Cardiovascular Risk in Growth Hormone Deficiency

Beneficial Effects of Growth Hormone Replacement Therapy

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KEYWORDS

• Growth hormone deficiency • Cardiovascular risk • Visceral adiposity
• Lipoprotein abnormalities • Endothelial dysfunction • Carotid intima-media thickness
• Vascular reactivity • Cardiac mass and function

KEY POINTS

- Growth hormone deficiency (GHD) may lead to an abnormal body composition, abnormalities in both fasting and postprandial lipoproteins, an increase in the concentrations of peripheral inflammatory and fibrinolytic markers, increased carotid artery intima-media thickness and vascular rigidity, as well as abnormalities in cardiac mass and function.
- These abnormalities have been detected as early as in childhood and adolescence and may contribute to increased cardiovascular morbidity and mortality in adults with GHD.
- The administration of growth hormone to subjects with GHD reverses many of the negative changes in body composition, exercise capacity, and strength and reduces total-cholesterol, low-density lipoprotein cholesterol, and fibrinogen levels.
- Alterations of the cardiovascular system are partially reversed with an increase in left ventricular mass, an improvement in cardiac performance, and a reduction in carotid artery intima-media thickness and vascular rigidity.

INTRODUCTION

Growth hormone deficiency (GHD) in adulthood is associated with an increased risk of developing adverse cardiovascular events and with reduced life expectancy. A number of cardiovascular risk factors such as increased visceral adiposity, abnormalities in lipoprotein metabolism, premature atherosclerosis, impaired fibrinolytic activity,

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abnormal cardiac structure and function and endothelial dysfunction have been reported in adults with untreated GHD[1,2] and have recently been confirmed in several double-blind, randomized, placebo-controlled trials.[3,4]

The administration of growth hormone (GH) to adults with GHD reverses many of the negative changes in body composition, bone mineral density, exercise capacity, and strength and reduces total-cholesterol, LDL-cholesterol, and fibrinogen levels. GH replacement has been found to increase left ventricular mass index, to improve cardiac performance, and to reduce carotid artery intima-media thickness (cIMT) and vascular rigidity in a homogeneous cohort of young adult patients with GHD. In addition, long-term follow-up of a large cohort of patients with adult-onset GHD suggests that GH therapy may contribute to a reduced risk of nonfatal stroke, particularly in women and to a decline in nonfatal cardiac events in GHD men.[5,6]

The existing evidence in healthy children and adolescents and in young adults suggests that the development of the atheromatous plaque begins early in childhood, before puberty.[7] Prepubertal children with untreated GHD have been found to have increased cIMT[7] and to have a higher risk of developing cardiovascular disease (CVD) at an early age.[8,9] Therefore, the identification of the early predictive markers for atherosclerotic CVD and primary prevention should begin in childhood.

Cardiovascular and metabolic abnormalities have so far been evaluated only in a small number of children with GHD and adolescents. In this article we review these abnormalities and their underlying mechanisms and discuss the beneficial effect of GH treatment in subjects with GHD.

ABNORMALITIES IN BODY COMPOSITION AND THE EFFECT OF GROWTH HORMONE THERAPY

Obesity and in particular abdominal adiposity appear to be major risk factors for cardiovascular disease, possibly through their association with atherosclerosis and arterial stiffness. Several studies have reported abnormalities in body composition in adults with GHD, adolescents, and children, with a reduction in lean body mass and an increase in fat mass, particularly with abdominal/visceral obesity; GH therapy reduces the volume of the adipose tissue and increases the amount of muscle. Two double-blind, randomized, placebo-controlled trials in GH-treated men and women confirmed significant decreases in total body and trunk fat and increases in lean body mass over baseline.[3,4]

