

Leading Article

Effects of Growth Hormone on Visceral Fat and Insulin Sensitivity

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Obesity is characterized by marked decreases of both spontaneous and stimulated growth hormone (GH) secretion [1], variable levels of circulating insulin-like growth factor I (IGF-I) [2,3], and insulin resistance [4]. Correspondingly, GH-deficient adults are commonly obese and have similar clinical features to obese subjects, including abnormalities of body composition such as increased abdominal and visceral fat mass, glucose intolerance, and insulin resistance [5].

The mechanism that results in low GH levels in obesity is not well understood, nor is it clear whether the relationship with visceral obesity is causal. By contrast, many studies have demonstrated that the beneficial effects of GH treatment on body composition in GH-deficient adults are primarily mediated by its lipolytic actions [6,7]. Although these studies differ considerably in terms of participant age, the presence or absence of multiple pituitary hormone deficiency, whether GH deficiency was of childhood or adult onset, and the various study methods employed, the results of the effects of GH on body composition are remarkably consistent. Using various methods to assess body composition, it has been shown that mean lean body mass increases by 2–5.5 kg in both childhood- and adult-onset GH-deficient adults compared with untreated controls [8–10]. Nevertheless, despite these positive effects on body composition, the effects of GH on glucose metabolism are more variable. Short-term studies have shown a reduction in insulin sensitivity associated with increases in

plasma glucose and insulin concentrations [8,11]. Long-term studies have been more variable, with some showing a gradual improvement [9,10,12] and others reporting a persistent impairment in insulin sensitivity, despite an increase in lean body mass and a reduction in fat mass [13–15]. These discrepancies may be related to differences in the severity of GH deficiency in the adults studied, body composition, the GH doses used, and the duration of these studies. The effects of GH on lipolysis in GH-deficient patients have thus led to the experimental supplementation of GH in viscerally obese GH-sufficient subjects. These studies have tested the hypothesis that low levels of GH contribute to central obesity and its related metabolic abnormalities, with the predicted results of reductions in intra-abdominal fat and improved glucose metabolism following GH therapy.

The present report reviews several human physiological studies characterizing the effects of GH on visceral fat and insulin sensitivity in obese subjects and in GH-deficient patients. As abdominal obesity and insulin resistance are central components of the metabolic syndrome [16], these “high risk” subjects are also discussed, and potential approaches for future exploratory intervention studies are suggested.

GH treatment in obese subjects

The regulation of the GH/IGF-I axis in obesity is complex and remains somewhat controversial. Although primary GH deficiency leads to central adiposity, visceral obesity

Table 1. Recent studies examining the effect of GH treatment on glucose metabolism and body composition in obese subjects.

First author [reference]	Year	n	Mean GH dose per day	Duration (weeks)	Effect of GH on glucose metabolism and body composition
Johannsson [18]	1997	30	9.5 µg/kg	40	↔Gluc ↔Ins ↑Si ↓FM
Kim [41]	1999	24	9.5 µg/kg	12	↔Ins ↓weight ↓FM
Norrelund [42]	2000	15	18.2 µg/kg	4	↑Ins ↑C-pep ↓weight
Munzer [43]	2001	110	8.6 µg/kg	26	↔FM
Nam [33]	2001	18	7.7 µg/kg	12	↓Gluc ↓AUCIns ↑Si ↓FM ↓weight
Albert [19]	2004	59	0.4-0.6 mg	24	↔Gluc ↔Si ↓FM ↓weight
Herrmann [34]	2004	25	9.5 µg/kg	72	↔Gluc ↔Si ↔FM
Franco [20]	2005	40	0.67 mg	52	↑Si ↓FM

AUCIns: area under the insulin curve; C-pep: C-peptide; FM: fat mass; GH: growth hormone; Gluc: fasting plasma glucose; Ins: fasting plasma insulin; Si: insulin sensitivity.

