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Comparison of two dose regimens of growth hormone (GH) with different target IGF-1 levels on glucose metabolism, lipid profile, cardiovascular function and anthropometric parameters in gh-deficient adults

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ABSTRACT

Objective: To compare the effects of two regimens of GH therapy with different target IGF-1 levels on anthropometric parameters, glucose metabolism, lipid profile and cardiac function in adults with GH deficiency (GHD).

Patients and methods: Retrospective analysis of 14 GHD adults from Clementino Fraga Filho University Hospital, Rio de Janeiro, Brazil, who were treated with a GH regimen aimed at maintaining serum IGF-1 levels between the median and upper reference limit (high dose group — HDGH) and 18 GHD adults from Federal University Hospital, Curitiba, Brazil, who received a fixed GH dose of 0.2 mg/day in the first year of treatment, followed by titration to maintain serum IGF-1 levels between the median and lower reference limit (low dose group — LDGH). All patients were followed for 2 years with analysis of anthropometric parameters, serum levels of IGF-1, glucose, insulin, HOMA-IR, lipid profile, and transthoracic echocardiography.

Results: Changes on weight, BMI and waist circumference were similar between the two groups. Insulin levels increased and HOMA-IR worsened in the LDGH group at 1 year and improved thereafter. Total cholesterol and triglycerides did not change with therapy. LDL cholesterol reduced in both groups, while HDL-cholesterol significantly increased only in the HDGH group ($p = 0.007$ vs LDGH). No significant variations on echocardiographic parameters were observed.

Conclusion: The HDGH and LDGH regimens resulted in similar changes on anthropometric, echocardiographic, glucose and lipid parameters in GHD adults, except for increase in HDL cholesterol that was only observed in the HDGH regimen.

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1. Introduction

Growth hormone deficiency (GHD) in adults is associated with several clinical, biochemical and cardiovascular consequences that might be ameliorated with growth hormone (GH) replacement therapy [1–4]. In the first years of GH therapy in adults with GHD, GH dosing was adopted from experience of treating GHD children, calculated according to the individual weight. This regimen was subsequently found to be supraphysiological, causing unacceptable rates of side effects, associated mainly with fluid retention. In general, adults are much more predisposed to these adverse effects than children, even at doses achieving similar insulin-like growth factor I (IGF-1) responses [5,6]. Thereafter, individually adjusted doses of GH – independent of body weight and body surface – started to be recommended. As a result, lower initial and maintenance GH doses with significant reduction of side effects were attained [5–7]. Nowadays, the guidelines for GH therapy in GHD adults recommend an initial daily dose varying from 0.1 to 0.5 mg according to age, which is subsequently increased until the achievement of normal IGF-1 levels [8].

However, normal reference range for serum IGF-1 can be wide and variable according to various parameters. Moreover, many GHD adults have normal IGF-1 levels at diagnosis [8]. Significant changes in body composition and lipid abnormalities have been reported after 3 and 12 months of GH replacement, even in those patients who maintained subnormal IGF-1 levels [7,16]. Consequently, controversies still persist regarding the better target for IGF-1 during GH therapy [8–10].

This retrospective study was carried out in two Brazilian research centers to compare changes on anthropometric parameters, glucose metabolism, lipid profile and cardiac function after 2 years of GH replacement therapy in GHD adults using two different regimens: one

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designed to maintain IGF-1 levels between the median and upper reference limit (high dose group — HDGH) and the other to maintain serum IGF-1 levels between the median and lower reference limit (low dose group — LDGH).

2. Patients and methods

2.1. Patients

The study group consisted of 32 GHD adult patients [22 women and 10 men; mean age 48 ± 11.4 years (range 31–72 years)], recruited from two Brazilian research centers. The high dose GH group (HDGH) included 14 subjects [4 men and 10 women; mean age 45.8 ± 10 years (range 33–62 years); body mass index (BMI) 24.6 ± 4.3 kg/m^2] who were followed at the Clementino Fraga Filho University Hospital, Rio de Janeiro, Brazil, and the low dose GH group (LDGH) included 18 individuals [12 women and 6 men; mean age 50.8 ± 12.7 years (range, 31–72 years); BMI 29.1 ± 4.9 kg/m^2] who were followed at the Endocrine Division (SEMPR) of the Federal University Hospital, Curitiba, Brazil. All GHD patients had multiple pituitary deficiencies and were undergoing stable conventional replacement therapy for at least 6 months before and during the study period. Prednisone (mean dose: 2.5 to 5 mg/day), levothyroxine (132.3 ± 26.1 μg/day), desmopressin (15 to 40 μg/day) and gonadal steroids were used as necessary, and the daily doses were similar in both centers. Every patient included in the study had severe GHD for at least 1 year before the start of GH replacement (maximum peak serum GH response to insulin-induced hypoglycemia and glucagon test < 3 ng/ml). Patients who did not complete 2 years of treatment or did not have all data available for the retrospective analysis were excluded. Exclusion criteria for receiving GH treatment included any acute severe illness during the previous 6 months, pregnancy or lactation, chronic liver or renal disease, diabetes mellitus, severe hypertension, psychiatric disease, drug or alcohol abuse, history of active malignancy, and use of chronic medication (except pituitary replacement therapy, contraceptives and treatment for mild hypertension). Individuals who developed clinical asymptomatic diabetes during the trial remained in the study and received dietary instructions.

