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Carotid artery intima-media thickness and lipid profile in adults with growth hormone deficiency after long-term growth hormone replacement

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Abstract

To investigate the effects of growth hormone (GH) replacement on carotid artery intima-media thickness (IMT) and lipid profile, 29 adults with GH deficiency (GHD), mean age 42.5 ± 10.1 years, were studied and compared with 29 control subjects matched for sex, age, body mass index, and smoking habits. Lipid profile (total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, apolipoproteins A and B, and lipoprotein), serum insulin-like growth factor 1 (IGF-1) levels, and ultrasonography of the carotid arteries were performed at baseline and at 6, 12, and 24 months during GH therapy on maintenance dose. At baseline, when compared with the control group, patients presented increased carotid artery IMT ($P < .05$) and triglyceride levels ($P < .001$) and lower HDL concentrations ($P < .01$). In a linear regression analysis, age and known mean duration of GHD were correlated with carotid artery IMT. After 24 months of GH replacement, a reduction in the mean of carotid artery IMT was observed ($P < .01$). The apolipoprotein B levels decreased significantly after the first 3 months of GH treatment ($P < .001$) and remained stable thereafter. Women also presented an increase in HDL cholesterol levels ($P < .01$). No differences were observed in the other lipids measured. Carotid artery IMT at baseline was inversely correlated with the change in carotid artery IMT (Δ = 24 months − baseline), $r = 0.63$, $P < .001$. In conclusion, 24 months of GH replacement therapy promoted favorable effects on carotid artery IMT and lipid profile in patients with GHD. Long-term follow-up studies are required to show whether these beneficial effects will result in reduction of morbidity and mortality from vascular disease.

1. Introduction

Studies have reported that patients with hypopituitarism have an increased mortality compared with the general population [1-5]. Some found the increase in mortality to be caused by cardiovascular disease [1,2,5]. Growth hormone deficiency (GHD) in adults is associated with a large number of cardiovascular risk factors: adverse lipid profile [6], premature atherosclerosis [7], abnormal body composition including reduced lean body mass, weight excess, and increased fat mass with a preponderance of abdominal fat [8], insulin resistance [9], impaired fibrinolysis [10], and decreased exercise capacity [11].

Adverse lipid profile is characterized by elevated concentrations of total cholesterol (TC), low-density lipoprotein (LDL), and apolipoprotein B (apoB). High-density lipoprotein (HDL) levels tend to be low and triglyceride (TG) levels tend to be high compared with those in healthy control subjects [12-16].

Premature atherosclerosis with intimal thickening, accelerated progression of atheromatous plaques, and reduced distensibility of the arterial wall have been found in the carotid arteries of adult patients with hypopituitarism [7,17]. Similar findings were reported in young-adult patients with childhood-onset GHD (COGHD) [18].

Hypopituitarism is a complex condition and combinations of other hormone deficiencies such as inappropriate

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replacement with sex hormones, thyroxine or glucocorticoids, may contribute to increased vascular risk [19]. However, several studies have indicated that GH replacement has beneficial effects on cardiovascular risk factors in patients with hypopituitarism with GHD [12,16,20-22].

The aim of this study was to investigate the effects of GH replacement on carotid artery intima-media thickness (IMT) and lipid profile in adults with GHD.

