Comparative results of a 4-year study on cardiovascular parameters, lipid metabolism, body composition and bone mass between untreated and treated adult growth hormone deficient patients

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Received 30 October 2007; revised 4 January 2008; accepted 7 January 2008
Available online 4 March 2008

Abstract

Objective: To evaluate the long-term evolution of cardiovascular parameters, lipid metabolism, body composition and bone mass in untreated and treated adult growth hormone deficient patients (AGHD) comparing the differences between the two groups and within each group.

Design: Seventy-one AGHD-patients were enrolled; 48 received growth hormone (GH) therapy: treated group (TG) and 23 received no GH therapy: control group (CG). In the TG, 22 were childhood-onset (CO) GH-deficient patients, 18–44 years (12 males) and 26 were adult-onset (AO) GH-deficient patients, 27–66 years (10 males). In the CG, 10 patients were AGHD-CO, 20–43 years (8 males) and 13 were AGHD-AO, 25–70 years (8 males). For patients in the TG, GH was administered at a starting dose of 0.1 mg/day, adjusted to maintain IGF-I levels between 0 and 2 SDS for gender and age. At baseline and during the 4th year of replacement therapy or follow-up, the following parameters were evaluated: body mass index, waist circumference, blood glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, total cholesterol/HDL-cholesterol ratio, systolic and diastolic blood pressure, 2-D echocardiogram with mitral Doppler, bone mineral density (total body, lumbar spine, and femoral neck), bone mineral content (BMC) and body composition.

Results: In the TG, there was a decrease in diastolic blood pressure (–4.0 ± 1.8 mmHg, p < 0.035) and an increase in blood glucose levels (0.67 ± 0.13 mmol/L, p < 0.025), bone mineral content (0.2 ± 0.0 kg, p < 0.015) and bone mineral density of lumbar spine (0.3 ± 0.1 SDS, p < 0.015) and femoral neck (0.4 ± 0.1 SDS, p < 0.001). All other variables did not show significant changes in any of the two groups. At year 4, changes (delta) differed between patients in the TG and those in the CG with regard to cholesterol levels (TG: –0.27 ± 0.16 mmol/L, CG: 0.34 ± 0.23 mmol/L, p < 0.045), blood glucose (TG: 0.58 ± 0.19 mmol/L, CG: –0.12 ± 0.19 mmol/L, p < 0.025) and BMC (TG: 0.2 ± 0.0 g, CG: 0.0 ± 0.0 g, p < 0.015). An assessment of the changes in variables over time, with and without therapy, considering CO and AO separately, revealed a significant difference in total cholesterol levels during year 4 in CO patients (TG: –0.28 ± 0.25 mmol/L and CG: 0.84 ± 0.25 mmol/L, p < 0.015). No differences related to the time of onset of GHD were found in changes in the remaining variables studied. There were no differences related to gender, GHD etiology or the presence of other pituitary hormone deficiencies in the evolution of the parameters analyzed.

Conclusions: Our 4-year study in GH deficient adults showed significant beneficial effects on some cardiovascular risk parameters and BMC in treated patients. However, there are still unsettled issues regarding long-term benefits and these patients should be carefully monitored.

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1. Introduction

The clinical and biochemical abnormalities in adults with growth hormone (GH) deficiency are well known. They involve mainly the cardiovascular system, lipid metabolism, body composition, mineral metabolism and quality of life [1,2]. Many studies have demonstrated that these abnormalities may be reversed by GH replacement therapy [3–6]. As GH deficiency (GHD) is in general an irreversible condition, it is essential to know whether the beneficial effects obtained from replacement therapy in relatively short periods continue in the long term [7]. This is a complex analysis, since many of the parameters evaluated change with age and with changes in the socioeconomic status over time, even in normal subjects. For this reason, to evaluate long-term results of GH therapy, it is also necessary to compare data on the evolution of patients on replacement therapy for all the pituitary axes, other than the somatotropic axis [8].

Therefore, we thought it would be interesting to conduct this study to evaluate a group of GH-replaced patients and a group of GH-untreated hypopituitary adults over a period of 4 years. Thus, we were able to assess the evolution of both groups comparing the differences between the two groups and within each group, in an attempt to minimize the changes related to time.

2. Patients and methods

2.1. Patients

Seventy-one patients with AGDH were enrolled. Forty-eight patients received GH therapy and constituted the treated group (TG). The remaining 23 patients received no GH therapy and constituted the control group (CG). The patients in the untreated group received no treatment because of their refusal to receive medication and/or for economic reasons.

