Growth Hormone & IGF Research 25 (2015) 294–297

Contents lists available at ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

Growth hormone and the risk of atherosclerosis in growth hormone-deficient children

Cigdem Binay [a,*], Enver Simsek [a], Ali Yıldırım [b], Pelin Kosger [b], Meliha Demiral [a], Zubeyir Kılıç [b]

[a] Division of Paediatric Endocrinology, Department of Paediatrics, Osmangazi University School of Medicine, Eskisehir, Turkey
[b] Division of Paediatric Cardiology, Department of Paediatrics, Osmangazi University School of Medicine, Eskisehir, Turkey

ARTICLE INFO

Article history:
Received 21 January 2015
Received in revised form 3 August 2015
Accepted 9 August 2015
Available online 12 August 2015

Keywords:
Growth hormone deficiency
Carotid intima-media thickness
Atherosclerosis

ABSTRACT

Objective: Growth hormone-deficient (GHD) children have been found to have higher cardiovascular mortality rates and an increased carotid intima-media thickness (CIMT). This study investigated the risk of atherosclerosis and the effect of recombinant growth hormone (rhGH) replacement therapy on the lipid profile and CIMT in GHD children.

Design: A total of 40 GHD children (mean age: 12.3 ± 2.04 years) were investigated before and after 1 year of rhGH therapy at a dosage of 0.03 mg/kg/day and 40 age- and sex-matched healthy children (mean age: 12.1 ± 2.23 years) were enrolled as a control group, in the same pubertal stage. Fasting blood samples were obtained for lipid profile, IGF-1, and IGFBP-3 analyses. The patients and controls underwent CIMT measurements before and after 1 year of rhGH treatment.

Results: The growth velocity and height standard deviation scores increased significantly over 1 year of treatment in all patients. The total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, and atherogenic index (Ai) values were increased while the high-density lipoprotein (HDL) cholesterol value was decreased in the GHD children, as compared to the controls; however, the triglyceride (TG) level was comparable. After 1 year of treatment, a significant decrease in the TC, LDL cholesterol, and Ai values as well as a significant increase in the HDL value were observed in the GHD patients, with the values becoming similar to those in the control group. The mean CIMT was significantly greater in the GHD subjects than in the controls. After 1 year of therapy, the CIMT in the GHD subjects had decreased significantly; however, it was still greater than that in the control group. IGF-1 was negatively correlated with TC, LDL cholesterol, Ai, right CIMT, and left CIMT.

Conclusions: GHD is associated with increased atherosclerotic risk in children. An improved lipid profile and CIMT were detected after 1 year of hormone replacement therapy.

1. Introduction

Recombinant human growth hormone (rhGH) replacement therapy is a standard treatment option for promoting linear growth in growth hormone-deficient (GHD) children. Growth hormone also has metabolic effects on body composition, muscle strength, bone mineral density, lipid profile, and endothelial function [1,2]. Impaired lipid metabolism in GHD children may contribute to an increased risk of morbidity and mortality due to cardiovascular disease [3,4].

Carotid intima-media thickness (CIMT) is a non-invasive predictive indicator of atherosclerotic processes in the coronary arteries [5]. Altered lipid profiles have been found to be associated with an increased CIMT in GHD patients [6]. In addition, previous studies have suggested that short- and long-term rhGH treatment exerts beneficial effects on abdominal fat, the lipid profile, and early morphological and functional atherosclerotic changes in the carotid arteries of both adults and children [3,7,8].

This study investigated the risk of atherosclerosis and the effects of rhGH therapy on the lipid profile and CIMT in GHD children.

2. Patients and methods

2.1. Patients

The present prospective study included 40 children (mean age: 12.3 ± 2.04 years, 25 boys and 15 girls) who were referred to our paediatric endocrinology outpatient clinic due to short stature and who were subsequently diagnosed with growth hormone deficiency; 8 subjects were prepubertal, 18 were classified as Tanner stage 2, and 14 were classified as Tanner stage 3. The control group included 40 healthy age- and sex-matched children (mean age: 12.1 ± 2.23 years) in the

Abbreviations: GHD, growth hormone deficiency; rhGH, recombinant human growth hormone; BMI, body mass index; SDS, standard deviation score; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low density lipoprotein; IGF-1, insulin-like growth factor-1; IGFBP3, insulin-like growth factor binding protein 3; Ai, atherogenic index; CIMT, carotid intima media thickness.