2. Subjects and methods

2.1. Subjects

Twenty-nine adults with GHD, 18 women (mean age, 46.3 ± 9.3 years) and 11 men (mean age 36.3 ± 8.3 years), compared with 29 control subjects matched for sex, age, body mass index (BMI), and smoking habits, were studied. All patients were undergoing appropriate replacement with levothyroxine (mean dosage, 132.3 ± 26.1 μg/d), glucocorticoids (prednisone, 2.5 to 5 mg/d), sex steroids, and desmopressin, when necessary, for at least 3 months. All men were treated with depot injection of testosterone esters (250 mg intramuscularly every 2 or 3 weeks). All women were taking estrogens and were undergoing medroxyprogesterone acetate replacement therapy, 9 with an oral regimen and the other 9 with transdermal estrogens. After the period of dose titration, 4 women changed from transdermal to oral estrogen replacement regimen. They were not included in the analysis when we compared women undergoing oral or transdermal estrogen replacement regimen. Growth hormone deficiency was defined as a GH peak response of less than 3 ng/mL in 2 provocative tests (insulin tolerance test and glucagon). The known mean duration of GHD was 9.5 (range, 1-30) years. Four patients (all men) had COGHD. The primary pathological events that resulted in hypopituitarism were nonfunctioning pituitary adenoma (n = 9), Sheehan's syndrome (n = 11), idiopathy (n = 4), craniopharyngioma (n = 2), pineal dysgerminoma (n = 1), histiocytosis-X (n = 1), and Cushing's disease (n = 1) [Table 1]. Two women in the oral estrogen group discontinued GH treatment after the period of dose titration: one with cured Cushing's disease because of edema and arthralgia and the other, who had had a craniopharyngioma, because of noncompliance.

Exclusion criteria included the following: GH replacement in the last 12 months, pregnancy, kidney or liver diseases, diabetes mellitus, prior acromegaly, severe hypertension, psychiatric disease, or history of malignancy. The ethics committee of the HUCFF/Medical School approved the study and written informed consent was obtained from each patient.

Table 1
Clinical data of patients

Patients	Age (y)	Sex	Diagnosis	GH peak (ng/mL)[a]	Other deficiencies
1	54	F	Cushing's disease	1.08	TSH, LH, FSH, ACTH
2	41	F	Sheehan's syndrome	0.05	TSH, LH, FSH, ACTH
3	30	F	Sheehan's syndrome	0.05	TSH, LH, FSH, ACTH
4	58	F	Sheehan's syndrome	0.05	TSH, LH, FSH, ACTH
5	55	F	NFPA	0.19	LH, FSH
6	48	F	NFPA	0.17	TSH, ACTH
7	37	F	Craniopharyngioma	0.12	TSH, LH, FSH, ACTH
8	53	F	Sheehan's syndrome	0.46	TSH, LH, FSH, ACTH
9	62	F	Sheehan's syndrome	0.51	TSH, LH, FSH, ACTH
10	39	F	NFPA	2	LH, FSH
11	46	F	Sheehan's syndrome	1.3	TSH, LH, FSH, ACTH
12	35	F	Sheehan's syndrome	0.05	TSH, LH, FSH, ACTH
13	36	F	Sheehan's syndrome	1.6	TSH, LH, FSH, ACTH
14	43	F	Sheehan's syndrome	0.05	TSH, LH, FSH, ACTH
15	49	F	NFPA	0.77	TSH, LH, FSH, ACTH
16	42	F	NFPA	0.05	TSH, LH, FSH, ACTH
17	45	F	Sheehan's syndrome	0.14	TSH, LH, FSH, ACTH
18	61	F	Sheehan's syndrome	0.05	TSH, LH, FSH, ACTH
19	24	M	Idiopathic	0.17	TSH, LH, FSH, ACTH
20	33	M	Idiopathic	0.05	TSH, LH, FSH, ACTH
21	21	M	Craniopharyngioma	0.07	TSH, LH, FSH, ACTH
22	44	M	NFPA	0.29	TSH, LH, FSH, ACTH
23	44	M	NFPA	0.5	TSH, LH, FSH, ACTH
24	38	M	Idiopathic	0.05	TSH, LH, FSH, ACTH
25	37	M	NFPA	0.25	TSH, LH, FSH, ACTH
26	34	M	Pineal dysgerminoma	1.1	TSH, LH, FSH, ACTH
27	49	M	Histiocytosis-X	0.4	LH, FSH, Desmopressin
28	37	M	Idiopathic	0.19	TSH, LH, FSH, ACTH
29	39	M	Idiopathic	0.16	TSH, LH, FSH, ACTH

F indicates female; M, male; NFPA, nonfunctioning pituitary adenoma.
[a] Insulin tolerance test.