Prepubertal children with GHD have been found to have higher waist circumference and higher waist-to-height and waist-to-hip ratio (WHR) than controls, thus suggesting increased visceral adiposity. Two years of GH therapy were associated with significantly reduced levels of WHR, therefore improving body composition.[9] During treatment, Kuromaru and colleagues[10] reported a decrease in the mean obesity index value of 6.1% in boys and of 9.7% in GHD girls, while the waist/hip ratio did not change appreciably in either sex. Body fat decreased significantly in both boys and girls during the first 6 months of therapy, remained constant in boys and increased in girls after 2 years, whereas lean body mass increased significantly in both sexes throughout the treatment period. Two studies suggest that discontinuation of GH therapy in adolescents with GHD at adult height could lead to long-term adverse physical and metabolic consequences. After discontinuing GH treatment, once adult height was attained and during a 2-year observation period, Johannsson and collaborators[11] detected a decrease in lean body mass and an increase in body fat and in the amount of truncal fat in adolescents with GHD. Carrol and colleagues[12] reported that skeletal muscle mass accrual remained static once GH was discontinued, whereas

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maintaining GH once adult height was attained resulted in ongoing accrual of lean body mass over the next year.

Although muscle mass increases in patients with GHD on GH treatment, an increase in muscle strength and improved exercise performance has also been noted in these patients. Svensson and colleagues[13] demonstrated how GH replacement therapy in subjects with adult-onset GHD normalized isometric and isokinetic knee flexor and extensor strength, while handgrip strength increased, and Ter Maaten and colleagues[14] demonstrated an increase in the maximal workload and in oxygen consumption in adults with GHD after long-term GH therapy.

BIOCHEMICAL ALTERATIONS AND THE EFFECT OF GROWTH HORMONE THERAPY

Fasting and Postprandial Lipids

An adverse lipid profile has been reported in prepubertal children with GHD through their life span, with an elevation in triglycerides, total-cholesterol, and low-density lipoprotein (LDL)-cholesterol levels, along with lower high-density lipoprotein (HDL)-cholesterol compared with healthy controls.[9,15] Elevated fasting cholesterol and triglyceride levels were detected by our group in 2 cohorts of untreated adolescents with GHD[16,17] (**Table1**) and an increase in total and LDL cholesterol after discontinuation of GH treatment in adolescents with GHD who had reached adult height were reported.[11] Recent blinded, randomized, placebo-controlled trials have confirmed a significant decrease in total-cholesterol and in LDL-cholesterol levels following GH-treatment in adults with GHD when compared with those of placebo-treated subjects.[18,19]

Abnormalities in serum lipids in patients with GHD may be due to an increase in the secretion rate and a reduction in the clearance rate of very low-density lipoproteins (VLDLs). Increased VLDL-apo B secretion is probably related to abdominal obesity in patients with GHD, as abdominal obesity when combined with insulin resistance increases VLDL-apo B secretion from the liver. Short-term GH treatment has been shown to increase the VLDL-apo B clearance rate.

Table 1
Adiponectin; total, LDL, and HDL cholesterol; triglycerides; apolipoprotein B; and insulin concentrations in treated and untreated adolescents with GHD and in healthy controls

	Treated GHD, n = 12	Untreated GHD, n = 12	Non-GHD Controls, n = 12	*P*
Adiponectin, μg/mL	16.5 ± 7.4	12.7 ± 6.1	16.2 ± 5.1	<.008[a]
Total cholesterol, mg/dL	154.9 ± 38.6	190.4 ± 51.6	155.1 ± 26.6	<.03[a]
LDL cholesterol, mg/dL	95.9 ± 28.9	123.9 ± 52.3	100.8 ± 39.1	<.01[a]
HDL cholesterol, mg/dL	47.8 ± 26.9	43.8 ± 10.1	45.0 ± 9.9	Non significant
Triglycerides, mg/dL	74.6 ± 29.8	88.3 ± 37.2	76.2 ± 40.3	<.001[a]
Apolipoprotein B, mg/dL	40.3 ± 15.4	59.6 ± 21.3	44.8 ± 22.9	<.009[a]
Insulin, μIU/mL	7.9 ± 5.2	5.3 ± 2.7	3.8 ± 2.1	<.05[b]

Abbreviations: GHD, growth hormone deficiency; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a] Untreated GHD versus treated GHD and controls.

[b] Treated GHD versus controls.

