Review

Effects of Growth Hormone Administration in Human Obesity

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Abstract

SHADID, SAMYAH AND MICHAEL D. JENSEN. Effects of growth hormone administration in human obesity. *Obes Res.* 2003;11:170–175.

Objective: To summarize the reports in the literature regarding the effect of growth hormone (GH) treatment of obesity.

Research Methods and Procedures: Clinical trials of GH treatment of obese adults were reviewed and summarized. Specifically, information regarding the effects of GH on body fat and body fat distribution, glucose tolerance/insulin resistance, and adverse consequences of treatment were recorded.

Results: GH administered together with hypocaloric diets did not enhance fat loss or preserve lean tissue mass. No studies provided strong evidence for an independent beneficial effect of GH on visceral adiposity. In all but one study, glucose tolerance during GH treatment suffered relative to placebo.

Conclusion: The bulk of studies indicate little or no beneficial effects of GH treatment of obesity despite the low serum GH concentrations associated with obesity.

Key words: glucose tolerance, body composition, visceral fat, insulin, free fatty acids

Introduction

Obesity is associated with a number of endocrine and metabolic abnormalities. These include, but are not limited to, insulin resistance (which is correlated with visceral adiposity) and decreased serum growth hormone (GH)[1] concentrations. The mechanism of the low GH in obesity is not understood nor is it clear whether the relationship with visceral obesity is causal. Nevertheless, the beneficial effects of GH on lipolysis and on fat distribution found in patients with GH deficiency have led to experimental supplementation of this hormone in viscerally obese patients. These studies have tested the hypothesis that low levels of GH contribute to central obesity and related metabolic abnormalities. The predicted results are reductions in intra-abdominal fat and improved metabolic health.

We reviewed the results of 16 published studies on GH administration in (predominantly central) obesity, which were found through MEDLINE searches. The terms included in the searches were growth hormone, treatment, obesity, and human. We also searched the references of the articles we identified. Only English language papers were used. One of these papers was a large study of overweight elderly adults with high waist-to-hip ratios (1).

A number of the authors provided optimistic comments on the results of GH treatment (2–5). Because details of the reported effects of GH administration were commonly at odds with the favorable conclusions, we elected to summarize the treatment trials to look for consistent findings.

A brief overview of the current knowledge of GH physiology and the pathophysiology of hyposomatotropinism in obesity are first provided to put the treatment trial results in perspective.

GH and Nutrient Partitioning

In addition to the induction of growth, an important function of GH is the regulation of nutrient partitioning. GH enhances the oxidation of fatty acids relative to glucose or amino acids (6). This is achieved by increasing (7–9) adipose tissue lipolysis and/or reducing triglyceride storage in a nonuniform manner such as to redistribute adipose tissue from intra-abdominal to peripheral depots in addition to decreasing body fat mass.

Furthermore, GH has protein anabolic and diabetogenic effects. The latter arise from the (direct or indirect) ability of GH to enhance endogenous glucose production and to inhibit cellular glucose uptake, thus raising plasma glucose

Received for review July 31, 2002
Accepted for publication in final form October 18, 2002.
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[1] Nonstandard abbreviations: GH, growth hormone; IGF, insulin-like growth factor; IGFBP, IGF binding protein; FFA, free fatty acid; FFM, fat free mass; rhGH, recombinant human GH.

concentrations. Prolonged excess GH can lead to pancreatic β-cell failure such that insulin secretion cannot overcome the insulin resistance, resulting in hyperglycemia and eventually diabetes. Another common adverse effect of excess GH is an abnormal expansion of extracellular fluid.

Many GH effects, such as its effects on growth and protein synthesis, are mediated through insulin-like growth factors (IGF), mainly IGF-1; GH largely mediates the production of IGF-1. An exception is the GH effects on fat metabolism, which are not IGF-1 dependent (6,10). IGF-1 exerts feedback inhibition of GH secretion at the hypothalamic and pituitary levels.

GH in Obesity

The role of GH in obesity is complex and somewhat controversial. Although primary GH deficiency leads to centripetal adiposity, visceral obesity per se also results in a *secondary* reduction in serum GH concentrations (2).

