METABOLIC ABNORMALITIES IN GROWTH HORMONE DEFICIENCY.

Roberto Lanes, M.D.
Pediatric Endocrine Unit,
Hospital de Clínicas Caracas,
Caracas, Venezuela.

Correspondence: M-209, P.O. Box 020010, Miami, Florida 33102 (mailing address). Phone: 58-212-5743624, Fax: 58-212-5749232, e-mail: lanes@telcel.net.ve
Increased cardiovascular morbidity and mortality has been reported in adult subjects with growth hormone deficiency (GHD). Adult hypopituitary patients with untreated growth hormone deficiency have been shown to have a cluster of cardiovascular risk factors such as increased visceral adiposity, disturbances in lipoprotein metabolism, premature atherosclerosis, impaired fibrinolytic activity, increased peripheral insulin resistance, abnormal cardiac structure and impaired cardiac performance. (1,2). Several of these risk factors, particularly the abdominal obesity and the hyperlipidemia and the beneficial effects of growth hormone treatment on these parameters have now been confirmed in double blind, randomized, placebo controlled trials (3,4). Metabolic changes noted in GH deficient children and adolescents have only recently begun to be investigated in more detail. In this article we will discuss the metabolic alterations and their underlying mechanisms in untreated GHD and we will review the beneficial effect of growth hormone therapy in adults, adolescents and children with GHD.

**Body Composition.**

Obesity and in particular central fatness appear to be major risk factors for cardiovascular disease, possibly through the association with atherosclerosis and arterial stiffness, while some degree of protection seems to be conferred by peripheral fat and lean mass. Several studies have reported abnormalities in body composition in GHD adults, adolescents and children with a reduction in lean body mass and an increase in fat mass with abdominal/visceral obesity; GH therapy reduces the volume of the adipose tissue and increases the amount of muscle. Two very recent 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). As described by Koranyi et al (5), body fat was increased in young adults with childhood-onset (CO) GHD and lean mass and muscle strength were decreased in this group, when compared to subjects with adult-onset (AO) GHD. The increase in lean mass during GH treatment was more marked in CO patients and after 5 years of therapy there were no differences between the CO and AO groups in any variable reflecting body composition.

Korumaru et al (6) reported a decrease in the mean obesity index values of 6.1% in GHD boys and of 9.7% in GHD girls during GH treatment, 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 period of therapy, then remained constant in boys and increased in girls after 2 years; lean body mass increased significantly in both sexes throughout the treatment period. After the discontinuation of GH treatment and during a 2 year observation period, Johannsson and collaborators (7) detected that the lean body mass percent decreased and that the body fat percent and the amount of truncal fat increased in GHD adolescents. In a very recent study by Carroll et al continuation of GH at completion of linear growth resulted in ongoing accrual of lean body mass, whereas skeletal muscle mass remained static after GH cessation in adolescents with GHD; whether discontinuation of GH therapy in the adolescent with GHD could lead to long-term irreversible adverse physical and metabolic consequences needs to be studied further.

Not only does muscle mass increase in GHD patients on GH treatment, but an increase in muscle strength and an improved exercise performance has been noted in these patients. Svensson et al (8) demonstrated how GH replacement therapy in adults with adult-onset GHD normalized isometric and isokinetic knee flexor and extensor strength, while hand grip strength increased, while Ter Maaten et al (9), demonstrated an increase in maximal work load and oxygen consumption in GHD adults after long term GH therapy.

Fasting and Postprandial Lipids.
Untreated GHD children, adolescents and adults have been found to have elevated cholesterol and triglyceride levels. Very recent blinded, randomized, placebo-controlled trials have confirmed a significant decrease in total cholesterol and in low density lipoprotein cholesterol (LDL) levels following GH-treatment in GHD adults when compared with baseline values and with those of placebo-treated subjects (10,11). Elevated fasting LDL and triglyceride levels have been reported by us in 2 recent studies in untreated GHD adolescents (and similar results were reported by Johansson et al who noted an increase in total and LDL cholesterol after discontinuation of GH treatment in GHD adolescents (12,13).

