Revista Argentina de Endocrinología y Metabolismo Vol 45 • No. 5


REVISIÓN

# Metabolic Abnormalities in growth hormone deficiency

## Anormalidades metabólicas en la deficiencia de la hormona de crecimiento

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**Resumen**

Se ha reportado un aumento en la morbilidad y mortalidad de pacientes adultos con deficiencia de la hormona de crecimiento (DHC). El seguimiento a largo plazo de una cohorte de pacientes con DHC sugiere que la administracion de hormona de crecimiento puede contribuir a una reducción en el número de los accidentes cerebrovasculares no fatales, particularmente en mujeres y de eventos cardíacos en hombres [1,2].

Pacientes adultos con hipopituitarismo y una DHC cursan con un acúmulo de factores de riesgo cardiovascular tales como un aumento en la adiposidad visceral, alteraciones en el metabolismo lipoproteico, ateroesclerosis prematura, actividad fibrinolítica alterada, resistencia a la insulina, masa y función cardíaca alterada y disfunción endotelial [3,4]. Varios de estos factores de riesgo han sido comprobados en estudios doble ciego, randomizados con placebo [5,6]. Las alteraciones metabólicas en niños y adolescentes deficientes de hormona de crecimiento han sido evaluadas sólo recientemente y de manera aún superficial. En este manuscrito discutiremos estas anormalidades y los mecanismos etilógicos subyacentes en sujetos DHC no tratados y revisaremos el efecto beneficioso de la terapia con hormona de crecimiento en niños, adolescentes y adultos.

**Abstract**

Increased cardiovascular morbidity and mortality has been reported in adult subjects with growth hormone deficiency (GHD). 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 in a decline in nonfatal cardiac events in GHD men[1,2].

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, impaired cardiac performance and endothelial dysfunction [3,4]. Several of these

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**Palabras clave:** deficiencia de hormona de crecimiento, alteraciones metabólicas, adiposidad visceral, alteraciones lipoproteicas, grosor de la íntima media y reactividad vascular, masa y función cardíaca.
**Keywords:** Growth hormone deficiency, metabolic abnormalities, visceral adiposity, lipoprotein abnormalities, intima-media thickness and vascular reactivity, cardiac mass and function.

risk factors have now been confirmed in double blind, randomized, placebo controlled trials [5,6]. Metabolic changes in GH deficient children and adolescents have been evaluated only quite recently and superficially. In this article we will discuss these metabolic abnormalities and their underlying mechanism in untreated GHD subjects and we will review the beneficial effect of growth hormone therapy in adults, adolescents and children with GHD.

**Body Composition**

Obesity and in particular abdominal adiposity 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 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[5,6]. As described by Koranyi et al [7], 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, so that after 5 years of therapy there were no differences between the CO and AO groups in any variable reflecting body composition.

Korumaru et al [8] 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 discontinuing GH treatment once final height was attained and during a 2 year observation period, Johannsson and collaborators [9] detected that the lean body mass decreased and that body fat and the amount of truncal fat increased in GHD adolescents. In a recent study by Carroll et al [10] in GHD adolescents at completion of linear growth, maintenance of GH resulted in ongoing accrual of lean body mass, whereas skeletal muscle mass remained static once GH was discontinued; whether discontinuation of GH therapy in adolescents 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 [11] demonstrated how GH replacement therapy in subjects with adult-onset GHD normalized isometric and isokinetic knee flexor and extensor strength, while handgrip strength increased, while Ter Maaten et al [12], demonstrated an increase in the maximal workload and in 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. 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 those of placebo-treated subjects [13,14]. Elevated fasting LDL and triglyceride levels have been reported by us [15,16] in 2 groups of untreated GHD adolescents and similar results were reported by Johansson et al [9] who noted an increase in total and LDL cholesterol after discontinuation of GH treatment in GHD adolescents who had reached final height [13,14].

