GROWTH HORMONE DEFICIENCY, LOW LEVELS OF ADIPONECTIN, AND UNFAVORABLE PLASMA LIPID AND LIPOPROTEINS

Roberto Lanes, MD, Arlette Soros, MD, Peter Gunczler, MD, Mariela Paoli, MD, Eduardo Carrillo, MD, Omar Villaroel, Msc, and Anselmo Palacios, MD

Objective To examine the impact of adolescent growth hormone deficiency (GHD) on circulating adiponectin levels and the relation between adiponectin, fasting insulin, plasma lipid, and lipoprotein levels.

Study design Twelve children with GHD on GH treatment with a chronological age (CA) of 14.4 ± 2.0 years and 12 untreated adolescents with GHD with a CA of 14.9 ± 2.3 years were studied. Adiponectin concentrations were measured in all patients, and the association of adiponectin with fasting insulin, total, LDL, and HDL cholesterol, triglycerides, apolipoprotein A-1, and apolipoprotein B was evaluated. Twelve healthy adolescents served as control subjects.

Results Adiponectin levels were significantly lower in untreated GHD adolescents than in treated GHD subjects or in control subjects ($P < .008$). Total and LDL cholesterol, triglycerides, and Apo B concentrations were increased in untreated GHD adolescents, whereas HDL cholesterol levels were similar in all three groups. Insulin levels were significantly increased in treated GHD adolescents when compared with control subjects ($P < .05$) but similar to those with untreated GHD. Adiponectin was found to be negatively associated with body mass index, waist-to-hip ratio, and with Apo B, total cholesterol, triglycerides, and LDL cholesterol concentrations in untreated GHD adolescents, whereas a positive correlation between adiponectin and HDL cholesterol was noted in both untreated and treated GHD subjects. Adiponectin correlated inversely with fasting insulin levels in untreated and treated GHD adolescents.

Conclusions GHD in adolescence is associated with low levels of adiponectin and with an unfavorable plasma lipid and lipoprotein profile. Our data suggest that treatment with GH may improve the abnormalities seen. *(J Pediatr 2006;149:324-9)*

Adipose tissue has been shown to be a highly active endocrine organ.[1] Adiponectin, a cytokine exclusively expressed in adipose tissue, is decreased in obesity, particularly visceral obesity, and hypoadiponectinemia has been found to be associated with insulin resistance, type 2 diabetes,[2] dyslipidemia,[3] and hypertension.[4] Adiponectin appears to have a protective effect against atherosclerosis as the result of its anti-inflammatory and antiatherogenic properties.[5]

The effect of growth hormone (GH) replacement on adiponectin levels is not clear. Although in two studies,[6,7] 9 months or 1 year of GH replacement increased serum adiponectin levels in adults with GH deficiency (GHD), in two other studies, 1 year or 1 week of GH replacement did not affect serum adiponectin.[8,9] In adults with GHD, serum adiponectin levels correlated negatively with serum insulin during OGTT at baseline, and, after 1 week of GH replacement therapy, serum adiponectin levels were inversely correlated with both fasting and stimulated levels of glucose and or insulin,[9] suggesting that the patients with the highest baseline serum adiponectin had the smallest impairment in glucose tolerance.

Adiponectin has been shown to be positively correlated with HDL cholesterol and negatively correlated with triglycerides and insulin resistance, confirming the close relation between adiponectin and the metabolic syndrome, even as early as in childhood.[10] Adolescents with GHD have been shown to have increased visceral adiposity,[12] fasting and postprandial hyperlipidemia,[13-16] impaired fibrinolytic activity,[15] increased peripheral insulin resistance,[17] increased levels of inflammatory activity,[16] and abnormal cardiac structure and increased stiffness of the carotid artery.[18] The association of adiponectin with these variables has not been evaluated in adolescents with GHD. We have measured adiponectin concentrations in a group of untreated and treated adolescents with GHD

Apo	Apolipoprotein	GHD	Growth hormone deficiency
BMI	Body mass index	VLDL	Very low density lipoprotein

From the Pediatric Endocrine Unit, Hospital de Clinicas Caracas; Division of Endocrinology, Hospital Universitario de Los Andes, Merida, and Division of Endocrinology, Hospital Central Dr. Carlos Arvelo and Clinica Avila, Caracas, Venezuela.

We thank Pfizer of Venezuela for the generous contribution, which allowed us to purchase the laboratory materials for this study.

Submitted for publication Jan 18, 2006; last revision received Mar 1, 2006; accepted May 9, 2006.

Reprint requests: Roberto Lanes, M-209, PO Box 020010, Miami, F 33102. E-mail: lanes@telcel.net.ve.

0022-3476/$ - see front matter

10.1016/j.jpeds.2006.05.010

and evaluated the association of adiponectin with fasting insulin and plasma lipid and lipoprotein levels.