Data from Lanes R, Soros A, Gunczler P, et al. Growth hormone deficiency in adolescence is associated with low serum levels of adiponectin and with an unfavorable serum lipid and lipoprotein profile. J Pediatr 2006;149:324–9.

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Evidence suggesting a positive correlation between the postprandial triglyceride response to an oral lipid load and atherosclerosis of the carotid and coronary arteries has been reported in adults. Elevated plasma levels of triglycerides and triglyceride-rich lipoprotein particles (TRP), consisting of VLDL containing apo B100 of hepatic origin and chylomicrons containing apo B48 of intestinal origin, have been found to be associated with increased cIMT and cardiovascular mortality. In adult subjects with GHD, Al-Shoumer and colleagues[20] and Twickler and colleagues[21] reported increased fasting and postprandial levels of triglycerides and TRP, suggesting that these changes may contribute to their increased vascular morbidity and mortality. Our group reported a significant increase in postprandial triglycerides following an oral lipid load in untreated adolescents with GHD, when compared with that of both treated subjects with GHD and that of healthy controls[17] (**Fig. 1**, **Table 2**). The accumulation of postprandial TRP in GHD may be explained by a decrease in their removal from the circulation via hepatic lipoprotein receptors, as the expression of several hepatic surface receptors, such as LDL and LDL-receptor–related protein receptors, has been found to be lower in GHD states than in healthy subjects.[22]

GH therapy would seem to improve both the fasting and the postprandial atherogenic lipoprotein profile of adolescents with GHD, as both these parameters were found to be significantly lower than those of untreated subjects.[17] In 2 recent studies, DeMarco and colleagues[23] and Capalbo and colleagues[9] reported significantly higher levels of triglycerides, total cholesterol, and LDL-cholesterol at baseline in children with GHD when compared with healthy controls; after 12 to 24 months of GH treatment, total cholesterol and LDL-cholesterol significantly decreased, reaching values comparable to those in controls. This beneficial effect of GH treatment has been shown to result from an increased expression of hepatic surface receptors.

Lipoprotein(a) is an independently atherogenic lipoprotein that can be thrombogenic and may be used as a marker for individuals at risk for cardiovascular events. Although we found lipoprotein(a) levels to be elevated in both treated and untreated adolescents with GHD when compared with healthy controls,[16] Capaldo and colleagues[9] found no such difference.

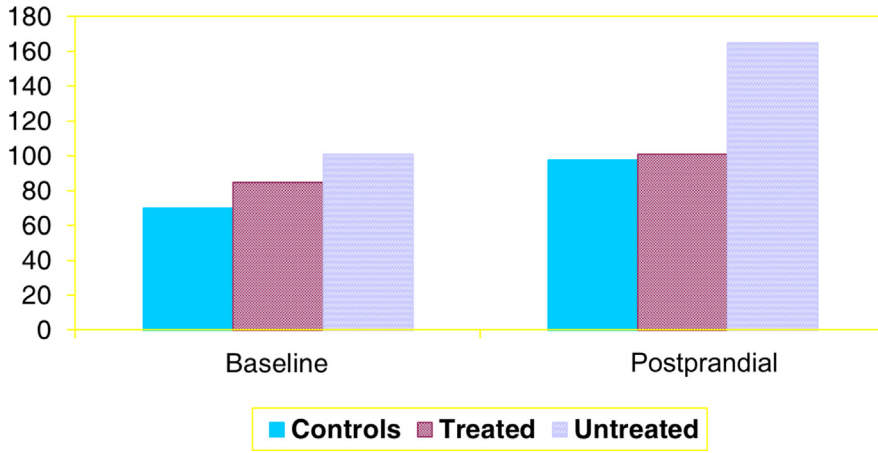

Fig. 1. Fasting and postprandial triglycerides in adolescents with GHD and healthy controls. (*Modified from* Lanes R, Paoli M, Carrillo E, et al. The Cardiovascular risk of young growth hormone deficient adolescents; differences in growth hormone treated and untreated subjects. Horm Res 2003;60:291–5.)