* Corresponding author at: Buyukdere Mah. Ataturk Bulvari, 186/7 Eskisehir, Turkey.
E-mail address: cigdembinay@gmail.com (C. Binay).

http://dx.doi.org/10.1016/j.ghir.2015.08.005
1096-6374/

same pubertal stage. The pubertal stages were assessed according to testicular volume in boys using an orchidometer (1 mL–3 mL denotes prepubertal, 4 mL–9 mL denotes stage 2 and 10 mL–14 mL denotes stage 3) and breast development in girls (stage 1 denotes prepubertal, stage 2 denotes a palpable subareolar bud before it can be seen as elevation and stage 3 denotes an obvious enlargement and elevation of the breast without the areolar mounding phase) [9]. The diagnosis of growth hormone deficiency was based on clinical, auxological, radiological, and biochemical criteria, including: 1) short stature, defined as a height more than two standard deviation scores (SDSs) below the mean, and a height velocity over 1 year more than one SDS below the mean for chronological age; 2) bone age <2 SDS; and 3) a peak GH concentration below 10 ng/mL after two stimulation tests (glucagon, clonidine, or L-dopa) in children with normal thyroid function [10]. Children with dysmorphic phenotypes, congenital heart disease, chronic renal failure, diabetes, or a primary lipid disorder were excluded from the study. All patients with a diagnosis of growth hormone deficiency were evaluated by hypothalamic/pituitary magnetic resonance imaging (MRI) scans. The GHD children, who exhibited any hypophyseal hormone deficiency or an organic pathology on the hypophyseal MRI scans, were not included in the study group to ensure a homogenous group of patients. The study protocol was approved by the Clinical Research Committee of Osmangazi University School of Medicine (Eskisehir, Turkey). Written informed consent was obtained from the childrens' parents after they had been informed of the aims and procedures of the study.

2.2. Methods

2.2.1. Study design

Height was measured in a standing position, without shoes and socks, using a wall-mounted stadiometer (Harpenden; Holtain Ltd., Crymych, UK) sensitive to 0.1 cm. Weight was measured using a portable, calibrated scale (SECA762; Voge and Hakle, Hamburg, Germany) sensitive to 0.1 kg, with the participants in light clothing. Body mass index (BMI) was calculated as weight (kg) divided by height $(m)^2$. Height, weight, and BMI were expressed as SDSs using 2007 growth reference percentiles for Turkish children and adolescents [11,12]. Bone age SDSs were evaluated using the method of Greulich and Pyle [13]. Tests for low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TGs), total cholesterol (TC), insulin-like growth factor-1 (IGF-1), and insulin like growth factor binding protein-3 (IGFBP-3) were performed in all children. In terms of the cut-off points for TG, TC, LDL and HDL, percentile values were used according to age and gender. TG, TC, and LDL levels greater than the 95th percentile or HDL levels less than the 5th percentile were considered to be significantly changed values. TG, TC, and LDL levels between the 90th and 95th percentiles and HDL levels between the 5th and 10th percentiles were considered to be borderline values [14–16].

All patients received rhGH at a standard dose of 0.03 mg/kg/day and were followed up every 3 months for an anthropometric assessment and to record any side effects. After 1 year of rhGH replacement, the anthropometric, lipid profile (TC, LDL cholesterol, HDL cholesterol, and TGs), IGF-1, IGFBP-3, and CIMT measurements were repeated.