METHODS

Twelve adolescents with GHD receiving GH treatment, 12 untreated adolescents with GHD, and 12 healthy control subjects were evaluated. All patients were in puberty (Tanner stage 2 to 4). Of the 12 treated children with GHD, six were boys. These patients had a mean chronological age of 14.4 ± 2.0 years, a mean bone age of 12.9 ± 1.9 years, and a mean height of 144.3 ± 10.5 cm (height SD score of −1.8 ± 0.9). Seven of the 12 patients had idiopathic, isolated GHD, whereas five subjects had organic GHD (three patients with a craniopharyngioma who had been treated with surgery and radiotherapy had multiple hormonal deficiencies, while the other two subjects, one with a hamartoma and one with anterior pituitary hypoplasia, had isolated GHD). These subjects were receiving GH treatment for the last 4.6 ± 3.8 years at a dose of 0.1 IU/kg per day (0.03 mg/kg per day). Of the 12 untreated adolescents with GHD, there were six boys and six girls. They had a mean chronological age of 14.9 ± 2.3 years, mean bone age of 12.9 ± 1.9 years, and a mean height of 140.3 ± 15.9 cm (height SD score of −2.8 ± 0.4). Seven of the 12 subjects had idiopathic isolated GHD and five had organic GHD (two subjects with a craniopharyngioma and one with a macroadenoma had been treated with surgery and radiotherapy and one patient with histiocytosis was treated with radiotherapy and they all presented with multiple hormonal deficiencies, whereas one patient with anterior pituitary hypoplasia had isolated GHD). Healthy adolescents (six boys and six girls) all comparable for bone age, body height, body mass index (BMI), pubertal status, blood pressure, and heart rate participated in the study as control subjects.

Initial blood samples were drawn in the morning after an overnight fast in all subjects. Serum concentrations of IGF-1 and IGFBP3 were determined in all subjects by using a two-site immunoradiometric assay (IRMA) (Diagnostic System Laboratories, Inc, Webster, Tex) with interassay and intra-assay coefficients of variation for IGF-1 of 3.9% to 7% and 3.8% to 7.4%, respectively, and with interassay and intra-assay coefficients of variation for IGFBP-3 of 4.2% to 8.3% and 5.3% to 6.7%, respectively. GH levels were obtained in all patients with GHD after oral administration of 100 μg of clonidine/m^2 and of 250 to 500 mg of Larodopa, as previously described,[19,20] and measured using an IRMA (Immunotech, Marseille, France) with interassay and intra-assay coefficients of variation of 13.43% to 14.03% and 0.66% to 1.29%, respectively. Adiponectin was determined by ELISA (DRG International, Inc, East Mountainside, NJ) according to the manufacturer's instructions; interasay and intra-assay coefficients of variation were 7.4% and 2.4% to 8.4%, respectively. Insulin was measured by using a solid-phase radioimmunoassay (Diagnostic Products Corporation, Los Angeles, Calif); intra-assay and interassay coefficients of variation were 5.0% to 9.3% and 4.9% to 10.0%, respectively. Serum total cholesterol and triglyceride concentrations were measured in all subjects by the enzymatic method (Roche Diagnostics, Basel, Switzerland). High-density lipoprotein cholesterol was assessed after precipitation of apo B–containing lipoproteins, and LDL was calculated according to the Friedwald formula. Apolipoprotein (Apo) A-1 and Apo B were measured with the use of a turbidimetric test (Spinreact SA, Sant Esteve de Bas, Spain); intracoefficients and intercoefficients of variation were 0.66% to 0.83% and 0.71% to 0.90% for Apo A-1 and 0.76% to 1.21% and 0.64% to 0.79% for Apo B.

GHD had been diagnosed in all 24 patients a mean of 5.1 ± 1.8 years before entry into the present study by means of two stimulation tests (clonidine and Larodopa; peak GH concentrations of 3.3 ± 1.9 and 3.1 ± 2.2 μg/L, respectively; range of 0.9 to 5.6 μg/L), as well as reduced IGF-1 and IGFBP3 levels for age (94.4 ± 20.6 ng/mL (−1.9 ± 0.6 SDS) and 2322.3 ± 581.9 ng/mL (−1.8 ± 0.4 SDS); normal values for age 498 ± 134 ng/mL for IGF-1 and 4492 ± 1280 ng/mL for IGFBP3). None of the patients was obese, and each had a normal BMI for age of between 15 and 25 kg/m^2. All patients had normal blood pressures and heart rate, as well as normal serum cortisol, prolactin, and thyroid function tests at the time of the study; LH, FSH, and testosterone/estradiol levels were appropriate for pubertal status (patients with multiple hormone deficiencies were receiving replacement therapy for their missing hormones).

Results are reported as mean ± SD. Between-group comparisons were made by using ANOVA to analyze differences between patients and control subjects. The influence of different independent variables on one dependent variable was analyzed by multiple regression analysis. Differences between patients were analyzed in terms of their BMI, sex, and pubertal status. This study was performed with parental consent and with the approval of the hospital ethics committee.

RESULTS

Baseline characteristics are presented in Table I. Adiponectin concentrations were 12.7 ± 6.1 μg/mL in untreated adolescents with GHD, 16.5 ± 7.4 μg/mL in treated subjects with GHD, and 16.2 ± 5.1 μg/mL in healthy control subjects. Adiponectin levels were significantly lower in untreated adolescents with GHD than in treated subjects with GHD or in control subjects ($P < .008$) (Table II).

Total cholesterol and triglyceride levels were190.4 ± 51.6 and 88.3 ± 37.2 mg/dL in untreated patients with GHD, 154.9 ± 38.6 and 74.6 ± 29.8 mg/dL in treated subjects with GHD, and 155.1 ± 26.6 and 76.2 ± 40.3 mg/dL in control subjects. Total cholesterol and triglyceride concentrations were significantly higher in untreated adolescents than in treated subjects with GHD or healthy control subjects ($P < .03$ and $<.001$). LDL cholesterol levels of untreated adolescents with GHD were also significantly increased when compared with those of GH-treated subjects with GHD or healthy control subjects (123.9 ± 52.3 mg/dL in untreated patients, 95.9 ± 28.9 in treated subjects, and 100.8 ± 39.1 mg/dL in healthy control subjects; $P < .01$). HDL cholesterol levels were similar in all three groups (Table II).