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Table 2
Fasting and postprandial triglycerides, IL-6, TNF-alpha, CRP, and fibrinogen concentrations in treated and untreated GH-deficient adolescents and in healthy controls

	GH-Treated		Untreated		Controls	
	Fasting	Postprandial	Fasting	Postprandial	Fasting	Postprandial
Triglycerides, mmol/L	0.9 ± 0.2	1.1 ± 0.7	1.3 ± 0.5[a]	1.9 ± 0.6[b]	0.8 ± 0.2	1.0 ± 0.5
IL-6, pg/mL	4.0 ± 2.2	3.9 ± 1.5	3.1 ± 1.3	2.9 ± 1.1	4.1 ± 1.6	—
TNF-alpha, pg/mL	21.1 ± 15.0	16.2 ± 4.1	25.2 ± 19.7[a]	22.5 ± 16.2	14.7 ± 4.1	—
CRP, pmol/L	2.8 ± 3.0	2.8 ± 2.9	3.5 ± 1.6[a]	3.1 ± 1.1	1.6 ± 0.7	—
Fibrinogen, μmol/L	4.9 ± 0.8[a]	7.9 ± 2.3[b]	5.6 ± 1.5[a]	8.0 ± 2.5[b]	4.3 ± 0.8	—

Abbreviations: CRP, C-reactive protein; GH, growth hormone; GHD, growth hormone deficiency; IL, interleukin; TNF, tumor necrosis factor.

[a] Fasting GHD versus controls: $P<.05$ and less than .01 for triglycerides; $P<.05$ for TNF-alpha; $P<.04$ for CRP; $P<.03$ for fibrinogen.

[b] Postprandial versus fasting: $P<.01$ for triglycerides; $P<.02$ and less than .001 for fibrinogen.

Data from Lanes R, Paoli M, Carrillo E, et al. Peripheral inflammatory and fibrinolytic markers in adolescents with growth hormone deficiency. Relation to postprandial dyslipidemia. J Pediatr 2004;145:657–61.

Coagulation Factors

Changes in markers linked to coagulation and fibrinolysis have been found in untreated adults with GHD. Fibrinogen, tissue plasminogen activator inhibitor (PAI-1), and factor VII concentrations have been reported to be elevated in adults with GHD, suggesting a defective fibrinolytic system. Plasma protein-A (PAPP-A), a member of the matrix metalloproteinase family, has been included among markers of cardiovascular risk being associated both with the presence of carotid atherosclerosis and with acute coronary syndrome.[24] Elevated levels of PAPP-A have been detected in adults with GHD.[25]

Colao and colleagues[19] demonstrated that both treated and untreated adults with GHD had elevated fibrinogen levels when compared with healthy subjects. In a cohort of young adult patients with GHD diagnosed either at childhood or at adulthood, 12 months of GH replacement significantly reduced fibrinogen, but without reaching normal levels. Our results in adolescents were similar, as both our treated and untreated subjects with GHD had elevated fasting fibrinogen levels[17] (see **Table 2**). A recent study by Capalbo and colleagues[9] in 71 children with GHD found fibrinogen concentrations to be elevated before treatment when compared with healthy controls, with a significant reduction of this parameter following 2 years of GH treatment. Although elevated PAI-1 concentrations were detected in untreated adults with GHD[26] and children,[27] levels of PAI-1 were not found to be increased in either of our treated or untreated adolescents with GHD.[16] Fibrinogen has been shown to be an independent risk factor for stroke and myocardial infarction,[28] whereas PAI-1 activity has been associated with an increased risk for recurrent myocardial infarction.[29] Additionally, abdominal adiposity has been found to be associated with increased concentrations of fibrinogen and PAI-1 activity, so that in subjects with GHD, the increase of these parameters may be linked to their increased waist-hip ratio, and elevated triglycerides might contribute to the elevated PAI-1 activity. This prothrombotic state, with reduced fibrinolytic activity, may therefore contribute to an increased risk for atherothrombotic events in patients with GHD.