Abnormalities in serum lipids in GHD patients may be due to an increase in the secretion rate and a reduction in the clearance rate of very low-density lipoproteins (VLDL). The increased VLDL-apo B secretion is probably related to the abdominal obesity of GHD patients, 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.

In recent years considerable evidence suggesting a positive correlation between the postprandial triglyceride response to an oral lipid load and atherosclerosis of the carotid arteries and coronary arteries has been found 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 carotid artery intima-media thickness and cardiovascular mortality and elevated postprandial levels of TRP are positively associated with atherosclerotic disease. Al-Shoumer et al (14) and Twickler et al (15) found increased fasting and postprandial levels of triglycerides and triglyceride-rich lipoproteins in adult-onset GHD patients, suggesting that these changes may contribute to their observed increased vascular morbidity and mortality. A significant increase in postprandial triglycerides following an oral lipid load was recently reported by our group in untreated GHD adolescents when compared to both treated GHD subjects and to healthy controls (13). In adult growth hormone deficiency VLDL apo B100 secretion has been found to be increased and VLDL particles are enriched in
triglycerides. The accumulation of postprandial TRP in adult onset 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 is lower in GHD states than in healthy subjects.

Growth hormone therapy would seem to improve both the fasting and the postprandial atherogenic lipoprotein profile in adult-onset GHD, as demonstrated by a decrease of fasting lipids and of postprandial lipoprotein remnants following GH administration (15,16). This beneficial effect of growth hormone was also noted in GHD teenagers, as both the fasting and the postprandial triglyceride levels of our treated GHD subjects were found to significantly lower than those of untreated GHD adolescents (13). GH-treatment has been shown to result in an increased expression of hepatic surface receptors.

Lipoprotein(a) is an independently atherogenic lipoprotein that can be thrombogenic and may be used as a plasmatic marker for individuals at risk for cardiovascular events. There is controversy regarding the lipoprotein(a) levels of GHD patients. We (12) found both treated and untreated GHD adolescents to have elevated lipoprotein(a) levels when compared to healthy controls, while, Capaldo et al (17) found no difference in lipoprotein(a) levels between untreated childhood-onset growth hormone deficient adults and controls.

**Coagulation Factors.**

Abnormalities of coagulation factors, suggestive of a defective fibrinolytic system, such as elevated tissue plasminogen activator inhibitor (PAI-1), fibrinogen and factor VII concentrations have been reported in GHD adults. Colao et al (11) in a recent study demonstrated how both treated and untreated GHD adults had elevated fibrinogen levels when compared to healthy subjects and in a cohort of younger adult patients with either CO or AO GHD, 12 months of GH replacement significantly reduced fibrinogen levels. Our results in young adolescents with GHD are similar to those reported by Colao et al in GHD adults, as both our treated and untreated GHD subjects had elevated fasting fibrinogen levels (18) While Johansson et al reported elevated PAI-1
concentrations in untreated GHD adults, levels of PAI-1 were not increased in either our treated or untreated GHD adolescents. Fibrinogen has been shown to be an independent risk factor for stroke as well as myocardial infarction, while PAI-1 activity has been associated with increased risk for recurrent myocardial infarction (26,27). Obesity and in particular abdominal fat is associated with increased concentrations of fibrinogen and PAI-1 activity; in subjects with GHD this high activity may be linked to their markedly higher waist-hip ratio and high triglycerides might contribute to the elevated PAI-1 activity in GHD men. The prothrombotic state with reduced fibrinolytic activity noted in GHD patients may therefore contribute to an increased risk for atherothrombotic events and play a role in the pathogenesis of cardiovascular disease.