Abnormalities in the serum lipids of 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). Increased VLDL-apo B secretion is probably related to abdominal obesity in 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 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 carotid artery intima-media thickness and cardiovascular mortality. In adult GHD subjects, Al-Shoumer et al [17] and Twickler et al [18] reported increased fasting and postprandial levels of triglycerides and TRP, suggesting that these changes may contribute to their increased vascular morbidity and mortality. A significant increase in postprandial triglycerides following an oral lipid load was recently report ed by our group in untreated GHD adolescents when compared to both treated GHD subjects and to healthy controls [16]. 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 [19]. 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 [16] . GH-treatment has been shown to result in an increased expression of hepatic surface receptors. However, while GH treatment had a reversible beneficial effect on body composition, on the metabolic profile and on cardiac morphology in a large Brazilian kind red with lifelong severe and isolated GHD due to a homozygous mutation in the GHRH receptor gene, it resulted in a progressive increase in the intima-media thickness and in the number of atherosclerotic carotid plaques [20], casting doubts on the positive effects of GH replacement therapy on these parameters.

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. We [15] found both treated and untreated GHD adolescents to have elevated lipoprotein(a) levels when compared to healthy controls, while, Capaldo et al [21] found no difference in lipoprotein(a) levels between untreated childhood-onset growth hormone deficient adults and controls.

**Coagulation Factors**

Tissue plasminogen activator inhibitor (PAI-1), fibrinogen and factor VII concentrations have been reported to be elevated in GHD adults, suggesting a defective fibrinolytic system. Colao et al [14] demonstrated that both treated and untreated GHD adults had elevated fibrinogen levels when compared to healthy subjects and in a cohort of young adult GHD patients diagnosed at childhood or in adulthood, 12 months of GH replacement significantly reduced fibrinogen levels, without reaching normal levels. In GHD adolescents we found results similar to those of Colao et al, as both our treated and untreated GHD subjects had elevated fasting fibrinogen levels [16]. While Johansson et al [22] reported elevated PAI-1 concentrations in untreated GHD adults, levels of PAI-1 were not increased in either our treated or untreated GHD adolescents [16]. Fibrinogen has been shown to be an independent risk factor for stroke and myocardial infarc-

tion [23], while PAI-1 activity has been associated with an increased risk for recurrent myocardial infarction [24]. Abdominal adiposity is associated with increased concentrations of fibrinogen and PAI-1 activity and in subjects with GHD this high activity may be linked to their increased waist-hip ratio and elevated triglycerides might contribute to the elevated PAI-1 concentrations. The prothrombotic state, with reduced fibrinolytic activity may therefore contribute to an increased risk for atherothrombotic events in GHD patients.

**Homocysteine**

Increased homocysteine plasma levels are believed to be independent risk factors for cardiovascular events. Experimental and clinical evidence indicate that homocysteine is prothrombotic and therefore high concentrations are associated with vascular endothelial injury and dysfunction. Evans et al [25] 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 [26] 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; when treated with GH vs. placebo a significant decrease in homocysteine was noted. However, controversy as to the levels of homocysteine exist, as in another report, Abdu et al [27] 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 and in a group of adult-onset GHD patients, Sesmilo et al [26] recently found homocysteine at baseline to be negatively correlated with plasma levels of fol ate. These results in adults are in agreement with our finding of increased homocysteine concentrat ions and decreased folate and vitamin B12 levels in young untreated GHD adolescents, when compared to those of both treated GHD subjects and healthy controls [16].

**Endothelial dysfunction**

Endothelial dysfunction in GHD patients may be a direct consequence of the low levels of GH and IGF1 seen in these patients. GH and IGF1 stimulate the production and the release of nitric oxide in the endothelium and induce vasodilation. IGF-1 is a potent stimulator of the phosphatidylinositol 3-kinase /protein kinase B/endothelial NO synthase pathway. In healthy middle age volunteers GH treatment induced markers of increased NO bioavailability and enhanced circulating endothelial progenitor cells 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 [28]. However recent data suggest that GH may also regulate vascular reactivity through a direct action on the GH receptor in the vascular endothelium to increase endothelial nitric oxide synthase phosphorylation and activity [29]. 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 nitric oxide synthase.