2.2. Study design

This was an open prospective study. Patients were evaluated each month during the period of dose adjustment and then every 3 months for 2 years. Growth hormone (Norditropin, Novo-Nordisk; 3 IU/mg) was administered subcutaneously at bedtime by the patient. The initial dose was 0.015 mg/(kg wk). Although the body weight was used

Table 2
Baseline characteristics of patients with GHD and matched control subjects

	Patients (n = 29)	Controls (n = 29)
Common carotid artery IMT (mm)	0.73 ± 0.13*	0.65 ± 0.10*
Carotid artery bifurcation IMT (mm)	0.74 ± 0.13	0.69 ± 0.13
TC (mg/dL)	193.7 ± 33.1	202.1 ± 49.5
LDL cholesterol (mg/dL)	116.7 ± 29.1	116.4 ± 33.8
HDL cholesterol (mg/dL)	45.2 ± 13.4**	55.3 ± 14.1**
TGs (mg/dL)	152.1 ± 72.3***	97.1 ± 62.3***
ApoA (mg/dL)	137.8 ± 38.2	143.4 ± 35.9
ApoB (mg/dL)	111.5 ± 27.7	101.1 ± 23.9
Lp(a) (mg/dL)	42.7 ± 35.4	40.6 ± 39.1
BMI (kg/m^2)	26.9 ± 5.5	26.6 ± 3.7
Waist circumference (cm)	85.4 ± 12.2	85.2 ± 8.5
Weight (kg)	68.2 ± 16.2	71.8 ± 9.1
Systolic blood pressure (mm Hg)	109.3 ± 15.5*	117.5 ± 11.8*
Diastolic blood pressure (mm Hg)	70.6 ± 9.8***	78.9 ± 6.4***
Pulse pressure	38.6 ± 8.9	38.6 ± 7.8
Smoking (n)	6	4
IGF-1 (ng/dL)	81.9 ± 58.2***	360.0 ±148.3***

Values are mean ± SD.
* $P < .05$ statistically significant difference.
** $P < .01$ statistically significant difference.
*** $P < .001$ statistically significant difference.

to define the initial dose of GH, the ideal dose was attained with a dose titration regimen, which was based on the analysis of side effects and serum insulin-like growth factor 1 (IGF-1) levels. The maintenance dose of GH was the one that kept IGF-I levels in the upper limit of the age-related reference range (defined by the IGF-1 assay manufacturer's instructions detailed in section 2.4). The mean dose at the end of the period of dose titration was 0.83 ± 0.2 mg/d (Table 4). Blood was drawn between 8:00 and 9:00 AM after 12 hours of an overnight fast. Serum IGF-1 was assessed every 4 weeks until a maintenance dose was reached; thereafter, lipid profile, serum IGF-1 levels, and ultrasonography of the carotid arteries were performed at 6, 12, and 24 months during GH therapy.

2.3. Carotid artery ultrasonography

The evaluation was performed using a high-resolution echo-color Doppler system (Acuson, Aspem advanced model) with a multifrequency 10 MHz linear ultrasound probe. The characteristic image was 2 parallel echogenic lines separated by a relatively hypoechogenic space. The IMT was defined as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line as described by Pignoli et al [23]. The first line represents the lumen-intimal interface, and the second line represents the medial-adventitial transition. The subjects were kept supine with the head slightly extended. Longitudinal scans were performed in the anteroposterior and coronal planes of the left and right common carotid arteries (CCA). The measurements of the far wall were obtained 1 and 2 cm below the bifurcation. Three measurements were performed, including the site of the greatest thickness, and the mean was used as the IMT of the CCA. Maximum IMT of the bifurcation was also measured. Plaque was defined, as previously described [7], as a localized area of wall thickening greater than 1.2 mm or a localized thickening 0.5 mm greater than the adjacent IMT or diffuse wall thickening over 1.5 mm. All measurements were carried out by the same examiner. The intraoperator coefficient of variation (CV) of repeated measurements was tested in 10 healthy subjects. The CV was 7.7% ± 4.3 % for 3 determinations of IMT performed at 7-day intervals.