per se also results in a secondary reduction in serum GH levels [2,3]. The difference in the pathophysiology of the two conditions is predominantly reflected by the variable IGF-I levels. In primary GH deficiency, IGF-I levels are usually low but can also be within the normal range [17]. In contrast, these levels may be normal, high, or low in obesity [2,3]. Nevertheless, the reasons for the abnormal GH/IGF-I axis in obesity and the mechanisms resulting in this abnormality have yet to be clarified. Some of the theories on the cause of the altered GH/IGF-I axis in obesity involve increased levels of leptin, insulin, free fatty acids, and IGF-I. Since both spontaneous and stimulated GH release have been shown to increase in obese subjects after administration of acipimox, an anti-lipolytic agent [2], it is thought that free fatty acid contributes to the low GH levels through feedback inhibition of pituitary GH secretion. However, the quantitative contribution of elevated free fatty acid concentrations to altered GH physiology in obesity remains unclear.

The association between obesity and reduced GH secretion has prompted investigators to examine the potential role of GH treatment in obese subjects (Table 1). In a study by Johannsson et al., 9 months of GH treatment (9.5 µg/kg) in 30 obese men significantly reduced abdominal subcutaneous and visceral fat, and this was

associated with improvements in insulin sensitivity [18]. In contrast, studies by Albert and Mooradian [19] and Franco et al. [20], using GH doses of 0.4–0.6 mg/day and 0.67 mg/day, respectively, reported reductions in body fat and abdominal visceral fat in obese men and women. However, improvements in insulin sensitivity were not consistently observed, which may reflect the possibility of counteracting lipolytic effects induced by these doses of GH [20]. Thus, a beneficial effect on insulin sensitivity through reductions in visceral fat may be opposed by increased stimulation of lipolysis in subjects treated with high doses of GH. This model parallels that observed in subjects with acromegaly, in whom the effects of elevated GH levels induce lipolysis in the visceral fat depot that probably outweighs any potential insulin-sensitizing effects of GH-induced IGF-I.

Currently, the available literature does not appear to support the use of GH therapy to achieve metabolic benefits in obesity in the absence of true GH deficiency. This is because the possible metabolic benefits of visceral fat loss may be outweighed by the anti-insulin effects of the doses of GH employed in these studies. Nevertheless, the normalization of GH levels after weight reduction in obesity [2] implies that low GH levels are probably more of a consequence rather than the cause of central obesity.

Table 2. Recent studies in GH-deficient adults examining the effect of GH replacement on glucose metabolism and body composition.

First author [reference]	Year	n	Mean GH dose (mg/day)	Duration (months)	Effect of GH on glucose metabolism and body composition
Hana [10]	2004	17 (AO/CO)	0.31	12	↔Gluc ↔Ins ↔Si ↓FM ↑LBM
Bülöw [9]	2004	11 (CO)	0.4–0.6	12	↔Gluc ↔Ins ↔Si ↓FM ↑LBM
Giavoli [12]	2004	20 (AO)	0.3	12	↑Gluc ↑Ins ↓Si ↓FM
Spina [44]	2004	24 (AO/CO)	0.84	12	↔Gluc ↔AUCgluc ↑Ins ↔AUCins ↓Si ↓FM
Spina [15]	2005	17 (AO/CO)	0.72	24	IGT ↑Ins ↓Si ↓FM ↓WHR
Arwert [13]	2005	23 (CO)	0.40–0.97	120	↑Gluc ↑HbA1c ↑LC ↑AC ↑WHR
Boguszewski [14]	2005	18 (AO/CO)	0.2	12	↔Gluc ↑Ins ↓Si ↓FM ↑LBM
Yuen [29]	2005	13 (AO)	0.1	12	↓Gluc ↔Ins ↑Si ↔FM ↔LBM

AC: arm circumference; AO: adult-onset GH deficiency; AUCgluc: area under the glucose curve; AUCins: area under the insulin curve; CO: childhood-onset GH deficiency; FM: fat mass; GH: growth hormone; Gluc: fasting plasma glucose; HbA1c: hemoglobin A1c; IGT: impaired glucose tolerance; Ins: fasting plasma insulin; LBM: lean body mass; LC: leg circumference; Si: insulin sensitivity; WHR: waist-hip ratio.

