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The Impact of Growth Hormone Treatment on Lipid Profile in Pediatric Growth-Hormone Deficiency

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Abstract

The lipid metabolism is not a stand-alone entity, and the hormonal involvement in this system appears of great importance. Growth hormone (GH) has a central role among the endocrine mediators, as demonstrated by studies in GH-deficient individuals. Atherogenic lipid profile is frequently described in these patients, and treatment intervention may help normalize them. Studies have revealed that gender and genetic polymorphism in genes involved in the growth process and metabolism may explain the variability of treatment responses. Until recently, hormonal substitution was used solely to improve final adult height, but there are indications that long-term treatment is advised and necessary to maintain adequate functionality of intermediary metabolism and protect from early cardiovascular disease morbidity and mortality.

Keywords: growth hormone; lipid profile; pediatric deficiency.

1. Introduction

During the last 100 years, the life hope of populations has increased substantially. This comes with the dire consequences of ageing on multiple systems and organs, among which cardiovascular disease is the most important cause of ill health. Traditionally, lipid biomarkers have been the gold standard in predicting the onset of cardiovascular events and stratifying specific risks of an individual. Contemporary studies have expanded the view on metabolic biomarkers as the sole performers in the intricate process of cardiovascular pathology.

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Deficient or excess hormonal states have highlighted the crucial role hormones have in modulating lipid metabolism. Metabolic changes secondary to hormonal disturbances preclude the appearance of dyslipidemia, atherosclerosis and consequent cardiovascular events [1]. GH deficient individuals are characterized by increased fat mass, especially visceral fat, a known risk factor for cardiovascular disease morbidity and mortality. With increases in atherosclerosis, alteration in lipid metabolism and endothelial dysfunction, individuals with GHD have a surge in mortality [2]. Through lipolytic actions of GH, treatment can reduce fat mass deposition and improve metabolic profiles [3]. Understanding the mechanisms involved in the interplay between hormones and intermediary metabolism is essential in developing interventions and refining the current treatment in individuals with GH deficiency.

2. Lipid metabolism and gh-igf1 axis interactions

The anabolic capacity of GH, most evident in the postabsorptive and fasting states, is mediated either directly or indirectly through increases in circulating levels of free fatty acids (FFAs), ketone bodies, insulin-like growth factor 1 (IGF-1), insulin and glucose [3,4]. According to the "feast and famine cycle" hypothesis, insulin is the most critical anabolic hormone during the feast, and GH (growth hormone) is the primary anabolic hormone during famine and stress [5]. In the peri-prandial period, GH induces stimulation of insulin and IGF-1, increasing the growth of lean body mass (LBM), adipose tissue, and glycogen reserve. During fasting and other catabolic states, through mobilization of lipid fuels, preferentially stimulating upper body lipolysis, and modulating adipose tissue lipogenesis, GH alleviates proteins and carbohydrates stores from immediate oxidative demands, thereby effectively conserving these substrates [3,4,5].

Age-related changes in cholesterol metabolism corresponding with a rise in LDL-C over the years in both men and women have been attributed to a gradual decline in GH secretion and circulating IGF-1 levels. It has been demonstrated that GH induces LDLr at the renal and hepatic levels, diminishing total serum cholesterol levels [1]. LDL is essential in determining plasma cholesterol, evidenced by patients with familial hypercholesterolemia, where LDLr is reduced by 50% in heterozygotes and absent in homozygous forms [6]. Removal of cholesterol from the body is done by conversion into bile acids. Here more, animal studies have demonstrated that GH regulates the activity of the rate-limiting enzyme involved in bile acid synthesis [1]. In humans, the effects of GH in lowering cholesterol were not related to stimulation of bile acid synthesis, suggesting species differences in the action of GH on lipid metabolism exist [6].

Adipose tissue is a target tissue for GH action, with the location-dependent expression of the GH receptor, preferentially located in the abdominal fat [7]. GH stimulates adipocyte differentiation. Patients with GH deficiency have fewer adipocytes, which is rectifiable by the hormonal intervention [1]. Although the number of adipocytes is decreased, the volume and lipid content increase in this category of patients, and GH intervention can rectify these abnormalities [7].

In terms of body composition, visceral fat rather than total adiposity has been correlated with growth hormone secretion. GHD patients have increased visceral fat, a potent cardiovascular and metabolic risk marker, and therapy reduces visceral fat [8].