2.4. Assay

Growth hormone was determined using an immunometric chemiluminescent assay (IMMULITE, Diagnostic Products Corp, Los Angeles, Calif). The intraassay and interassay CVs were 5.8% and 5.7%, respectively, at a mean GH concentration of 3.1 ng/mL; lowest detection limit, 0.01 ng/mL. IGF-1 was measured by an immunoradiometric assay that uses a modified version of the standard acid-ethanol extraction procedure (immunoradiometric assay, DSL-5.600 ACTIVE, Diagnostic System Laboratories, Inc, TX), intraassay and interassay CVs of 1.5% and 3.7%, respectively. The upper limit of the age-related reference range was 30 to 40 years, 494 ng/mL; 40 to 50 years, 303 ng/mL; and 50 to 60 years, 258 ng/mL. Total cholesterol and TGs were measured by enzymatic methods (Colestat enzimático, Wiener Lab, Rosario, Argentina, and Ecoline 25, Merck Diagnostica, Darmstadt, Germany respectively). The interassay CVs for TC and TGs were 2.32% and 2.81%, respectively. The cholesterol content of HDL was determined using an inhibition-selective method (HDL LE, Labtest Diagnostica, Minas Gerais, Brazil), the interassay CV was 2.06%. Apolipoprotein A (apoA) and apoB were measured by immunonephelometry (N antisera to human Apolipoprotein A1 and ApolipoproteinB, Dade Behring, Marburg, Germany). The apoA intraassay and interassay CVs were 2.2% and 5.7% at mean levels of 158 and 145 mg/dL, respectively. The apoB intraassay and interassay CVs were 1.9% and 2.4% at mean levels of 104 and 108 mg/dL.

Table 3
Linear regression models in 29 patients with GHD taking baseline carotid artery IMT as dependent variable

Characteristic	Linear regression			
	Simple		Multiple*	
	Regression coefficient (SE)	*P*	Regression coefficient (SE)	*P*
Age (y)	0.0008 (0.0002)	.004	0.00048 (0.0002)	.040
Duration of GHD (y)	0.0007 (0.0002)	.011	0.00053 (0.0002)	.067

* Adjusted for all variables in the table.

Table 4
Evolution of 27 adults with GHD during 2 years on GH replacement

	Baseline	6 months	12 months	24 months
Common carotid artery IMT (mm)	0.73 ± 0.13	0.72 ± 0.13	0.70 ± 0.10	0.66 ± 0.10*
Carotid artery bifurcation IMT (mm)	0.74 ± 0.13	0.74 ± 0.13	0.74 ± 0.13	0.74 ± 0.11
TC (mg/dL)	194.7 ± 33.7	189.5 ± 34.8	190.1 ± 39.1	190.0 ± 32.12
LDL cholesterol (mg/dL)	116.7 ± 29.1	116.4 ± 33.8	115.6 ± 36.2	111.4 ± 29.4
HDL cholesterol (mg/dL)	45.7 ± 13.6	45.9 ± 15.3	49.0 ± 16.0	52.3 ± 16.9
TGs (mg/dL)	146.7 ± 64.3	136.0 ± 70.2	120.8 ± 53.3*	133.4 ± 52.3
ApoA (mg/dL)	137.8 ± 38.2	143.4 ± 35.9	145.4 ± 44.6	152.2 ± 8.7
ApoB (mg/dL)	111.5 ± 27.7	101.1 ± 23.9**	96.5 ± 26.5**	93.9 ± 22.4**
Lp(a) (mg/dL)	41.5 ± 35.2	50.2 ± 38.7	45.6 ± 35.9	43.4 ± 33.6
BMI (kg/m^2)	26.6 ± 5.6	26.2 ± 5.9	26.4 ± 6.1	26.6 ± 6.0
IGF-1 (ng/mL)	85.9 ± 74.3	349.5 ± 134.6**	449.0 ± 173.2**	395.0 ± 141.0**
GH dose (mg/d)	0.26 ± 0.06	0.83 ± 0.20***	0.81 ± 0.19	0.60 ± 0.18***

Values are mean ± SD.
* $P < .05$ (vs baseline) statistically significant difference.
** $P < .001$ (vs baseline) statistically significant difference.
*** $P < .01$ statistically significant difference.

Expected values for apoA1 and apoB were 110 to 215 mg/dL and 55 to 140 mg/dL, respectively. Lipoprotein (a) [Lp(a)] was measured by imunonephelometry (LPA, Beckman Galway, Ireland). The intraassay and interassay CVs were 5% or less and 8% or less, respectively. Low-density lipoprotein cholesterol concentrations were calculated using the Friedewald equation [24].