The causes of hypopituitarism in the HDGH group were Sheehan syndrome (n = 8), nonfunctioning pituitary adenoma (n = 2), idiopathic (n = 2), histiocytosis (n = 1) and other pituitary pathologies (n = 1), and in the LDGH group the causes were Sheehan syndrome (n = 5), craniopharyngioma (n = 3), non-functioning pituitary adenoma (n = 2), empty sella (n = 2), idiopathic (n = 1), Pit-1 deficiency (n = 1), pituitary apoplexy (n = 1), brain trauma (n = 1), prolactinoma (n = 1), and after treatment for acromegaly (n = 1). Three patients in the HDGH group and five in the LDGH received radiation therapy.

Informed written consent was obtained from each patient and the study protocol was approved by the Human Research Ethics Committee of both participating institutions.

2.2. Study protocol

This was a retrospective study carried out in two distinct Brazilian research centers using the same inclusion and exclusion criteria to select GHD patients and the same anthropometric measurements, biochemical assays and echocardiographic technique. GH (Norditropin®, Novo-Nordisk, 3 IU/mg) was administered subcutaneously at bedtime by the patient. The injection site was either abdomen or the anterior thigh, according to patient's preference. The HDGH group was treated with a standard initial GH dose followed by adjustments to attain serum IGF-1 levels between the median and upper reference limit. The LDGH group received a fixed GH dose of 0.2 mg/day in the first year of treatment, followed by a subsequent titration to maintain serum IGF-1 levels between the median and lower reference limit. Normal IGF-1 reference range was defined according to the manufacturer's instructions.

Anthropometric and clinical variables were evaluated at baseline and every month during the periods where dose adjustments were necessary and every 3 months during maintenance periods. Patients were oriented to keep their diet and level of physical activity. Blood samples were drawn between 08:00 and 09:00 h in the morning after an overnight fast. Aliquots were immediately centrifuged and stored at −20 °C for subsequent analysis. Serum IGF-1 was assessed at baseline (along with plasma glucose and insulin levels, HOMA-IR, total cholesterol, triglycerides, HDL cholesterol and LDL cholesterol) and every month in the titration periods. When GH maintenance dose was achieved, serum measurements were performed every 3 months. However, only the values obtained after 1 and 2 years of GH therapy were considered for the retrospective analysis. Transthoracic echocardiography was performed at baseline and after 1 and 2 years of GH therapy.

2.3. Anthropometric parameters

Body weight was measured to the nearest 0.1 kg via mechanical scales with subjects wearing light clothes. Body height was assessed with subjects barefoot by stadiometer and to the nearest 0.5 cm. BMI was calculated as body weight (kg) divided by squared height (m^2). Waist circumference was taken at a point half-way between the lower rib margin and the iliac crest and was evaluated by the same investigator at each center, using a soft tape in the standing position.

2.4. Glucose metabolism

The ADA criteria [11] were used for glucose tolerance classification. The insulin resistance (IR) in the fasting state was estimated by the homeostasic model assessment (HOMA) according to the formula described by Matthews et al. [12]: HOMA IR = fasting insulin (μU/ml) × fasting glucose (mmol/l) / 22.5.

2.5. Transthoracic echocardiography

The evaluation was performed with an ultrasound mechanical system (Hewlett–Packard Sonos 100 CF ®, USA, 3.5 MHz) according to a standardized protocol used at both investigating centers. M-mode measurements were performed according to the recommendations by the American Society of Echocardiography [13]. These measurements were used to determine the left atrial diameters, left ventricular (LV) end-diastolic and end-systolic dimensions, as well as the interventricular septal and LV posterior wall thicknesses. Percentage of LV fractional shortening was calculated as the difference between LV diastolic and systolic internal dimensions divided by the LV internal diastolic dimension. Left ventricular volumes were derived from 2D echocardiography investigations. LV mass was calculated with Devereux's formula [14]: LV mass = 0.8 [1.04 (LV end-diastolic diameter + interventricular septum thickness + LV posterior wall diastolic thickness)^3 − (LV end-diastolic diameter)^3] + 0.6. The LV mass was corrected for body surface area (LV mass index): LVMi = LVM / BSA.

2.6. Biochemical assays

Serum IGF-I levels were measured by immunoradiometric assay (DSL-5600 ACTIVE™, Diagnostic System Laboratories, Inc., TX, USA), with an intra-assay CV of 1.5% and inter-assay CV of 3.7% and a reference range of 80 to 500 ng/ml. The upper limit of the age-related reference range was: 30 to 40 years = 494 ng/ml; 40–50 years = 303 ng/ml; 50–60 years = 258 ng/ml; 60–70 years = 198 ng/ml. GH was determined using an immunometric chemiluminescent assay (IMMULITE-DPC, LA, CA). The intraassay and interassay coefficients of variation (CVs) were 5.8% and 5.7%, respectively, at a mean GH concentration of 3.1 ng/ml; the lowest detection limit was 0.01 ng/ml. Plasma glucose was measured by the glucose oxidase method. Insulin was measured by a two-site fluroimmunometric assay (AutoDELFIA-

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