Of the 48 patients in the TG (mean ± SEM: 38.2 ± 1.8 years), 22 were childhood-onset (CO) GH-deficient patients with an age range between 18 and 44 years (10 females and 12 males) and 26 were adult-onset (AO) GH-deficient patients with an age range between 27 and 66 years old (16 females and 10 males). The etiologies of GHD for AGHD-AO were: idiopathic (n = 13); craniopharyngioma (n = 5); perinatal trauma or asphyxia, meningitis, cholesteatoma, and pinealoma (n = 1 each). GHD etiologies for AGHD-AO were: non-functioning pituitary tumor (n = 5); prolactinoma (n = 5); Sheehan’s syndrome (n = 5); craniopharyngioma (n = 2); pituitary epidermoid cyst, oligodendroglioma, Cushing’s disease, pituitary granuloma, hypophysis, empty sella, and idiopathic (n = 1 each).

Of the 23 patients in the CG (mean ± SEM: 42.7 ± 3.6 years), 10 were AGHD-CO with an age range between 20 and 43 years (2 females and 8 males) and 13 were AGHD-AO with an age range between 25 and 70 years (5 females and 8 males). The etiologies of GHD for AGHD-CO were: idiopathic (n = 6); perinatal trauma or asphyxia (n = 2); craniopharyngioma and empty sella (n = 1 each). GHD etiologies for AGHD-AO were: non-functioning pituitary tumor (n = 6); prolactinoma and Cushing’s disease (n = 2 each); disgerminoma, myoblastoma and postsurgical hypoxia (n = 1 each).

Isolated GH deficiency was found in 4/48 patients in the TG and in 1/23 patients in the CG, while all other patients had multiple pituitary hormone deficiencies.

The diagnosis of AGHD was made by the insulin tolerance test (ITT) and in patients in whom this test was contraindicated, an arginine test was performed. In patients with isolated deficiency and in idiopathic patients, both tests were performed. Only patients with severe GH deficiency, defined by a peak GH response < 0.14 pmol/L to the ITT and < 0.7 pmol/L for the arginine test were enrolled.

Patients in the TG received GH at a starting dose of 0.1 mg/day, adjusted to maintain IGF-I levels between 0 and 2 SDS for gender and age. In the AGHD-CO group, the maintenance dose (mean and range) was 0.52 mg/day (0.17–1.07) in females and 0.33 mg/day (0.13–0.67) in males; in the AGHD-AO group, the maintenance dose was 0.38 mg/day (0.13–0.8) in females and 0.31 mg/day (0.13–0.67) in males. In the AGHD-CO group, 19 patients had received GH therapy in childhood, but had discontinued such therapy at least 1 year before their enrollment in the study.

All patients in the TG and the CG with any other hormone deficiency received appropriate replacement therapy. All females with estrogen deficiency were treated mainly with oral estrogens (90%), except in cases of menopause or contraindicated estrogen therapy.

Written informed consent was obtained from all patients, and the Ethical and the Education and Research Committees approved the study. The study was conducted according to the Declaration of Helsinki II and the Guidelines for Good Clinical Practice.
2.2. Evaluated parameters

At baseline and during the 4th year of replacement therapy in the TG or of follow-up in the CG, the following evaluations were performed:

(a) **Anthropometric parameters:** Body mass index (BMI) and waist circumference.

(b) **Carbohydrate and lipid metabolism:** Blood glucose, glycosylated hemoglobin (Hb A1C), total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and total-cholesterol/HDL-cholesterol ratio.

(c) **Cardiologic evaluation:** Systolic and diastolic blood pressure (BP), 2D echocardiogram with mitral Doppler (Esaote Model AU3). Diastolic function (A/E waves ratio and deceleration time), systolic function (ejection fraction) and cardiac mass index (CMI).

(d) Bone mineral density of lumbar spine, femoral neck and total body, bone mineral content and body composition (percentages of lean and fat mass) analyzed with Lunar DPX-L densitometer (DEXA).

2.3. Assays

Two different assays were used to determine plasma levels of GH. First, an IRMA-Magnetic Solid Phase was used (Serono Maia Clone, Milan, Italy), calibrated against the 1st IRP 66/217. Then, a two-site chemiluminescent enzyme immunometric assay (ICMA, Immulite, Diagnostic Products Corporation, Los Angeles, USA) was employed, calibrated against the WHO IRP 80/505. The equation for the linear regression line comparing the two methods was 

$$\log y = 0.9069 \log x + 0.3172,$$

where $x$ was the IRMA and $y$ was the ICMA ($r$: 0.9523). Serum IGF-I level was measured using IRMA after acid–ethanol extraction (Diagnostic Systems Laboratories, Inc., Webster, TX, USA). Age- and sex-adjusted IGF-I values were obtained from a reference population obtained from blood donors: 384 serum samples from healthy adults (191 males and 193 females) with an age range between 18 and 70 years. The individual IGF-I SD scores (SDS) could then be calculated [9].