2.5. Statistical analysis

Statistical analysis was performed with Stata software (version 7.0, 2001, Stata Corp, College Station, Tex). Data were expressed as mean ± SD. Pretreatment patients' data were compared with the values for control subjects by the Student *t* test. In addition, regression linear analysis was used to assess the association between carotid artery IMT (dependent variable) and the following baseline explanatory variables: sex, diastolic pressure, systolic pressure, pulse pressure, smoking habits, age, weight, BMI (kg/m^2), waist circumference, baseline plasma lipid levels, known mean duration of GHD in years, maximum GH peak response in a provocative test (GH peak), and IGF-1 levels. The statistical analysis was carried out in 2 stages. In the first stage, each explanatory variable was tested. Then, the variables that reached a significant association at the 15% level were included in a multiple linear regression model. Analysis of variance for repeated measures was carried out to compare the different periods studied. If the F value was significant ($P < .05$) on analysis of variance, differences between basal values and values obtained at various time points were compared by paired *t* tests using the Bonferroni correction. Finally, we calculated Pearson's product moment correlation coefficients to evaluate the correlation between the

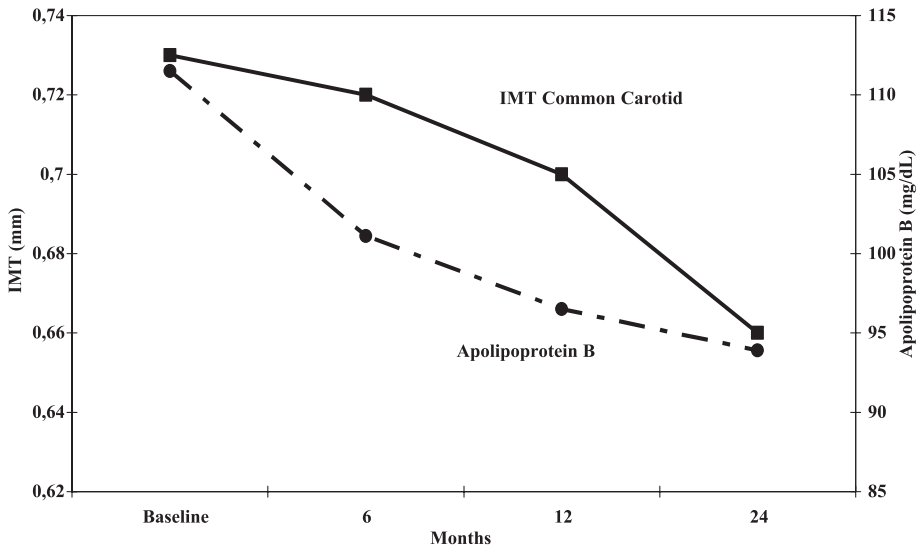

Fig. 1. Mean levels of common carotid and apoB at baseline and after GH replacement.

Table 5
Changes in lipid profile of 16 women and 11 men during 2 years on GH replacement

	Baseline		24 months	
	Women	Men	Women	Men
TC (mg/dL)	195.4 ± 32.9	193.6 ± 36.6	197.1 ± 35.2	187.0 ± 40.6
LDL cholesterol (mg/dL)	117.2 ± 29.6	116.1 ± 29.7	111.3 ± 34.2	115.0 ± 33.0
HDL cholesterol (mg/dL)	48.5 ± 14.3	41.7 ± 12.1	59.9 ± 12.6*	41.0 ± 15.8
TGs (mg/dL)	137.1 ± 47.6	160.6 ± 83.6	133.0 ± 51.9	154.8 ± 86.9
ApoA (mg/dL)	150.0 ± 43.2	120.0 ± 20.4	172.1 ± 51.6	122.2 ± 26.8
ApoB (mg/dL)	108.7 ± 28.0	115.5 ± 28.1	95.0 ± 22.9*	94.1 ± 22.5*
Lp(a) (mg/dL)	30.0 ± 21.4	58.5 ± 44.8	30.0 ± 21.1	58.1 ± 39.9

Values are mean ± SD.
* $P < .01$ (vs baseline).

variation of carotid artery IMT (Δ = 24 months − baseline) and the following variables: level of carotid artery IMT at baseline, variation of apoB and triglycerides levels during treatment (Δ = 24 months − baseline), and mean levels of IGF-1 during treatment. The square root or the logarithmic transformations were applied when appropriate. A P value less than .05 was accepted as significant for all analyses in the study.