GH replacement in GH-deficient adults

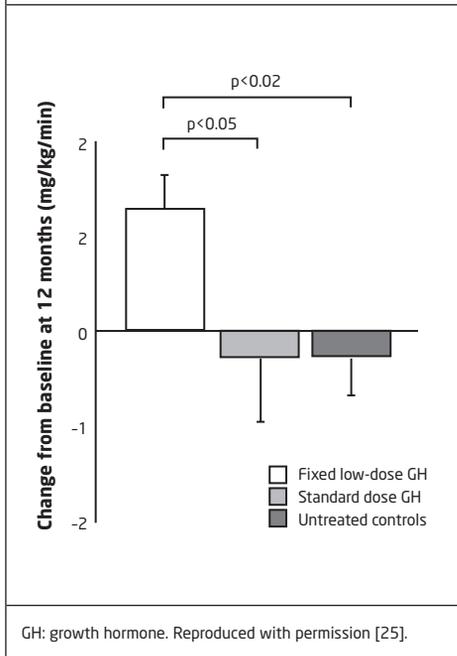
A number of studies have shown improvements in the abnormal features of body composition in GH-deficient adults over time following GH replacement [13–15]. In individuals who are GH-deficient, total body water is reduced by approximately 2.4 kg in males and 3.2 kg in females compared with the predicted total body water values for weight [21]. Furthermore, studies of GH replacement in these subjects have consistently shown replenishment of total body water of around 2–4 kg [22,23], which appears to occur within the first few weeks of GH replacement [24].

Standard doses of GH replacement in GH-deficient adults lead to consistent reductions in truncal fat, but with variable changes in insulin sensitivity [10,25,26]. Hana et al. recently reported the effects of standard dose GH replacement therapy in adults with GH deficiency [10]. The GH dose was adjusted to normalize serum IGF-I levels according to sex and age, and the subjects received a mean GH dose of 0.31 mg/day (range 0.13–0.67 mg/day). Over the 12-month study period, significant reductions in truncal fat were observed; however, no concomitant change in insulin sensitivity was observed. In keeping with these data, Bülöw et al. reported similar findings in a group of patients with radiation-induced GH deficiency following childhood cancer [9].

The authors did not observe any changes in insulin sensitivity in these patients despite reductions in visceral adiposity following 12 months of GH treatment (**Table 2**).

From our previous physiological experiments in young healthy adults [27,28], we hypothesized that a low GH dose could exert beneficial effects on insulin sensitivity in GH-deficient adults. To test this hypothesis, we recently conducted a study of 25 GH-deficient adults who were randomized to receive either a fixed low dose of recombinant GH (0.1 mg/day) or a standard GH dose (the GH dose titrated to normalize serum IGF-I levels according to sex and age; mean GH dose administered, 0.5 mg/day) over 12 months [29]. In contrast to the standard GH dose, low-dose GH reduced fasting blood glucose levels and improved insulin sensitivity, as assessed by the hyper-insulinemic–euglycemic clamp (**Figure 1**). In contrast, in those subjects treated with the standard GH dose, insulin sensitivity was unchanged but significant increases in free fatty acid levels were noted, implying that this GH dose induced lipolysis. These observations suggest that IGF-I deficiency is probably the major determinant of insulin resistance in adults with GH deficiency, and that while standard and high GH doses exert beneficial effects on visceral adiposity, they are not likely to improve insulin sensitivity because of their lipolytic

Figure 1. Changes in insulin sensitivity (glucose infusion rate derived from hyperinsulinemic-euglycemic clamp studies) after 12 months of fixed low-dose (0.1 mg/day) and standard dose (mean 0.5 mg/day) GH replacement in GH-deficient adults.



effects. In contrast, the low GH dose appears to improve insulin sensitivity and, over a longer period of administration, could potentially lead to reductions in circulating insulin levels and visceral fat.