2.4. Statistical methods

Baseline variables and characteristics were compared between the TG and the CG using the Chi-square test (categorical data) and the $T$-test (numeric data). Changes after therapy (TG) and follow-up (CG) are expressed as changes from baseline for each group (delta) and analyzed by a repeated-measures ANOVA or Wilcoxon’s test when distributions were not normal.

The effect of each variable was studied, as well as its interaction with changes over time with and without therapy, considering the effect of the other variables using a factorial ANOVA. The variables analyzed in both groups were: time of onset of GHD (CO vs. AO), gender, GHD etiology (organic vs. idiopathic) and presence of other pituitary hormone deficiencies (isolated deficiency vs. multiple deficiency). Values are expressed as mean ± standard error of the mean or median (interquartile range) when a non-parametric test was used for comparison.

SPSS software, version 10.1 (SPSS Inc, Chicago, Il, USA) was employed.

3. Results

Clinical characteristics of both groups are depicted in **Table 1**. No significant differences in age and clinical characteristics were observed between the two groups.

Baseline evaluation of the various variables studied in both groups showed statistically significant differences in blood glucose levels (TG: 4.46 ± 0.09 mmol/L, CG: 4.83 ± 0.13 mmol/L, $p < 0.025$) without any difference in glycosylated hemoglobin (TG: 5.3 ± 0.8%, CG: 5.3 ± 0.7%, $p = 0.659$). There were, also, differences in bone mineral density (BMD) total Z-score (TG: $-1.0 \pm 0.2$, CG: $0.0 \pm 0.4$, $p < 0.015$). No significant differences were found in the remaining variables studied (Table 2).

At baseline, IGF-1 levels were 5.11 nmol/L (0.92–20.04) in the TG and 6.03 nmol/L (2.10–23) in the CG. These levels, expressed as SDS, correspond to −4.54 ± 0.42 and −3.59 ± 0.44, respectively. No significant differences were found in IGF-1 levels between the two groups. Chronological age was 42.7 ± 3.6 years in the TG and 38.2 ± 1.8 years in the CG ($p = NS$).

**Table 3** shows the changes from baseline in the various variables after therapy or follow-up (delta) in the treated and control groups, respectively. In the TG, there was a significant decrease in diastolic blood pressure ($p < 0.035$) and an increase in blood glucose ($p < 0.025$), bone mineral content ($p < 0.015$) and bone mineral density of lumbar spine ($p < 0.015$) and femoral neck ($p < 0.001$). In the CG, there was a tendency to...
increase in bone mineral density of the lumbar spine (p = 0.053). All other variables did not show significant changes in any of the two groups.

After therapy (TG) and follow-up (CG), IGF-1 levels were 28.16 nmol/L (1.27–48.47) and 5.76 nmol/L (0.79–31.44), respectively. These levels, expressed as SDS, correspond to 0.36 ± 0.25 and −4.5 ± 0.8, respectively (p < 0.0001). At the year 4 analysis, changes differed statistically between patients in the TG and those in the CG with regard to cholesterol levels (TG: −0.27 ± 0.16 mmol/L, CG: 0.34 ± 0.23 mmol/L, p < 0.045), and BMC (TG: 0.2 ± 0.0 g, CG: 0.0 ± 0.0 g, p < 0.015). Blood glucose changes were statistically different (TG: 0.58 ± 0.19 mmol/L, CG: −0.12 ± 0.19 mmol/L, p < 0.025) with no difference in glycosylated hemoglobin (TG: 4.8 ± 0.6%, CG: 5.4 ± 0.5%, p = 0.258).