3. Results

When compared with a control group, patients presented increased carotid artery IMT ($P < .05$) and TG levels ($P < .001$) and lower HDL concentrations ($P < .01$). Presence of plaque was observed in 8 patients and 5 control subjects. Although patients had lower systolic and diastolic blood pressures, no differences were observed in pulse pressure (systolic pressure-diastolic pressure) levels between groups. No differences were observed in TC, LDL, apoA, apoB, or Lp(a) levels (Table 2). The same findings were observed when we separately compared female and male patients and their respective controls (data not shown). On linear regression analysis, only age and known duration of GHD were associated with carotid artery IMT. The associations remained significant after adjustment in a multiple linear model that included both variables although, for known duration of GHD, the significance became borderline after adjustment (Table 3). A reduction in carotid artery IMT (Table 4 and Fig. 1) was observed after 24 months of GH replacement ($P < .01$). The apoB levels decreased significantly after the first 3 months of GH treatment ($P < .001$) and remained stable thereafter (Table 4 and Fig. 1). A decrease in TG levels occurred at 12 months ($P < .01$) but failed to be significant at 24 months, although an overall tendency of decrease was observed ($P = .07$; Table 4). CT, LDL cholesterol, apoA, and Lp(a) did not change after 24 months of GH replacement (Tables 4 and 5). Regarding sex, women also presented an increase in HDL cholesterol levels

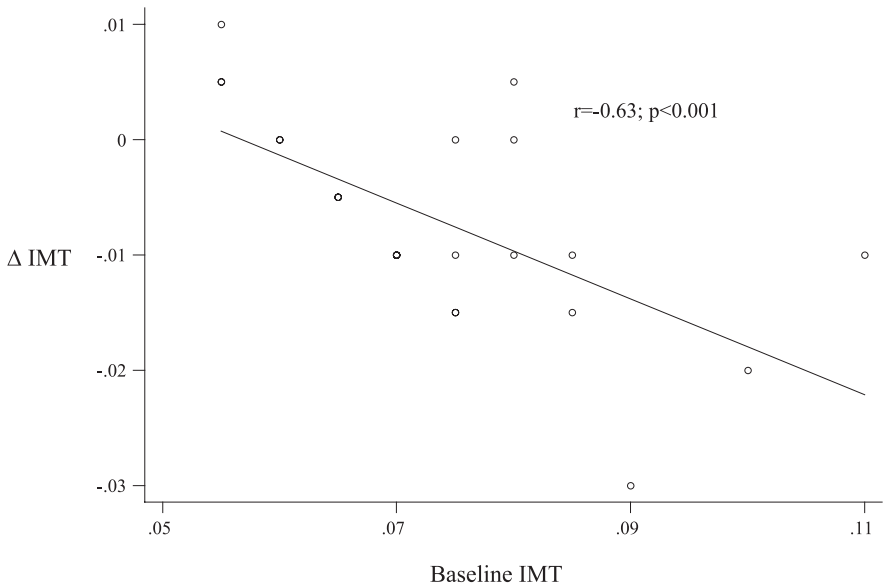

Fig. 2. Relation between variation in carotid artery IMT (Δ = 24 months − baseline) during GH replacement and carotid artery IMT at baseline in 27 patients with GHD.

($P < .01$; Table 5). Carotid artery IMT at baseline was inversely correlated with the variation of carotid artery IMT (Δ = 24 months − baseline; Fig. 2). No other factor studied showed a significant correlation with the carotid artery IMT.

4. Discussion

This was an open prospective study that observed the IMT of the carotid arteries and the lipid profile of adults with GHD compared with a group of healthy control subjects matched for age, sex, BMI, and smoking habits. The same variables were evaluated during 24 months of GH replacement therapy.