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Homocysteine

Homocysteine is believed to be an independent risk factor for cardiovascular events. Experimental and clinical evidence indicates that homocysteine is prothrombotic and therefore high concentrations are associated with vascular endothelial injury and dysfunction. Evans and colleagues,[30] in a preliminary report in a small number of subjects, reported a doubling of plasma homocysteine levels in adults with GHD when compared with matched controls. Sesmilo and colleagues[31] found the median homocysteine level at baseline in adults with GHD to be almost identical to the reported 90th percentile of a comparable subset from a large cross-sectional US study of adults without GHD; when treated with GH, a significant decrease in homocysteine was noted. Folate intake is inversely correlated with fasting homocysteine, and folate supplement administration, with or without vitamins B6 and B12, has been reported to reduce homocysteine levels. In a group of adult-onset patients with GHD, Sesmilo and colleagues[31] found homocysteine at baseline to be negatively correlated with plasma levels of folate. These results are in agreement with our finding of increased homocysteine concentrations and decreased folate and vitamin B12 levels in untreated adolescents with GHD, when compared with both treated subjects with GHD and healthy controls.[17] More recently, Capaldo and colleagues[9] detected elevated homocysteine concentrations in children with GHD before treatment, with a significant reduction of these levels after 2 years of GH therapy.

Endothelial Dysfunction

GH and insulinlike growth factor (IGF)-1 stimulate the production and the release of nitric oxide (NO) in the endothelium and induce vasodilation. Endothelial dysfunction in GHD may be a direct consequence of the low levels of GH and IGF-1. IGF-1 is a potent stimulator of the phosphatidylinositol 3-kinase/protein kinase B/endothelial NO synthase pathway. In healthy middle-aged volunteers, GH treatment induced markers of increased NO bioavailability and enhanced circulating endothelial progenitor cell numbers and this effect was mediated via an increase in IGF-1 plasma levels; blocking of the IGF-1 receptor in vivo abolished the GH-mediated effect on markers of increased NO bioavailability.[32] However, more recent data suggest that GH may regulate vascular reactivity through a direct action on the GH receptor in the vascular endothelium to increase endothelial NO synthase phosphorylation and activity.[33] This conclusion is based on data that indicate that GH exerts an acute vasodilatory effect independent of both systemic and local IGF-1 production, that human aortic endothelial cells express abundant amount of GH receptors, and that GH causes a time-dependent increase in the phosphorylation and activity of endothelial NO synthase.

An indirect action in the atherogenic process induced by alterations in lipoprotein metabolism, with the accumulation of lipoproteic remnants, may also lead to endothelial dysfunction. In the postprandial phase, these remnants are predominantly and highly atherogenic, stimulating an increased formation of macrophages and the induction of vascular inflammation. Twickler and colleagues[21,22] demonstrated that plasma levels of proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) are increased during the postprandial period in adults with GHD and are related to the presence of elevated levels of lipoprotein remnants, suggesting that lipoprotein remnants may induce an inflammatory response in endothelial cells and macrophages. In addition, Leonsson and colleagues[34] demonstrated that untreated adults with GHD have increased levels of C-reactive protein (CRP) and IL-6 and that IL-6 concentrations are independently associated with the degree of common carotid artery intima-media thickness. We have reported elevated serum

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levels of CRP, TNF-alpha, and fibrinogen, when compared with healthy controls, in adolescents with GHD[35] (see **Table 2**), suggesting that a pronounced inflammatory response seems to exist as early as in adolescence in these subjects. In adults with GHD, GH replacement has been shown to reduce the increased monocytic production and the serum levels of proinflammatory cytokines, so that GH may play a role in the regulation of the vascular wall inflammation.[21]

Asymmetric dimethylarginine (ADMA) is an endogenous plasmatic inhibitor of endothelial NO synthase and an emerging cardiovascular marker. Elevated ADMA levels are associated with increased inhibition of endothelial NO synthase and with vasoconstriction, which represents the first phenomenon leading to endothelial dysfunction and to correlate with intima-media thickness, therefore being considered strong predictors of CVD and/or mortality. ADMA levels have been found to be elevated in prepubertal patients with GHD in some reports,[23] but not in others,[24] and GH therapy has been found to decrease ADMA levels, reaching values comparable to those in control children.[23]