Moreover, levels of adiponectin in GH deficient individuals are lower when compared with levels in normal individuals. Adiponectin, secreted by adipocytes, regulates fatty acid metabolism that improves insulin sensitivity and offers a cardioprotective effect [1].

Also, lipolysis is induced by GH by increasing the expression and activity of hormone-sensitive lipase [1]. The mechanism by which lipolysis is stimulated in GHD individuals after treatment is by increasing responsiveness to epinephrine acting on β2-adrenoreceptors on adipocytes [7]. In addition, by reducing lipoprotein lipase activity, GH impairs the accumulation of lipids in human adipose tissue [7].

Cellular insulin response also requires preceding GH exposure [1]. Additionally, GH counter regulates insulin by antagonizing its hepatic and peripheral effects on glucose metabolism and increasing FFA flux and uptake [5]. Furthermore, the substrate competition hypothesis states that GH exposure, by the increase in fatty acid oxidation, interferes with glucose uptake in muscle cells and promotes endogenous glucose production through various mechanisms. Lastly, GH induces insulin resistance through both FFA-dependent and FFA-independent mechanisms [5].

Leptin is a hormone synthesized in adipose tissue that acts through binding to hypothalamic receptors and prompting a cerebral response of satiety. It mediates lipid metabolism and is presumed to be inhibited by GH action [1].

GH and IGF-1 may have distinct effects on the development of the metabolic syndrome. Although IGF-1 is a mediator of GH action, its role in metabolism is exerted through different mechanisms. In a study performed on healthy individuals without GH/IGF-1 axis abnormalities and using factor analysis that enables clustering of variables within a population, authors found an effect IGF-I, but not for GH in men, on MetS (metabolic syndrome) factors (lipids, waist circumference and glycaemia). In women, a role for GH was found in waist circumference and glycaemia, and IGF-I on lipids, waist circumference and glycaemia. The absolute values and the balance between GH and IGF-1 are essential in modulating cardiovascular and diabetes risk profiles. Also, sex hormones may explain gender-related differences in risk profiles [9].

IGF-1 also has a role in fat metabolism by negatively mediating cellular uptake of HDL. HDL has been suggested to have an anti-atherogenic role and reduce CVD risk through reverse cholesterol transport. HDL acquires excess cholesterol from peripheral tissues during this process and then transports it to hepatocytes. It is converted into bile acids and subsequently excreted in faeces, effectively removing excess cholesterol from the body [1].

Regarding the vascular system, GH and IGF1 stimulate the production of nitric oxide (NO). NO is essential in endothelial function and vascular contractility. In addition, NO protects the vessels from atherosclerotic plaque formation by reducing platelet adhesion and mediating lipoxygenase activity and LDL-cholesterol oxidation [10].

3. Metabolic And Genetic Alterations In Gh Deficient Patients

Prolonged GH deficiency due to absent lipolytic and protein anabolic effects leads to a state similar to metabolic syndrome [5]. This state is characterized by dyslipidemia, insulin resistance, hemostatic alterations, oxidative stress and chronic inflammation [11].

Concerning glucose metabolism, a pervasive phenomenon in GH deficient patients is fasting hypoglycemia, especially in young, lean children. Moreover, GHD children are hyperresponsive to insulin, making a recovery from hypoglycemia in response to iv insulin more cumbersome. Surprisingly, GHD adults have an increased prevalence of impaired glucose tolerance despite hyperinsulinemia. Although unclear, the root mechanism behind insulin insensitivity is increased FFA flux from visceral fat [5]. Insulin resistance in both deficient and substituted GH patients may be explained by an increased influx of free fatty acids due to excess visceral adipose tissue in untreated patients and increased lipid oxidation in the former [11]. Extensive studies have suggested an increased incidence of type 2 diabetes in predisposed GH-treated individuals [11].

In adult life, the lipoprotein metabolism is altered in GHD individuals, increasing total and LDL cholesterol and hypertriglyceridemia. Dyslipidemia has been observed with similar frequencies in patients with onset of GH deficiency in childhood or adulthood and correlates significantly with the duration and severity of the disease [10]. In addition, lipid levels appear to be inversely associated with IGF-1 concentration [3]. However, studies in children have reported discrepant results with no change [12], only marginal changes or an increase in total and LDL cholesterol, with no changes in HDL and triglyceride levels [11,13].