The difference in the pathophysiology of the two conditions is primarily reflected by the disparate IGF-1 responses. IGF-1 is very low in primary GH deficiency, but may be normal, high, or modestly reduced in obesity (2,11). In the latter case, a simultaneous change in the availability of IGF-binding proteins (decreased IGFBP 1 and 2, as well as increased IGFBP 3) usually results in normal to elevated free biologically active IGF-1 concentrations, equaling or exceeding those in lean subjects (2). This might explain the fact that IGF-dependent functions of GH, such as the growth ability of obese children, remain unchanged (2). Successful weight loss is reported to improve or normalize GH parameters (2), strongly suggesting that this is a secondary, not primary, phenomenon.

Nevertheless, the reasons for the hyposomatotropinism in obesity and its mechanisms have yet to be clarified. Reductions in spontaneous GH secretion [as much as 6% for each unit increase in BMI (12)] and in the half-life of circulating GH (13) have been reported. Moreover, the GH response to pharmacological (growth hormone releasing hormone, L-Dopa) and physiological stimuli, such as sleep, physical exercise, insulin-induced hypoglycemia, and corticosteroids, is impaired in obesity (2).

Some of the theories on the cause of altered GH physiology in obesity involve the increased concentrations of leptin, insulin, free fatty acids (FFAs), and IGF-1. Conflicting reports on the effect of leptin have been published, however, with in vitro and in vivo studies finding both stimulation and inhibition of GH release (2).

IGF-1 and FFAs are thought to contribute to the hyposomatotropinism through feedback inhibition of GH secretion; spontaneous and stimulated GH release increase in obese subjects after administration of acipimox, a nicotinic acid analog that lowers FFA concentrations (2). The quantitative contribution of elevated FFA concentrations to altered GH physiology in obesity, however, remains unclear.

GH Administration in Obesity

The low GH concentrations in visceral obesity have led to experimental administration of this hormone in obese subjects. Its lipolytic effects were expected to induce weight loss, and its protein anabolic effects were expected to protect against the negative nitrogen balance often accompanying hypocaloric diets. In addition, GH's fat-redistributing qualities were predicted to reduce visceral fat and, thus, improve metabolic health, analogous to the insulin-sensitizing effects seen after the reduction of intra-abdominal adipose tissue by exercise, diet, or surgery (4,5,14–21).

The rational for these expectations is supported by the finding that GH replacement therapy in patients with primary GH deficiency increases abnormally low muscle mass and redistributes intra-abdominal fat toward peripheral depots (6,8,22–24). We found little or no evidence, however, that the goals of favorable fat redistribution or metabolic improvement were achieved by GH supplementation of obese subjects (Tables 1 and 2).

Effects on Body Composition

The subcutaneous administration of recombinant human GH (rhGH) to obese volunteers in combination with an energy-restricted diet has not been found to result in a greater decrease in fat mass or preservation of lean tissue when compared with diet alone (3,4,7,21,25). Only when given in the context of an isoenergetic diet has GH been reported to decrease total body fat relative to placebo, although the differences were relatively minor (5,14).

In this context, it is critical to understand that the methods commonly used to assess body composition (DXA, underwater weighing, bioimpedance analysis) have serious limitations when applied to conditions in which extracellular fluid shifts can occur. Each of these techniques measures fat free mass (FFM), a component of which is extracellular fluid. These approaches, therefore, cannot distinguish changes in FFM caused by changes in body cell mass as opposed to changes in extracellular fluid. This limits the interpretation of FFM as a surrogate measurement for lean body mass/body cell mass (which is therefore confounded by GH-induced water retention) and, therefore, percent body fat. If weight increases by fluid retention, percent body fat will decrease even if total body fat does not change. This could well explain why some authors (4) report similar fat and weight loss in GH vs. placebo, but claim a significant difference in fat loss as a *fraction* of weight change.

