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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☆

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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 ± 22.5 g/m^2 vs untreated: 72.9 ± 21.3 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 ± 60.1 ms vs untreated: 260 ± 79.8 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.

1. 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 characteristics 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.

☆ The authors declare that they have no conflict of interest.
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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.

2. Methods

2.1. 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 <5 ng/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.

2.2. 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.

2.3. 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 disks. 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 0.5 cm into the right upper pulmonary vein in the apical four chamber to obtain peak systolic (S) velocity, peak anterograde 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].

2.4. 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%.

2.5. 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.

3. Results

3.1. 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 ± SD: 50.8 ± 13.8 years) were receiving GH treatment