GH treatment in the metabolic syndrome

The metabolic syndrome shares many similarities with adult GH deficiency syndrome [30], with the central features in both of these syndromes being abdominal/visceral obesity and insulin resistance [31,32]. These similarities, and the association of central adiposity with reduced GH secretion [1], have prompted several investigators to explore the potential effects of GH treatment on body composition and glucose metabolism in subjects with the metabolic syndrome. In a study by Nam et al., the authors demonstrated that 6-day administration of GH (9 µg/kg/day) over a 12-week period improved insulin

sensitivity and fat distribution in 18 obese type 2 diabetic subjects [33]. In contrast, more recently, Herrmann et al. demonstrated that co-administration of GH (9.5 µg/kg/day) with metformin over 18 months did not affect body composition and glucose metabolism in subjects with the metabolic syndrome [34]. In another study, Attallah and Hoffman reported that 40-week administration of GH (8 µg/kg/day) reduced visceral adipose tissue [35]. Furthermore, the addition of pioglitazone, a peroxisome proliferator-activated receptor-γ agonist with insulin-sensitizing effects, prevented the worsening in fasting plasma glucose levels associated with the lipolytic effects of GH by enhancing endogenous insulin sensitivity in abdominally obese glucose-intolerant adults.

These divergent results may be explained by the differences in GH doses used and the duration of GH administration. We have recently reported data from a pilot study examining the effects of low-dose recombinant GH therapy (1.7 µg/kg/day) on glucose tolerance in subjects with impaired glucose tolerance and concurrent features of the metabolic syndrome [36]. Following an oral glucose tolerance test, we found that low-dose recombinant GH therapy reduced the area under the glucose curve but did not affect the area under the insulin curve, suggesting that such therapy could improve peripheral glucose disposal. However, the hypothesis that low IGF-I levels may contribute to the reduction in pancreatic β-cell function in subjects with metabolic syndrome, and that this reduction in β-cell function could be improved with low-dose GH therapy, requires confirmation with further exploratory studies.

Adverse effects and potential risks of GH replacement

Evidence from several large multicenter clinical trials has shown that GH replacement is generally safe and well tolerated [37], and that the adverse effects arise mainly from the use of high GH doses. Individuals most at risk are older and more obese, with the largest IGF-I response upon GH replacement [38]. The commonly encountered side effects arise

from the anti-natriuretic action of GH, which precipitates fluid retention, and manifest as dependent edema, paresthesia, and carpal tunnel syndrome. In addition, arthralgias involving small or large joints are frequently observed, although there is usually no evidence of effusion or inflammation, and no abnormalities detectable on X-rays [31]. These side effects were frequently reported in earlier studies employing supraphysiological doses of GH that were based on pediatric experience. However, these side effects are generally mild and resolve in the majority of patients, either spontaneously or with dose reduction [39]. Indeed, more recent trials employing lower GH doses have seen a reduction in the incidence of such adverse events [40].

Conclusion

The GH/IGF-I axis plays an important role in the balance of normal insulin sensitivity and the development of insulin resistance. Supraphysiological doses of GH reduce visceral fat but tend to impair insulin sensitivity in humans. Low-dose GH therapy could potentially improve insulin sensitivity without affecting body composition, which may be related to its ability to increase free IGF-I generation and the lack of lipolytic actions. The ability of the low GH dose in enhancing insulin sensitivity raises the possibility that this may be the optimal GH replacement dose in improving insulin sensitivity in GH-deficient patients, particularly in those with concurrent obesity and glucose intolerance, in whom the risk of cardiovascular disease is substantially increased. At present, there are sufficient data to justify further exploratory trials using low-dose GH therapy in the treatment and prevention of type 2 diabetes in both “high-risk” glucose intolerant subjects with the metabolic syndrome and GH-deficient adults.

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