Endothelial dysfunction may also be due to an indirect action in the atherogenic process induced by alterations in lipopropotein metabolism and the accumulation of lipoproteic remnants. In the post prandial phase these remnants are predominantly and highly atherogenic stimulating an increase formation of macrophages and the induction of vascular inflammation. Twickler et al [18,19] 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 [30] have demonstrated that untreated GHD adults 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. In GHD adolescents we have recently reported elevated serum levels of CRP, TNF-alpha and fibrinogen when compared to healthy controls [31], so that a pronounced inflammatory response seems to exist as early as in adolescence in GHD subjects. 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.

Endothelial cells were long considered inactive, acting only as a semi permanent barrier between blood and tissue. However, there is now increas ing data that support the role of the vascular endothelium in the maintenance of homeostasis and vascular tone and when activated the vascular endothelium changes the balance between mechan isms 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 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 [32] and how the flow-mediated endothelium-dependent vasodilation following hyperemia correlated with P-selectin in these patients, suggesting a role for GHD, as early as in adolescence, in the the development of the atherogenic process of GHD adults. An association between biochemical and biophysical markers of endothelial dysfunction has been detected in adults with hypopituitarism and severe GH deficiency [33].

**Adiponectin**

Adipose tissue was considered to be an organ for fat storage and mobilization, but recent evidence suggests 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 [34]. GHD adults and adolescents display many features of the metabolic syndrome includ ing 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 stud ies and has led to conflicting results [35,36]. We have found adiponectin concentrations to be decreased in untreated GHD adolescents when compared to both treated GHD subjects and to healthy controls; 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 untreated GHD adolescents [37].

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 mechan ism 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. In untreated GHD low adiponectin could possibly contribute to the increase secretion of VLDL-Apo B-100 and triglycerides, 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**

The impairment of cardiac performance in young GHD adults is manifested by a reduction of the left ventricular mass, an inadequate ejection fraction and in abnormalities of left ventricular diastolic filling [38]. In these patients GH administration has been shown to increase left ventricular mass and function [39]. 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 our adolescents had a normal left ventricular ejection fraction at rest, as well as normal pulmonary venous flow velocities. Cardiac mass or function on or off growth hormone therapy were also not different (15).

Colao et al [40] and Salerno et al [41] 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 [42] and ourselves [43], which demonstrated that cardiac growth may be impeded by severe childhood GHD; an increase in the left ventricular mass normalized for changes in body size was noted by Shulman following GH therapy, while we were unable to find differences in cardiac mass between GH treated and untreated GHD subjects.

**Intima-Media Thickness and Vascular Reactivity**

Increased intima-media thickness (IMT), with more atheromatous plaques in the carotid and the femoral arteries when compared to controls matched for age, sex and body weight was recently detected in GHD adults [44]. 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 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 recently shown to reverse early atherosclerotic changes, so that a decrease in carotid artery intima-media thickness [44] 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, this improvement in arterial performance is maintained long-term [45]. Colao et al [40] and ourselves [15,43] found no difference between the carotid artery IMT of untreated GHD adolescents and that of healthy controls or treated GHD subjects; however there was a tendency towards an increase in IMT in our untreated GHD adolescents [43] and in the patients of Colao et al [40] after discontinuing GH for 6 months. The flow-mediated endothelium-dependent increase in the diameter of the brachial artery during hyperemia was found by us to be lower in untreated GHD adolescents than in GHD treated subjects or healthy controls, while the blood flow increase of the brachial artery after hyperemia was greater in treated than in untreated adolescents [43].

**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 [46] 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 child ren 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. Carrol et al demonstrated that 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 [10].

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, was noted. Growth hormone replacement therapy increases lypolysis 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 [47] 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 and on IGF-1 titration could probably minimize changes in insulin sensitivity noted in adults during the first few months of growth hormone treatment.

## Conclusions

In conclusion, GHD subjects may present with an abnormal body composition, elevated fasting cholesterol and triglycerides levels and increased postprandial triglyceride concentrations and peripheral inflammatory and fibrinolytic markers have been found to be increased in GHD. Increased carotid artery intima media thickness and vascular rigidity, as well as abnormalities in cardiac mass and function have also been noted 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 on 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 mechan isms 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.

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