Our patients presented increased carotid artery IMT and TG levels and lower HDL compared with the control subjects. After GH replacement, a reduction in the mean of carotid artery IMT and apoB levels was observed.

The development of high-resolution B-mode ultrasonography has allowed the noninvasive quantification of the severity of atherosclerosis in large superficial arteries [25]. The increased carotid artery IMT measured by this method represents an early change in the process of atherogenesis [26,27] and correlates closely with results of pathological examination [23,28]. Progression of carotid artery IMT over time has been reported as a risk factor for atherosclerosis [25]. An increased carotid IMT was a predictor of coronary artery disease [27] and of the future occurrence of myocardial infarction [29].

The present study observed an increased IMT of the CCA of patients with GHD when compared with control subjects; IMT at the bifurcation was similar between patients and control subjects. This may be because atheromatosis is a precocious event at the bifurcations [25,30]. Markussis et al [7] were the first to describe an increase in carotid artery IMT in patients with GHD compared with control subjects matched for age, sex, BMI, and smoking habits. This difference was significant in the group of patients aged 40 years or older. Similar findings were shown in other studies that evaluated young patients with COGHD [19], relatively young men with GHD [31] and Japanese patients with adult-onset GHD and COGHD [32]. However, some studies failed to show a difference between the carotid artery IMT of patients with GHD and control subjects [33-35]. The cause of these discrepant results is unknown. In one study [36], the carotid artery IMT was significantly increased in adults with GHD when compared with healthy control subjects matched for age, sex, and smoking habits but not when compared with control subjects also matched for BMI, suggesting that high BMI in patients with GHD contributes to increased IMT. The present study and other studies [31,37] have shown that GH replacement decreases the IMT even without a reduction in BMI [37]. Gibney et al [38], in studying 21 adults with GHD for 10 years (10 patients received GH replacement whereas 11 did not), observed that carotid IMT decreased in those who underwent GH replacement when compared with the untreated group. No obvious regression of atherosclerotic plaques was detected in the 8 patients who presented them. The same was observed in another study [37].

A correlation was observed between carotid artery IMT and age and known duration of GHD in the patients. Age was the dominant variable determining IMT, as was also observed by Markussis et al [7]. On the other hand, known duration of GHD presents a tendency to influence the IMT that could become evident in a larger group of patients with GHD. The reduction that occurred in carotid artery IMT after GH replacement correlated positively with the IMT at baseline—suggesting that the more IMT was increased at the beginning of the study, the more beneficial the effect of GH therapy was.

Much research has been done on the influence of GH replacement on morphological and functional changes in peripheral arteries, but the mechanisms by which GH mediates these changes are not fully understood. Increased carotid IMT in adults with GHD was reported even in the absence of classical cardiovascular risk factors [18]. Presence of associated hypopituitarism was correlated with an increased IMT [7], and reduction of IMT was related to increases in IGF-1 levels [31].

Patients with GHD present endothelial dysfunction [39], which GH replacement could potentially reverse [40]. Endothelial dysfunction is an early and potentially reversible event in the process of atherogenesis [41]. Attenuation of the effect of nitric oxide (NO) leads to enhanced cell adhesion, proliferation, and vasoconstriction and accounts for mostly what is described as endothelial dysfunction. This occurs in response to atherosclerosis or its risk factors [42]. Endothelial cells possess high-affinity binding sites for IGF-1 and the hemodynamic effects of IGF-1 appear to be dependent upon the release of NO from the endothelium [43]. A study that investigated vascular reactivity in patients with COGHD measured forearm release of NO metabolites during strain-gauge plethysmography and found reduced levels. After GH replacement, the levels of NO metabolites were similar to those of control subjects [44]. However, it is still unclear whether replacement of GH in vivo leads to increased NO synthesis by the endothelium, decreased inactivation by free radicals, such as superoxide, of endothelium-derived NO, or increased sensitivity of vascular smooth muscle to NO [45]. On the other hand, other potential mechanisms that account for endothelial dysfunction must be considered in GHD premature atherosclerosis such as qualitative alterations in atherogenic lipoprotein phenotype [46,47] and increased oxidative stress [48]. Furthermore, atherosclerosis is an inflammatory disease and inflammatory and rheological factors are recognized as cardiovascular risk markers [45,49]. Growth hormone replacement induces a reduction in plasminogen activator antigen and tissue plasminogen activator antigen [50] and in inflammatory mediators such as C-reactive protein and interleukin-6 [51]. Thus, GH may have a protective effect on the vascular endothelium [52].