Endothelial cells were long considered inactive, acting only as a semipermanent barrier between blood and tissue. However, there are now increasing data to support the role of the vascular endothelium in the maintenance of homeostasis and vascular tone, so that when activated, the vascular endothelium changes the balance between mechanisms that control vasoconstriction and thrombosis and those favoring vasodilation and fibrinolysis. Endothelial cells are known to express a number of molecules, including adhesion molecules such E-selectin, intercellular adhesion molecule (ICAM)-1, and vascular cell adhesion molecule (VCAM)-1, which play a role in the modulation of leukocyte recruitment and platelet adhesion during thrombosis and inflammation. Upregulation of endothelial adhesion molecules plays a key role in the earliest phases of atherogenesis by allowing leukocyte and monocyte adhesion to the endothelial cell surface and their migration to the subendothelial space, where they facilitate the atherogenic process. Activated platelets also participate in this process by modulating chemotactic and adhesive properties of endothelial cells. An elevation in the levels of several biochemical markers of endothelial cell activation, such as VCAM-1 and P-selectin, has been reported by us in adolescents with GHD[36] (**Table 3**); flow-mediated endothelium-dependent vasodilation following hyperemia correlates with P-selectin in these patients. An association between biochemical and biophysical markers of endothelial dysfunction has also been detected in adults with hypopituitarism and severe GH deficiency,[37] suggesting a role for GHD in the development of the atherogenic process.

Table 3
CRP, P-selectin, and VCAM-1 concentrations in treated and untreated adolescents with GHD and in healthy controls

	Treated GHD, n = 28	Untreated GHD, n = 16	Non-GHD Controls, n = 16	*P*
CRP, mg/L	3.62 ± 1.32	4.18 ± 0.96	3.07 ± 1.12	<.02[a]
P-selectin, ng/mL	88.4 ± 33.6	134.3 ± 48.0	100.8 ± 48.6	<.02[a]
VCAM-1, ng/mL	555.2 ± 260.2	524.6 ± 208.6	404.4 ± 186.3	<.007[b]

Abbreviations: CRP, C-reactive protein; GHD, growth hormone deficiency; VCAM, vascular cell adhesion molecule.

[a] Untreated GHD versus treated GHD and controls.

[b] Treated and untreated GHD versus controls.

Data from Lanes R, Marcano H, Villaroel O, et al. Circulating levels of highly sensitive C-reactive protein and soluble markers of vascular cell activation in growth hormone deficiency. Horm Res 2008;70:230–5.

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Adiponectin

Adipose tissue was considered until recently to be an organ for fat storage and mobilization. However, recent evidence suggests that it is a highly active endocrine organ. Adiponectin is an adipocytokine that is exclusively and abundantly expressed in adipose tissue and has been proposed to contribute to the development of insulin resistance and type 2 diabetes, coronary artery disease, and endothelial dysfunction in adults. Adiponectin is secreted principally by visceral adipose tissue and the size of the visceral fat depot is an important correlate of adiponectin levels. In obese adolescents, adiponectin is positively correlated to HDL cholesterol and negatively associated with triglycerides and insulin resistance. A recent report provided the first evidence of early atherosclerotic lesions associated with hypoadiponectinemia in obese juveniles.[38] Subjects with GHD of all ages display many features of the metabolic syndrome, including increased abdominal fat with more visceral adiposity than that of healthy controls for a given body mass index (BMI), elevated levels of LDL-cholesterol and triglycerides, and endothelial dysfunction, and it would seem that these abnormalities can be reversed by GH therapy. Several studies have evaluated the effect of GH replacement on adiponectin levels in adult patients with GHD with conflicting results.[39,40] We have found adiponectin concentrations to be decreased in untreated adolescents with GHD when compared with both treated subjects with GHD and healthy controls (see **Table 1**); adiponectin correlated positively with HDL cholesterol concentrations in both treated and untreated patients and negatively with BMI, waist-hip ratio, fasting total and LDL cholesterol, triglycerides, Apo B, and insulin levels in our untreated adolescents with GHD.[41] In a recent study Capalbo and colleagues[9] found 2 years of GH therapy to be associated with a significant increase in adiponectin levels in children with GHD.