In a study examining the cardiovascular alterations in GH-deficient adolescents, authors did not find echocardiographic changes in cardiac mass and function in GHD individuals compared to controls. Still, GHD adolescents had cardiovascular risk factors such as dyslipidemia, with increased LDL-C and lipoprotein (a), but TC, HDL-C and TG serum levels similar to that of controls, which could indicate increased cardiovascular morbidity over time. In addition, abdominal obesity leads to increased secretion of VLDL in GHD patients and, in association with decreased clearance rates, can result in altered lipid profiles. Lipoprotein (a) is an atherogenic and thrombogenic lipoprotein, and it is used as a marker for evaluating the risks of cardiovascular events. Also, the authors divided GHD patients into children who had received GH treatment and subsequently discontinued it and children who never received GH and noted no echocardiographic or lipid profile difference between groups [14]. This suggests that the effects of GH treatment are not long-lasting.

There is an open debate about whether these risk factors may predispose GH children to increased cardiovascular morbidity or appear secondary to supraphysiological levels of GH and IGF-1 secondary to treatment.

A Korean study aiming to assess the association between height and lipid profiles among adolescents and adults and encompassing more than 5200 adolescents with a median age of 15 years, had found associations between TC and LDL-C and height in both adolescent boys and girls and an inverse association between HDL-C and size only in boys. There were gender-related differences with increased severity of dyslipidemia in shorter boys. Because of the cross-sectional design, causality between short stature and dyslipidemia could not be inferred. Possible explanations for these findings stem from the role of GH and thyroid hormones in both bone growth

and lipid metabolism. Furthermore, individuals with high growth velocity have an increased cholesterol consumption to adequately produce cell membranes and steroid hormones, which have cholesterol as an essential component. Besides that, the skeletal system is an important endocrine organ involved in lipid metabolism. Osteoblasts decrease the levels of lipoproteins and non-esterified free fatty acids by using fatty acids as an energy source. Adiponectin expression in adipocytes is also increased by osteoblast-derived osteocalcin and, in turn, increases HDL-c concentrations and lowers serum TG levels by enhancing VLDL catabolism in skeletal muscle adipose tissue [15].

A genome-wide association study reported an association between a genetically determined shorter height and an increased risk of CAD, partially explained by the association between a decrease in size and adverse lipid profiles. However, shared biological processes (among whom GH signalling, STAT3 pathway and IGF-1 signalling are described) that determine height and atherosclerosis development may be of graver importance. They observed a relative increase of 13.5% in CAD risk per 1-SD decrease in genetically determined size [16].

Genetic polymorphisms in genes related to lipid metabolism were also demonstrated to contribute to individual differences in baseline serum lipid profiles in adults with GHD. Besides, polymorphisms in the APOB and PPARG genes influenced the GH treatment response in TC and LDL-C. APOB has a role in the catabolism of lipid-rich lipoproteins in the intestine and liver. More than 50% of the variation in serum levels can be explained by genetic determination. GH exerts a direct role in producing lipoproteins containing APOB (VLDL, IDL, LDL) and increases their removal by upregulating hepatic LDLr and modifying VLDL composition. The PPARG gene controls adipocyte differentiation and function and is involved in lipid metabolism [17].

A study investigating the association between polymorphisms in GHR and changes in height SDS and lipid metabolism during GH treatment in GHD children found that the Leu544Ile polymorphism of the GHR gene was associated with increased cholesterol levels in boys with GH deficiency both before and after treatment. The GHR is requisite for GH signalling. Located in the intracellular region of the GHR, the Leu544Ile is an SNP that influences lipid metabolism in patients with familial hypercholesterolemia. [18].

The JAK2-STAT5 pathway, which transmits signals from the GH receptor, has also been linked to the regulation of lipid profile in GH deficiency. In pediatric patients, SNPs in the STAT5B gene significantly contributed to higher serum TC or non-HDL-C levels before and after GH treatment for 12 months [19].

Familial hypercholesterolemia is a genetic disorder caused by mutations in genes involved in LDL-C metabolic pathway. Children with this disorder have increased levels of LDL-C and positive family history of CVD or dyslipidemia and are predisposed to premature cardiovascular disease. Due to its high prevalence worldwide, of 1/500 people, FH can sometimes be present concurrently with GH deficiency. In FH, hypercholesterolemia negatively influences growth by disturbance of cell growth and metabolism, accumulation and subsequent morphological alteration of pituitary cells and promoting hypothalamic inflammation with functional interference. Thus, GH and FH have a bidirectional relationship, with each negatively affecting the outcomes of the other clinical entity. By improving lipid profile, GH treatment could lower the statin requirements in these patients. [18]. A caveat of this reduction is the capability to express LDLr as a prerequisite for GH's LDL

lowering effect. Homozygous FH patients who demonstrate absent LDLr expression do not benefit from this treatment [6].