**Homocysteine.**

Moderate elevations in homocysteine plasma levels are thought to play an independent role in the risk of cardiovascular events. Experimental and clinical evidence indicate homocysteine is prothrombotic and high concentrations are associated with vascular endothelial injury and dysfunction. Evans et al (19) in a preliminary report in a small number of GHD adults showed a doubling of plasma homocysteine levels compared to matched controls. Sesmilo et al (20) found the median homocysteine level at baseline in GHD adults to be almost identical to the reported 90th percentile of a comparable subset from a large cross-sectional U.S. study in non-GHD adults, with a significant decrease when treated with GH vs placebo. However, in another recent report, Abdu et al (21) did not detect an elevation in plasma homocysteine in GHD adults when compared to controls. Folate intake is inversely correlated with fasting homocysteine and folate supplements, with or without vitamins B6 and B12, have been reported to reduce homocysteine levels; in a group of adult-onset GHD patients, Sesmilo et al (20) recently found homocysteine at baseline to be negatively correlated with plasma levels of folate. These results in adults are in agreement with our finding of increased homocysteine concentrations and decreased folate and vitamin B12 levels in untreated young GHD adolescents, when compared to those of both treated GHD subjects and healthy controls (13).

**Endothelial dysfunction.**
Endothelial dysfunction in GHD patients is probably a direct consequence of the low levels of GH and IGF1 seen in these patients. GH and particularly IGF1 stimulate the production and the release of nitric oxide in the endothelium, therefore inducing vasodilation. Endothelial dysfunction may also be due to an indirect action in the atherogenic process induced by alterations in lipoprotein metabolism and the accumulation of lipoproteic remnants. In the postprandial phase these remnants are predominantly and highly atherogenic stimulating an increase formation of macrophages and the induction of vascular inflammation. Twickler et al (15,16) recently 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 GHD adults 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 et al (22) have demonstrated that untreated GHD patients 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, so that the increased inflammatory activity of the vessel may be the cause of the high IL-6 levels. We have recently shown how serum levels of CRP, TNF-alpha and fibrinogen are also elevated in GHD adolescents when compared to healthy controls (18). Therefore, a pronounced inflammatory response also seems to exist as early as in adolescence in GHD subjects and seems to be related to elevated levels of fasting and postprandial triglycerides. GH replacement has been shown to reduce the increased monocytic production and the serum levels of proinflammatory cytokines in GHD adults, suggesting that GH may play a role in the regulation of the vascular wall inflammation.

While endothelial cells were long considered inactive, acting only as a semipermanent barrier between blood and tissues there is now increasing data that support the role of the vascular endothelium in the maintenance of homeostasis and vascular tone. When activated the vascular endothelium changes the balance between mechanisms that control vasoconstriction and thrombosis and those favoring vasodilation and fibrinolysis. In response to their activation endothelial cells are known
to express a number of molecules, including adhesion molecules such as E-selectin, ICAM-1 and VCAM-1 which play a role in the modulation of leukocyte recruitment and platelet adhesion during thrombosis and inflammation. Up-regulation 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. We have recently demonstrated that GHD adolescents display significant abnormalities of several biochemical markers of endothelial cell activation such as elevated concentrations of VCAM-1 and P-selectin (23). The presence of these biochemical markers of endothelial dysfunction early on in life help to explain the excess vascular events seen in adult GHD patients secondary to the development of early atherosclerosis (24,25).

Adiponectin.

Until recently adipose tissue was considered to be an organ for fat storage and mobilization, but recent evidence has suggested that it is a highly active endocrine organ. Adiponectin, an adipocytokine that is exclusively and abundantly expressed in adipose tissue, has been proposed to contribute to the development of insulin resistance and type 2 diabetes, coronary artery disease and endothelial dysfunction in adults. Adiponectin seems to be secreted principally by visceral adipose tissue, so that the size of the visceral fat depot is an important correlate of adiponectin levels. Several recent studies in obese adolescents have demonstrated that adiponectin is positively correlated to HDL cholesterol and negatively associated with triglycerides and insulin resistance; in addition a recent report provided the first evidence that early atherosclerotic lesions are associated with hypoadiponectinemia in obese juveniles (26). GHD adults and adolescents display many features of the metabolic syndrome including increased abdominal fat with more visceral adiposity than normal healthy controls for a given BMI, elevated levels of LDL cholesterol and triglycerides, and endothelial dysfunction. Several reports have suggested that these abnormalities can be reversed by GH therapy. The effect of GH-replacement on adiponectin levels in adult
GHD patients has been evaluated by several recent studies and has led to conflicting results (27,28). We have evaluated the concentrations of adiponectin in both treated and untreated GHD adolescents. Adiponectin was found to be decreased in untreated GHD adolescents when compared to both treated GHD subjects and to healthy controls. In addition, adiponectin concentrations 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 untreated GHD adolescents (29).

