (62.5%)	0.36
Gonadotropin deficiency, number (%)	11 (78.6%)	8 (100%)	0.16
IGF-I level (ng/ml)	157.7 ± 75.1	103.3 ± 54.3	0.06
IGF-I/upper limit of normal	0.46 ± 0.23	0.33 ± 0.18	0.16
Tobacco use			0.27
-Current	4 (26.7%)	0	
-Former	3 (20%)	2 (25%)	

Table 2

Parameters of diastolic function at baseline and after 12-months of follow-up

	Group receiving GH (n=15)	Untreated group (n=8)	p-value	Group receiving GH at time of baseline (n=9)	All subjects not on GH at time of baseline visit (n=14)	p-value
Baseline						
E/A ratio	1.22 ± 0.30	1.18 ± 0.34	0.81 0.59 ^a 0.17 ^b 0.41 ^c	1.26 [0.86, 1.32] [*]	1.25 [0.95, 1.55] [*]	0.42 0.41 ^a 0.13 ^b 0.09 ^c
Deceleration time (ms)	223.2 ± 45.3	228.8 ± 43.9	0.78 0.61 ^a 0.85 ^b 0.94 ^c	223.3 ± 26.5	226.3 ± 53.2	0.86 0.87 ^a 0.92 ^b 0.99 ^c
12-month						
E/A ratio	1.21 ± 0.39	1.08 ± 0.39	0.50 0.56 ^a 0.81 ^b 0.85 ^c			—
Deceleration time (ms)	224.5 ± 60.1	260.0 ± 79.8	0.32 0.47 ^a 0.33 ^b 0.43 ^c			—

Mean ± standard deviation unless data are non-normally distributed in which case

^{*} median [interquartile range] listed

^a when controlling for age

^b when controlling for history of hypertension

^c when controlling for baseline BMI

Table 3

Changes in diastolic function over the 12-month study period (Pearson's chi-squared test: $p = 0.90$)

Diastolic Function	Normal --> Normal	Normal --> Delayed Relaxation	Delayed Relaxation --> Normal	Delayed Relaxation --> Delayed Relaxation
GH-treated # of subjects (%)	6 (42.9%)	4 (28.6%)	1 (7.1%)	3 (21.4%)
Non-treated # of subjects (%)	3 (42.9%)	2 (28.6%)	0	2 (28.6%)