Increased circulating adiponectin levels have been shown to inhibit both the expression of hepatic gluconeogenic enzymes and the rate of endogenous glucose production, with an improvement in insulin sensitivity. However, the mechanism explaining the link between adiponectin and triglycerides is not clear. In obese adolescents, Weiss and colleagues[42] suggested that adiponectin might affect the production of VLDL particles from the liver, thereby regulating serum triglycerides, so that one could speculate that in untreated GHD, low adiponectin may contribute to the increased secretion of VLDL-apo B-100 and triglycerides.

ULTRASOUND ABNORMALITIES AND THE EFFECT OF GROWTH HORMONE THERAPY

Cardiac Mass and Function

Most of the studies in this field point out the importance of GH for the maintenance of normal cardiac function. GH, directly or indirectly, through the effect of IGF-1, is not only involved in the regulation of somatic growth in children, but also in cardiac growth, probably through the modulation of the size of cardiomyocytes.[8,43]

The impairment in cardiac performance in young adults with GHD is manifested by a reduction in left ventricular mass, an inadequate ejection fraction, and in abnormalities of left ventricular diastolic filling.[44] GH administration has been shown to increase left ventricular mass and function in these patients.[45] In an initial study in untreated adolescents with GHD, we were unable to find any abnormalities in cardiac mass or function.[16] Although Colao and colleagues[46] and Salerno and colleagues[47] found no change in the heart rate, systolic and diastolic blood pressure, and in the left ventricular ejection fraction of adolescents with GHD on discontinuing GH for 6 months, GH withdrawal slightly decreased cardiac size and impaired the diastolic filling of adolescents with GHD. This is in agreement with the echocardiographic findings of 2 other

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studies in children and adolescents,[48,49] which demonstrated that cardiac growth may be impeded by severe childhood GHD (**Table 4**). An increase in left ventricular mass normalized for changes in body size was noted in one of these studies following GH therapy[48] and more recently, Nygren and colleagues[50] reported that left ventricular mass indexed to body surface area increased significantly during 2 years of GH treatment in a large population of children with GHD, irrespective of dose. This change was already apparent at 3 months of treatment, when standard deviation scores (SDS) of wall thickness and diameter were increased; at 24 months, left ventricular diameter SDS remained increased, whereas myocardial thickness SDS returned to baseline values. Similar findings were also recently reported by Esen and colleagues.[51] These 2 studies[48,51] demonstrated that GH therapy may cause an increase in myocardial mass without changing the geometry or function of the myocardium. Therefore, the increase in myocardial mass appears to be concentric, thus causing remodeling instead of hypertrophy.

Intima-Media Thickness and Vascular Reactivity

cIMT represents the area of tissue from the luminal edge of the artery to the boundary between the media and the adventitia. cIMT increases at a rate of 0.005 to 0.010 mm per year and its values are age-dependent.[52] In young individuals, a cIMT of greater than 1.00 mm is considered abnormal.[53]

cIMT with more atheromatous plaques in the carotid and the femoral arteries when compared with controls matched for age, sex, and body weight was recently detected

Table 4
Left ventricular mass, interventricular septal thickness, left ventricular posterior wall thickness, left ventricular ejection fraction, carotid artery intima media thickness, increase in brachial artery diameter and blood flow and epicardial tissue in untreated and GH-treated adolescents with GHD and in healthy controls