2.2.2. Laboratory measurements

Growth hormone was measured using an immunometric electrochemiluminescent assay (Roche Modular E170; Basel, Switzerland). For three different sets of samples, the intra-assay coefficients of variation (CVs) were 2.3, 2.2, and 2.5%, and the inter-assay CVs were 3, 3, and 3.4%. The lowest detection limit was 0.030 ng/mL. Serum IGF-1 and IGFBP-3 levels were measured by an enzyme-amplified immunoassay (DIAsource ImmunoAssays, Belgium) with intra- and inter-assay CV for IGF-1 of 6.1 and 12.9%, respectively, and intra- and inter-assay CV for IGFBP-3 of 5.1 and 6.4%, respectively. TC, TG, and HDL cholesterol concentrations were measured by enzymatic methods (Roche Modular DP). LDL cholesterol was calculated according to the Friedwald Formula [17]. The atherogenic index (Ai) was calculated as follows: Ai = TC/HDL cholesterol.

2.2.3. CIMT measurement

All of the subjects were evaluated using Vivid I color Doppler ultrasonography with a 12-MHz linear probe. During the evaluation, the child was in a supine position with a thin pillow under his/her neck, which was turned in the opposite direction. Within the first 2 cm distal from the main carotid arterial bulbous, a 1-cm segment was identified and the images were transferred to a computer. The mean value for the designated segment was calculated by a special intima-media thickness assessment programme based on the distant rim measurement. This measurement was repeated and the mean was obtained for both main carotid arteries.

2.2.4. Statistical analysis

IBM SPSS Statistics 20 (Armonk, NY) was used to perform a statistical analysis of the data. Variables with a normal distribution were identified using the Shapiro–Wilk test and *t*–test with independent samples, and the mean ± standard deviation was determined. The Mann–Whitney U test was applied for variables with a non-normal distribution, and median and percentile values (25%–75% percentiles) were obtained. To compare before and after treatment measurements, Paired-samples t test for normal distribution and Wilcoxon signed-rank test for non-normal distribution was performed. Pearson Chi-Square Test was used to identify associations between categorical variables. To identify associations between variables, a Spearman correlation analysis was performed; $p < 0.05$ was accepted as statistically significant.

3. Results

The auxological variables and baseline laboratory values of the GHD and control subjects are shown in Table 1. At study entry, the height and serum IGF-1 and IGFBP-3 values were significantly lower in the GHD subjects than in the healthy children. In children with deficiencies of growth hormone, borderline high and elevated TC values were observed in 12.5% (n = 5) and 22.5% (n = 9) of the patients, respectively, and borderline high and elevated LDL values were observed in 7.5% (n = 3) and 10% (n = 4) of the patients, respectively. In addition, borderline high and elevated TG values were observed in 17.5% (n = 7) and 20% (n = 8) of the patients, respectively, and low and borderline low HDL cholesterol levels were observed in 32.5% (n = 13) and 12.5% (n = 5) of the patients, respectively. The TC, LDL cholesterol, and Ai levels were increased while the HDL cholesterol level was decreased in the GHD patients, as compared to the control group. The TG levels were similar in the GHD patients and the control group. The changes in the baseline variables after rhGH replacement therapy are shown in Table 1. The growth velocity and height SDSs increased significantly over 1 year of treatment in all patients. After treatment, the IGF-1 and IGFBP-3 levels were significantly increased, with the values becoming similar to those in the control group. In addition, a significant decrease in TC, LDL cholesterol, and Ai and a significant increase in HDL cholesterol were observed in the GHD patients during rhGH therapy, with the values becoming similar to those in the control group (Table 1).

The mean right and left CIMTs were significantly greater in the GHD patients than in the controls ($p = 0.002$ and $p = 0.005$, respectively; Table 1). A significant decrease in CIMT was observed in the GHD subjects after rhGH therapy; however, it was still greater than in the control subjects, though the difference was not significant ($p > 0.05$; Table 1).

IGF-1 was negatively correlated with TC, LDL cholesterol, Ai, right CIMT, and left CIMT ($p = 0.05$, $p = 0.25$, $p = 0.05$, $p = 0.007$, and $p = 0.23$, and $r = 0.309$, $r = 0.311$, $r = 0.311$, $r = 0.298$, and $r = 0.255$, respectively). Neither TC ($p = 0.233$ and $r = -0.135$ for the right CIMT; $p = 0.058$ and $r = -0.213$ for the left CIMT) nor LDL