4. Growth Hormone Treatment And Effects On Lipid Metabolism

Since the origins of atherogenic disease are attested to begin in childhood, and there is evidence of CVD disease in adults with untreated GHD, it is paramount to address metabolic disturbances starting from an early age [11].

Although glucose tolerance and insulin sensitivity are altered during GH substitution, proportionally with dose and especially at the beginning of therapy, secondary to an increase in lipid oxidation, it also appears to gradually normalize secondary to improvement in body composition, physical fitness and reduction of dose throughout therapy [5].

An improvement in lipid profile with a reduction in total cholesterol, LDL cholesterol, and triglyceride levels with a concomitant increase in HDL has been reported in GHD children after 1-2 years of treatment [13], [12]. A study comparing GH treatment effects in mildly GHD children and controls stated that although the baseline lipid profiles did not differ, at the end of the six-month trial period, statistically significant differences in Apo-B, LDL, and smaller lipoparticles (LDL-3 and non-HDL) in GH-treated children compared to untreated GH-sufficient short children were observed [19]. These beneficial effects on metabolic status appear to wane in adolescents discontinuing GH treatment [11]. Another study supporting these findings found beneficial results of GH treatment in both girls and boys with GHD but with essential gender differences. Statistically significant differences in mean cholesterol and LDL-C decreases, increases in HDL-C and Apo(a) with declines in TC/HDLC and Apo-B/Apo-AI ratios were observed only in boys. Triglycerides and other apolipoproteins showed no modifications from baseline. Discontinuation of treatment also leads to negative alterations on lipid profiles, suggesting treatment maintenance after cessation of linear growth is needed to maintain normal metabolism [21].

Changes in height SDS induced by GH treatment correlated significantly with reductions in body fat and excess body weight (deviation from mean weight adjusted for size, age and sex) but not with changes in LDL cholesterol. These results demonstrate, first of all, that GH is a mediator of the interaction between growth and adiposity in childhood. Secondly, LDL cholesterol levels differed from height and adiposity at baseline and even after treatment. Even though GH induces a decrease in LDL-C, it does that directly, in a different way than the stimulation of anthropometric processes that are IGF-1 mediated [21].

Not long ago, GH treatment was discontinued when the final height was reached, with no regard for beneficial metabolic outcomes. However, studies have reported an increased number of metabolic comorbidities in patients with childhood-onset GH deficiency soon after cessation of treatment, at a younger age and lower median BMI: 23.5 kg/m2 for those with hypertriglyceridemia, 26.0 kg/m2 for those with NAFLD, 20.9 kg/m2 for those with hypercholesterolemia and 27.2 kg/m2 for those with DM. Around a third of patients experienced a cluster of more than two comorbidities [20]. Hitherto, insurance subsidized treatment is not given on a life-long basis. Such findings may change the perspective of the current view on the impact of GH deficiency and may modify

current practice.

5. Conclusion

GH exerts several essential actions in the regulation of lipid metabolism. Deficient children experience metabolic sequelae starting from an early age which perpetuate in adulthood and possibly lead to cardiovascular morbidity and mortality. There is considerable individual and gender-related variability in treatment response that may be adequately assessed in the future by genetic studies. Currently, the emphasis of the research is on adults with GHD and cardiovascular outcomes. Still, long-term prospective studies on GH deficient patients starting from early ages could help assess whether alteration in risk factors such as lipid profile in childhood translates into increased morbidity and mortality later in life and whether treatment intervention and maintenance into adult life would help alleviate the outcomes.

6. List of Abbreviations

APOA, apolipoprotein A; APOB, apolipoprotein B, CAD, coronary artery disease; CVD, cardiovascular disease; DM, diabetes mellitus; FFA, free fatty acid; FH, familial hypercholesterolemia; GH, growth hormone; GHD, growth hormone deficiency; GHR, growth hormone receptor; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; IGF-1, insulin growth factor-1; JAK2, Janus kinase 2; LBM, lean body mass; LDL-C, low-density lipoprotein cholesterol; LDLr, low-density lipoprotein receptors. MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NO, nitric oxide; SD, standard deviation; PPARG, recombinant protein of human peroxisome proliferator-activated receptor-gamma; SNP, single nucleotide polymorphism; STAT3, Signal .

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