Data regarding changes in the lipid profile of patients with GHD before and after GH replacement are controversial. When compared with age-matched healthy control subjects, adults with GHD have shown increased or unchanged TC, LDL, TG, and apoB serum levels [6,10,13-16,34-36,46,47,52,53]. Serum HDL and apoA1 levels were decreased or unchanged [6,13-16,34,36,46,47,52-54]. Lipoprotein (a), an independent cardiovascular risk factor, was usually unchanged [36,50,54]. We observed higher levels of TG and HDL in patients with GHD when compared with age-matched control subjects. No differences were found in other lipids and lipoproteins.

The GH enhances the available intrahepatic lipid substrate via its lipolytic action on fat tissue, stimulating very low-density lipoprotein (VLDL) apoB secretion. However, this is probably exceeded by the GH effect in up-regulating a hepatic LDL receptor [55], which increases the clearance of LDL as well as the hepatic uptake of partially delipidated VLDL particles, thereby decreasing the conversion rate from VLDL to LDL [56].

Replacement of GHD with GH promoted favorable changes in lipids in most studies. However, these changes were not the same in all trials [12]. Several factors may be involved in these discrepant findings including heterogeneity of age at onset of GHD (childhood vs adulthood) [57,58], sex [57,59], preexisting plasma lipid levels [58,60], and methodological issues such as dose and duration of treatment.

Long-term GH replacement in patients with GHD may [57,60-65] or may not [58,66,67] reduce TC and LDL levels. Triglycerides were decreased [62,64,65] or unaltered [38,53,58,60,61,63,66-69] whereas HDL levels may [38,53,57,64,68] or may not [58,60-64,67,69] increase. In the present study, no changes were observed in TC, TG, LDL, and HDL after 2 years of GH replacement when all patients were analyzed together. The same was shown in other studies [58,67]. The Lp(a) levels increased in most studies [61,65,66,69] but not in all [37,70]. We did not detect an increase in Lp(a) concentration.

There are few reports regarding apoA1 and apoB evolution during long-term GH therapy. Beshyah et al [71] found unaltered levels of apoA1 and apoB after 18 months of GH replacement in 11 patients. O'Neal et al [61] and Al-Shoumer et al [63] also showed no differences in apoA1 and apoB after long-term GH therapy in patients with GHD. Several studies [16,59,72,73] of 6 and 12 months' duration have shown a reduction in apoB and no change in apoA levels after GH replacement, which are compatible with our findings.

Sex differences in response to GH replacement in lipids have been reported. Burman et al [69] showed a decrease in LDL, apoB, and CT in men whereas no reduction in these variables was observed in women. Johannsson et al [59] found an increase in HDL and a decrease in apoB only in men who also presented a more pronounced increase in Lp(a). Bengtsson et al [74], in studying 665 patients with GHD for 12 months, observed a reduction in TC and LDL in men whereas only women presented an increase in HDL. In our data, men and women had a significant reduction in apoB while HDL levels increased only in women. In this study, no differences were observed in lipid and lipoprotein concentrations before and after GH replacement between women with oral or transdermal estrogen regimen (data not shown). The same was shown by Burman et al [69] in studying women with and without estrogen therapies.

In summary, patients with GHD present increased carotid artery IMT and adverse lipid profiles characterized by increased TGs and decreased HDL levels when compared with control subjects. After 2 years of GH replacement, a reduction occurred in carotid IMT, which is an established intermediary end point for clinical trials that study the inhibitory effects of an intervention on atherogenesis [75-78]. Furthermore, a significant reduction occurred in apoB levels and in female patients we also observed a reduction in HDL levels. Long-term follow-up studies are required to show whether these beneficial effects will result in the reduction of morbidity and mortality from vascular disease.

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