An assessment of the changes in variables over time, with and without therapy, considering CO and AO separately, revealed a significant difference in total cholesterol levels during year 4 in CO patients (TG: −0.28 ± 0.25 mmol/L and CG: 0.84 ± 0.25 mmol/L, p < 0.015). No differences related to the time of onset

| Table 3 | Changes after follow-up (Control group) and therapy (Treated group) expressed as changes from baseline for each group (delta) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Control group p | Treated group p |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Systolic BP (mm Hg) | −0.9 ± 3.5 | 0.81 | −3.8 ± 2.5 | 0.15 |
| Diastolic BP (mm Hg) | −3.5 ± 2.4 | 0.16 | −4.0 ± 1.8 | <0.035 |
| Total cholesterol (mmol/L) | 0.34 ± 0.23 | 0.15 | −0.27 ± 0.16 | 0.10 |
| HDL cholesterol (mmol/L) | 0.09 ± 0.06 | 0.13 | 0.06 ± 0.07 | 0.37 |
| Total cholesterol/HDL ratio | 0.2 (−2.7 to −1.7) | 0.87 | −0.2 (−10.2 to −8.4) | 0.19 |
| LDL cholesterol (mmol/L) | 0.33 ± 0.27 | 0.24 | −0.21 ± 0.21 | 0.32 |
| Triglycerides (mmol/L) | 0.11 (−3.19 to 12.42) | 0.21 | −0.07 (−6.29 to −1.92) | 0.32 |
| Glucose (mmol/L) | −0.12 ± 0.19 | 0.54 | 0.58 ± 0.19 | <0.025 |
| Fat mass (%) | −0.2 ± 1.3 | 0.86 | −1.8 ± 0.9 | 0.06 |
| Lean mass (%) | 0.6 ± 1.0 | 0.57 | 1.5 ± 0.9 | 0.11 |
| Lumbar spine BMD (SDS) | 0.3 ± 0.1 | 0.053 | 0.3 ± 0.1 | <0.015 |
| Femoral neck BMD (SDS) | 0.2 ± 0.2 | 0.50 | 0.4 ± 0.1 | <0.001 |
| Total BMD (SDS) | 0.1 ± 0.2 | 0.52 | 0.1 ± 0.1 | 0.59 |
| BMC (kg) | −0.0 ± 0.0 | 0.31 | 0.2 ± 0.0 | <0.015 |
| Shortening fraction (%) | −2.6 ± 2.2 | 0.27 | 0.9 ± 0.8 | 0.27 |
| Left ventricular mass index (g/m²) | 1.0 ± 3.9 | 0.80 | −0.0 ± 3.9 | 0.99 |
| Ejection fraction (%) | −2.3 ± 9.6 | 0.83 | 1.1 ± 2.3 | 0.65 |
| E/A waves | 1.4 ± 0.1 | 1.6 ± 0.1 | 0.171 |
| Deceleration time (cm/s) | −8.9 ± 15.9 | 0.60 | −7.8 ± 7.8 | 0.33 |

Values expressed as mean ± SEM except for C/HDL and triglycerides expressed as median and interquartile range.
of GHD were found in changes in the remaining variables studied (Table 4). There were no significant differences related to gender, GHD etiology or the presence of other pituitary hormone deficiencies in the evolution of the parameters analyzed.

4. Discussion

There are still many controversies over the benefits of GH replacement therapy in AGHD patients in the medium and long term. This becomes more evident when the various parameters studied are analyzed separately [10–13]. In order to know the actual efficacy of long-term GH therapy, the gold standard would be to conduct randomized, double-blind and placebo-controlled trials [8].

From a practical viewpoint, it is almost impossible to conduct these studies for long periods. Hence, only a few reports have been published of long-term controlled trials in a significant number of patients [14–16].

In this first study in Argentinian population, we analyzed the evolution of clinical, metabolic, bone, cardiovascular and body composition parameters, on both, GH-treated and non-treated AGHD patients followed during 4 years. It is worth noting that patients on GH therapy received individualized doses to maintain serum IGF-I levels appropriate for gender and age.

In our study, the evaluation of cardiovascular parameters showed changes in diastolic BP, with a statistically significant decrease of 4 mmHg in treated patients. This finding is consistent with a publication by Maison et al., who in an important metaanalysis also reported improved diastolic BP with a weighted mean difference of −1.80 mmHg [15]. It is worth noting that only 1/48 patients of the treated group was taking antihypertensive medication at the time of enrollment in the study, therefore its relationship with the results obtained is highly unlikely.

As regards lipid profile, we found a significant improvement in total cholesterol levels in treated patients. It should be noted that this improvement was observed in the AGHD-CO subset of patients and not in AGHD-AO patients. In a previous study (data not published) where we analyzed only the childhood-onset subset of patients, we also found an improvement in total cholesterol, accompanied by an increase in lean mass unrelated to the obesity parameters evaluated.