	Untreated GHD, n = 12	Treated GHD, n = 10	Non-GHD Controls, n = 14	*P*
Left ventricular mass, g/m^2	42.2 ± 2.4	43.5 ± 6.3	49.9 ± 9.0	<.05[a]
Interventricular septal thickness, mm	6.9 ± 1.1	6.9 ± 0.6	7.0 ± 1.1	Non significant
Left ventricular posterior wall thickness, mm	6.5 ± 1.1	6.6 ± 1.3	6.9 ± 1.3	Non significant
Left ventricular ejection fraction, %	64.9 ± 5.4	68.6 ± 3.0	65.0 ± 5	Non significant
Carotid artery intima media thickness, mm	0.9 ± 0.2	0.7 ± 0.1	0.8 ± 0.2	Non significant
Increase in brachial artery diameter, %	15.4 ± 1.1	23.7 ± 1.3	29.8 ± 2.1	<.02[b]
Increase in brachial artery blood flow, %	179 ± 69	253.2 ± 43.1	144 ± 70.7	<.001[c]
Epicardial adipose tissue, mm	2.76 ± 1.36	2.39 ± 0.51	2.25 ± 0.75	<.02[b]

Abbreviations: GH, growth hormone; GHD, growth hormone deficiency.
[a] Untreated and treated GHD versus controls.
[b] Untreated GHD versus treated GHD and controls.
[c] Treated GHD versus untreated GHD and controls.
Data from Lanes R, Soros A, Flores K, et al. Endothelial function, carotid artery intima-media thickness, epicardial adipose tissue and left ventricular mass and function in growth hormone deficient adolescents. J Clin Endocrinol Metab 2005;90:3978–82.

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in adults with GHD.[54] This increased cIMT, which represents the earliest morphologic change in the arterial wall in the process of atherogenesis, has been detected in the absence of clear-cut abnormalities of classic vascular risk factors. GH treatment in adults with GHD has been recently shown to reverse early atherosclerotic changes, with a decrease in cIMT and an improvement of flow-mediated dilation of the brachial artery.[55] With long-term GH substitution, this improvement in arterial performance is maintained.

Although cIMT was not found to be significantly different between treated and untreated adolescents with GHD and healthy controls in studies by Colao and ourselves,[16,46,49] there was a clear tendency toward an increase in cIMT in our untreated adolescents with GHD (see **Table 4**) and in the patients of Colao and colleagues[46] after discontinuing GH for 6 months. Additionally, in a recent study, Khadilkar and colleagues[56] detected an increase in the cIMT of a cohort of 20 untreated children with GHD; GH replacement had a beneficial effect on this parameter. As to vascular reactivity, the flow-mediated endothelium-dependent increase in the diameter of the brachial artery during hyperemia was found by us to be lower in untreated adolescents with GHD than in GHD treated subjects or healthy controls; however, the blood flow increase of the brachial artery after hyperemia was greater in treated than in untreated adolescents[49] (see **Table 4**).

Epicardial adipose tissue was found to be increased in our untreated adolescents with GHD when compared with treated subjects with GHD and to healthy controls and to correlate positively with BMI.[49] A very good correlation between both abdominal visceral adipose tissue and epicardial fat has been shown in adults using MRI and epicardial fat measurement has been related to both anthropometric and clinical parameters of the metabolic syndrome.

However, not all studies have demonstrated a positive effect of GH therapy on these parameters. Although GH treatment had a reversible beneficial effect on body composition, on the metabolic profile, and on cardiac morphology in a large Brazilian kindred with lifelong severe and isolated GHD due to a homozygous mutation in the GH-releasing hormone receptor gene, it resulted in a progressive increase in the intima-media thickness and in the number of atherosclerotic carotid plaques,[57] casting doubts on the positive effects of GH replacement therapy on these parameters.

SUMMARY

Subjects with GHD may present with an abnormal body composition, with elevated fasting cholesterol and triglycerides, and with increased postprandial triglyceride concentrations. In addition, concentrations of peripheral inflammatory and fibrinolytic markers have been found to be increased in GHD. Increased cIMT and vascular rigidity, as well as abnormalities in cardiac mass and function have also been noted in GHD.

Children with GHD may already present with detectable biochemical and clinical markers of CVD in the prepubertal or adolescent years. Most of these alterations are reversible after GH supplementation with a beneficial impact on body fat distribution, lipid abnormalities, and on flow-mediated dilation, a biophysical marker of endothelial function. Effective treatment of children with GHD throughout childhood will therefore lower the burden of cardiovascular risk that these young people could carry into adulthood.

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