An increase in circulating adiponectin levels has been shown to inhibit both the expression of hepatic gluconeogenic enzymes and the rate of endogenous glucose production, which could explain the improvement in insulin sensitivity. The mechanism explaining the link between adiponectin and triglycerides is not clear. In a recent study in obese adolescents, Weiss et al suggested that adiponectin might affect the production of VLDL particles from the liver, thereby regulating serum triglycerides. Abnormalities in serum lipids noted in GHD patients may be due to an increase in the secretion rate and a reduction in the clearance rate of VLDL. In a state such as that seen in untreated GHD in adolescence, low adiponectin could possibly contribute to the increase in VLDL-Apo B-100 and triglyceride concentrations, while the higher adiponectin levels seen in treated GHD might possibly contribute to a decrease in hepatic VLDL-APO B production.

**Cardiac Mass and Function.**

In young adults with GHD the impairment of cardiac performance is manifested as a reduction in left ventricular mass, an inadequate ejection fraction and in abnormalities of left ventricular diastolic filling (30). In these patients GH administration has been shown to increase left ventricular mass and function (31). In a recent study in untreated GHD adolescents we were unable to find any abnormalities in cardiac mass, as the interventricular septal thickness, the left ventricular posterior wall thickness and the left ventricular mass after correction for body surface area were all similar to that of healthy controls. Cardiac function of untreated GHD adolescents was also not different from that of healthy controls, as these adolescents had a normal left ventricular ejection
fraction at rest, as well as normal pulmonary venous flow velocities. We were also unable to detect any difference in cardiac mass or function between GHD patients on or off growth hormone therapy at the time of the study (12).

Colao et al (32) and Salerno et al (33) also found no change in the heart rate, systolic and diastolic blood pressure and in the left ventricular ejection fraction of GHD adolescents upon discontinuing GH for six months. GH withdrawal, however, slightly decreased cardiac size and impaired the diastolic filling of GHD adolescents. This is in agreement with two recent echocardiographic studies of children with classical GHD by Shulman et al (34) and ourselves (25) where we demonstrated that cardiac growth may be impeded by severe childhood GHD; however while an improvement with GH therapy, with an increase in the left ventricular mass normalized for changes in body size was noted by Shulman, we were unable to find differences between treated and untreated GHD subjects.

**Intima-Media Thickness and Vascular Reactivity.**

Recent studies have reported increased intima-media thickness (IMT), with more atheromatous plaques in the carotid and the femoral arteries in GHD adults when compared to controls matched for age, sex and body weight (35). This increased IMT, which represents the earliest morphological change in the arterial wall in the process of atherogenesis, has been detected in the absence of clear-cut abnormalities of the classic vascular risk factors. In addition, endothelial function is impaired in GHD adults and this involves the reduced availability of endothelial nitric oxide (NO), a vasodilatory compound.