Our study showed a trend towards a decrease in fat mass with no changes in BMI or waist circumference. The beneficial effects of GH therapy on body composition have been reported in many studies [17–20]. However, these results must be interpreted with caution, since they involve a relatively low number of patients when follow-up periods are long [8,21]. Furthermore, many of these trials are uncontrolled. In addition, during long-term follow-up in open-label trials, eating habits, physical activity and the socioeconomic status of patients may change, which might contribute to changes in the final outcome that cannot be easily weighed.

As regards bone densitometry findings, it is interesting to highlight the increase in lumbar and femoral BMD in treated patients. However, patients in the control group also showed some improvement in the lumbar spine. Therefore, caution is required in the interpreta-
tion of these results. Anyway, the increase in BMC, seen only in treated patients, is consistent with reports from various studies, some of them being long-term trials [22,23]. Different degrees of impairment of bone mass and structure have been reported, depending not only on GH therapy but also on the association with other pituitary deficiencies and their treatment [24]. In this regard, it has shown that, even if both isolated GHD patients and those with multiple deficiencies had a severe impairment of bone mineral content, the prevalence of fractures was markedly increased in patients with multiple deficiencies [24]. The different variables studied (BMC, areal BMD and volumetric BMD) also contribute to the discrepancies in the interpretation of results among different investigations. In most studies, both BMD and BMC have been used; however, prospective studies have based their fracture predictions mainly on BMD [25,26]. Measurement by DEXA includes bone mass and projected surface area and uses both parameters to calculate areal BMD. This measurement, in fact, Underestimates volumetric density when the size of bones is small. Therefore, we should be cautious when drawing conclusions, since some AGHD-CO patients, particularly those with poor treatment during childhood, have short stature with a severely reduced areal BMD and normal volumetric BMD [24]. Finally, results obtained should also be analyzed considering the duration of treatment, since a three-phase effect of GH on BMD has been reported: a decrease during year 1, a sustained increase during a period of up to 5 years, and a subsequent stable plateau [22].

There is a known relationship between GH therapy and alterations in glucose tolerance, and even diabetes [27]. However, GH effects on fasting glucose and insulin vary among different studies [15]. The action on carbohydrate metabolism could be explained by the antagonistic effect of GH on insulin. However, it has been published that the administration of low fixed doses of GH (0.1 mg/day) improves insulin sensitivity and could have a beneficial effect, reducing the risk of type 2 diabetes in adults with severe GHD [28]. Different studies show, in general, that the mean glucose concentration remains within normal ranges [15]. In our study, in patients under GH therapy, baseline blood glucose levels significantly increased, remaining within normal ranges. As patients in the TG had significantly lower blood glucose levels at baseline, the increase in year 4, though significant, resulted in blood glucose levels that did not differ statistically between the TG and the CG. No significant differences were found in glycosylated hemoglobin levels at year 4 between these two groups. Anyway, it should be noted that, in terms of cardiovascular morbidity, the consequences of an increase in fasting glucose levels have not been defined yet, but a positive correlation has been established between blood glucose levels and the occurrence of cardiovascular events in the short term, even below the diabetes threshold [29,30]. The analysis of published data has shown that males are more sensitive to the effect of GH on insulin sensitivity [15]. Even if in this study we could not measure insulin concentrations throughout follow-up or treatment, we have not found gender-related differences in blood glucose levels.

In conclusion, our 4-year study in GH deficient adults on GH replacement therapy vs. untreated GH deficient adults showed significant beneficial effects on some cardiovascular risk parameters and BMC. Even if we have not found deleterious effects on glucose, we cannot rule out the possibility of alterations of the carbohydrate metabolism in a larger number of patients or in a longer follow-up period. In spite of the fact that GH replacement therapy has been in use for almost two decades, there are still unsettled issues regarding its long-term benefits and GH-treated patients should be carefully monitored. Finally, it should be noted that the number of AGHD patients under treatment and long-term follow-up in Argentina, and even throughout South America, is still relatively low. However, the results obtained from our study are similar to the findings published in papers worldwide.

Acknowledgements

The present work was partially supported by Pfizer Argentina SRL and by a Grant of the Consejo de Investigacion en Salud, Gobierno de la Ciudad de Buenos Aires.

We thank Carina Fideleff for her assistance in the correction of the English version.

We wish to thank the following KIMS Investigators of Argentina for referring patients: A. Chervin, N. Vitale (Hospital Santa Lucia, Buenos Aires); I. Sinay, P. Arias (Hospital Francés, Buenos Aires); H. Claus Hermberg, J. Pozzo (Hospital Alemán, Buenos Aires); O. Levalle (Hospital Durand, Buenos Aires); M. Miras (Hospital de Niños, Córdoba) and D. Bruera (Hospital de Clínicas, Córdoba).

References


