Metabolic implications of GH treatment in small for gestational age

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Abstract

Fetal growth retardation is associated with decreased postnatal growth, resulting in a lower adult height. In addition, a low birth weight is associated with an increased risk of developing diseases during adulthood, such as insulin resistance, type 2 diabetes mellitus, hypertension, dyslipidemia, and cardiovascular diseases. Children with persistent postnatal growth retardation, i.e., incomplete catch-up growth, can be treated with human GH. The GH/IGF-I axis is involved in the regulation of carbohydrate and lipid metabolism. The question of whether treatment with GH in children born small for gestational age (SGA) has long-term implications with respect to glucose/insulin and lipid metabolism has not been answered yet. In this article, the available data are reviewed.

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Introduction

Growth hormone (GH) is known to have metabolic effects. It antagonizes insulin effects by increasing hepatic gluconeogenesis and glycogenolysis, thereby decreasing peripheral glucose consumption. These effects also attribute to the lipolytic effects of GH (1).

Acute GH administration elicits a decrease of the glucose uptake in muscles and glucose oxidation, while lipid oxidation increases, resulting in an increase of the blood levels of free fatty acid (2, 3). The lipolytic effect of GH depends on the fat localization. The highest lipolytic effect is exerted at the abdominal fat tissue. This explains the increased amount of abdominal fat deposits in patients with a GH deficiency.

In turn, disturbances of the carbohydrate metabolism can also modulate the secretion of GH. Patients with type 1 diabetes mellitus display a GH profile characterized by increased GH baseline levels, increased GH pulse amplitude, and by a decreased GH pulse periodicity (4). The high GH pulse amplitude in patients with type 1 diabetes is thought to be related to changes in insulin sensitivity, while the high GH baseline levels are associated with increased lipolysis and ketogenesis (5). In adults after prolonged fasting and in children with malnutrition, a similar increase of the GH secretion is observed, which may be mediated by a hypoinsulinemic state (6, 7). The increased GH release induces lipolysis, which in malnourished children may be the metabolic adaptation to achieve energy in order to survive.

Adults with either GH deficiency (GHD) or acromegaly with a GH overproduction reveal insulin resistance that develops due to increased lipolysis as the result of exposure to high amounts of GH. Visceral fat deposition is decreased in these patients (8). In contrast, patients with GHD will eventually develop insulin resistance as a result of increased visceral fat deposition (9).

Insulin-like growth factor-I (IGF-I), named as a result of its effects as an insulin sensitizer, is produced and secreted in the liver as well as in many organs. GH plays a major role in the regulation of the production and release of IGF-I in the liver. The IGF-I peptide has a structure similar to those of proinsulin and insulin molecules.

In contrast to the insulin antagonist effects of GH, IGF-I induces hypoglycemia by the suppression of the hepatic glucose production and stimulation of the peripheral glucose uptake. Whether IGF-I can influence lipid metabolism is not clear. Recently, Simpson et al. (10) described no direct effect on lipolysis, while the IGF-I challenge did reduce the hepatic glucose production and increased the peripheral glucose uptake.

The IGF-I half-life is only 10–12 min. By binding to carrier proteins, the IGFBPs family, bioavailability and bioactivity of IGF-I are extended. The levels of IGFBP-3 and IGFBP-1 are regulated by GH and insulin respectively (11). In turn, the numbers of GH receptors

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The important role of insulin in the GH/IGF-I axis makes the axis vulnerable for nutritional variations. During a hypoinsulinemic state of acute fasting, IGF-I and IGFBP1 levels will decrease. In the longer term, due to the feedback mechanism, the low IGF-I levels initiate an increase of GH in order to restore IGF-I levels. These high GH levels induce lipolysis and ketogenesis. When the fat depots are completely exhausted, GH release will drop into a complete hyposomatotropic state (7).

In conclusion, GH has insulin antagonist effects on the glucose metabolism in combination with a lipolytic effect, especially at the level of abdominal fat depots. In contrast, IGF-I has a strong insulin-like activity on glucose metabolism, while there is no direct effect of IGF-I on lipid metabolism.

Although IGF-I and GH have antagonistic effects with respect to insulin activity, both the primary IGF-I deficiency and the GHD syndrome are associated with insulin resistance.

Metabolic consequences of being born small for gestational age (SGA)

Intrauterine growth retardation or fetal growth retardation are the terms usually applied to fetuses with a lower birth weight than expected for gestational age. In general practice, infants with reduced size at birth are described as being born SGA. There are many definitions of being born SGA with cut-offs at the tenth centile, third centile, or below 2 S.D. from the mean after adjustment of gestational age and gender. In addition, one may distinguish small for weight, for length, or for head circumference. Intrauterine growth retardation is the term usually applied to fetuses with a lower birth weight than expected for gestational age.

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GH treatment in short children born SGA

Born SGA and incomplete or lack of postnatal catch-up growth at the age of 4 years is an indication to treat with GH (25). Many studies of GH treatment in short SGA children have now been performed. Studies till final height show that GH treatment is effective to increase adult stature.

Previous studies in patients with Turner syndrome, also a non-GH-deficient indication for GH treatment, reported a reversible insulin insensitivity during GH treatment (26). In children born SGA, the treatment
with GH results in a reduction of insulin sensitivity as well (27). During OGTT, higher fasting insulin and glucose stimulated insulin levels can be observed, which are increasingly elevated with a higher GH dose. Although the glucose and HbA1c levels show a slight increase, they remain in the normal range (27). Similar increases in glucose and insulin levels are seen in large groups of SGA children on GH treatment as described in the US trial and KICS study (28).

Recently, data have been published on carbohydrate metabolism in adults treated with GH, several years after discontinuation of GH. These data show that in patients treated for a mean period of 7.3 years with GH, the carbohydrate metabolic status 6.5 years after GH discontinuation is comparable with untreated young adults born SGA (29). However, this study did not use the hyperinsulinemic–euglycemic clamp technique, which may be necessary to find differences in insulin sensitivity during young adulthood.

The question is still whether the long-term hyperinsulinemia as observed during GH treatment can have effects in later life. The only conclusion we can draw from the available data is that after GH treatment, the carbohydrate metabolism in the GH-treated SGA adult may be similar to the untreated SGA adult. However, during infancy and childhood short SGA children have a favorable metabolic profile. This favorable metabolic profile may turn unfavorable when the child is treated with GH for its short stature. The advantage of gaining height should be balanced against the possible disadvantage of metabolic damage whenever GH therapy is considered in a short child born with a low birth weight.

Disclosure

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