Growth hormone treatment has been very recently shown to reverse early atherosclerotic changes in GHD adults, so that a decrease in carotid artery intima-media thickness (35) and an improvement of flow mediated dilation of the brachial artery has been demonstrated in GHD adults and in patients with long term GH substitution, improvement in arterial performance is maintained (36). In recent studies, Colao et al (32) and ourselves (12,25)) found carotid artery IMT for both the right and left carotid arteries in untreated GHD adolescents to be similar to that of healthy controls and treated GHD subjects; however a tendency towards increased IMT was noted in our
untreated GHD adolescents (25) and similar findings were noted by Colao et al (32) after discontinuing GH for 6 months. The flow-mediated endothelium-dependent increase in the diameter of the brachial artery during hyperemia was, however, lower in untreated GHD adolescents than in GHD treated subjects or healthy controls, while the blood flow increase in the brachial artery after hyperemia was greater in treated GHD patients than in untreated adolescents (25).

**Insulin Resistance**

Growth hormone has antagonistic effects to that of insulin and a decrease in insulin sensitivity has been reported in acromegaly, in puberty or during growth hormone replacement therapy. Children with GHD have a larger tendency to present with hypoglycemia both fasting and induced, possibly due to an alteration in the regulation of counteregulatory hormones and an increase in insulin sensitivity. This susceptibility to hypoglycemia tends to diminish with age and adults with GHD present with insulin resistance even before growth hormone administration; this could be due to changes in body composition, metabolic responses to growth hormone or to the interaction with sexual hormones.

Husbands and collaborators (37) measured the glucose disappearance rate following a modified insulin tolerance test in children with GHD and demonstrated that these patients were more sensitive to insulin than children with normal growth hormone secretion. This effect decreased with advancing age and puberty, possibly due to the development of central obesity and the secretion of sexual steroids, but the insulin resistance reported in GHD adults was not observed in adolescents. After cessation of GH treatment, insulin sensitivity increased at both 6 and 12 months in a group of GHD adolescents; these increases were noted despite a trend toward increased fat mass and no gain in lean body mass over the same time period. Several studies in adults with hypopituitarism have reported insulin resistance in these patients even without replacement therapy. The administration of growth hormone further decreases insulin sensitivity, but after this initial deterioration an improvement of insulin sensitivity with a return to basal levels, is noted. Growth hormone replacement therapy increases lipolysis with an increment in the concentrations of free fatty acids which could diminish
the uptake of glucose into skeletal muscle. Studies using acipimox, a free fatty acid blocker, have confirmed the inverse relation that exists between circulating free fatty acid concentrations and insulin sensitivity in adults with GHD. Bramnert et al (38) demonstrated very recently how the administration of growth hormone increases lipid oxidation with an increase of the circulating levels of free fatty acids and a deterioration of insulin sensitivity. The effect of growth hormone in the long term, is however, beneficial with a reduction in body fat mass and an improvement in insulin sensitivity. Individualization of growth hormone therapy, with an initial administration of lower growth hormone doses and a gradual increase in dose based on the clinical response could probably minimize the decrease in insulin sensitivity noted in adults during the first few months of growth hormone treatment.

Conclusions.

In conclusion, GHD subjects present with an abnormal body composition, elevated fasting cholesterol and triglycerides levels and increased postprandial triglyceride concentrations. Peripheral inflammatory and fibrinolytic markers are increased and seem to be related to the elevated levels of fasting and postprandial triglyceride rich lipoproteins and to be independently associated with the degree of common carotid artery intima-media thickness in GHD adults. Increased homocysteine and lipoprotein(a) concentrations, independent risk factors for atherosclerosis and increased carotid artery intima-media thickness, impaired flow mediated dilation and abnormal cardiac mass and function have been reported in GHD. Many of these abnormalities seem to be already detectable early on in life, so that adolescents with severe GHD need to be followed carefully as they enter into adulthood. GH treatment has a beneficial impact on body fat distribution, lipid abnormalities and flow mediated dilation, a biophysical marker of endothelial function and seems to result in a reduction of the risk of cardiac events in GHD subjects. Although the precise atherogenic mechanisms in GHD are as of yet not fully understood, an improvement in endothelial function seems to be among the most important effects of GH therapy.
REFERENCES

growth hormone deficiency is related to plasma remnant-like particle cholesterol concentration. J Clin Endocrinol Metab 88:1228-1232.