These limitations do not apply to measurement of total body potassium as a measure of lean body mass. The only study taking advantage of this body composition measurement technique found no difference between GH and placebo treatment (5). One group reported an increase in FFM

Table 1. Effect of GH administration in obesity on body composition

Authors (Ref. no.)	*n*	Mean daily dose	Duration (weeks)	Diet	Weight loss*	Body comp method	Fat loss
Clemmons et al. (25)	8	50 μg/kg IBW	11†	hypocal	4%	UWW	Similar (2.5%)
Drent et al. (18)	15	1.9 mg	8	hypocal‡	13.7%	BIA	Similar (14%)
Johansson et al. (5)	30	9.5 μg/kg	40	isocal	NR	Total body $^{40}K^{+}$	GH (2.5%) > plac§¶
Kim et al. (4)	24	9.5 μg/kg IBW	12	hypocal	9%	BIA	Similar (4.5%)
Münzer et al. (1)	110‖	8.6 μg/kg	26	isocal	NR	anthropometric	NR
Nam et al. (27)	18**	7.7 μg/kg	12	hypocal	6%	BIA	GH (7%) > plac (4.5%)¶
Norrelund et al. (3)	15	18.2 μg/kg IBW††	4	hypocal	4.5%	DEXA	NR
Richelsen et al. (7)	9‡‡	30 μg/kg IBW	5	isocal	−2% (GH); 0% (plac)	DEXA	GH (2.5%) > plac§
Richelsen et al. (14)	18	13.3 μg/kg	4	hypocal	4.5%	DEXA	Similar (8%)
Skaggs and Crist (20)	12§§	80 μg/kg IBW	4	isocal	−1% (GH); plac§	UWW	GH (2%) > plac§
Snyder et al. (16)	8	100 μg/kg IBW	15¶¶	hypocal	7.5%	UWW	Similar (4.1%)
Snyder et al. (17)	11‡‡	50 μg/kg IBW‖‖	5.5	hypocal	7.3 (GH) vs. 8.4 kg¶***	UWW	Similar (2.7%)
Snyder et al. (19)	20‡‡	50 μg/kg IBW	10	hypocal	14 kg***	UWW	Similar (8%)
Snyder (26)	11‡‡	50 μg/kg IBW	10	hypocal†††	8 kg***	UWW	GH (3.7%)‡‡‡ > plac (2.8%)¶
Tagliaferri et al. (15)	20	46.6 μg/kg IBW	4	hypocal	6%	DEXA	Similar (9.5%)
Thompson et al. (21)	33§§§	25 μg/kg	12	hypocal†	3.5%	DEXA	Similar (16%)

Studies were placebo controlled unless indicated otherwise. "Similar" refers to GH vs. placebo.
BIA, bio-electric impedance analysis; CT, computed tomography; comp, composition; IBW, ideal body weight; NR, not reported; plac, placebo; UWW, under water weighing; isocal, isocaloric; hypocal, hypocaloric.
* Weight loss similar in GH and placebo in all studies unless listed otherwise.
† GH given from weeks 3 to 5 or 8 to 10 only.
‡ Plus exercise.
§ No change.
¶ Significant.
‖ Four groups: GH, HRT, GH + HRT, plac; all subjects >65 years old.
** Type II diabetic subjects; mean BMI = 28 kg/m^2.
†† Gradual build up.
‡‡ Placebo crossover.
§§ Baseline weight of GH group is 18 kg higher than placebo.
¶¶ GH or plac, each for 5 weeks during either weeks 2 to 6 or 9 to 13.
‖‖ Only GH for 28 days; remainder: diet only.
*** Initial weight NR.
††† High-carbohydrate vs. high-fat diet; parameters mentioned in this table were similar.
‡‡‡ Inter-individual differences ++.
§§§ Four groups: GH, IGF, GS + IGF, plac; least weight loss in GH group, most in IGF + GH group (6%).

when GH was combined with an isoenergetic diet; however, this finding is open to interpretation given that the investigator used DXA for body composition measurement (14).

Changes in muscle mass/lean tissue can also be estimated by assessing nitrogen balance and muscle strength. Muscle strength was reported to be increased equally in obese adults treated with GH vs. placebo-treated with a hypocaloric diet and an exercise program (21). Nitrogen balance has been found to be more negative in the placebo-treated than GH-treated obese volunteers treated with energy-restricted diets (4,15,16,18,25,26). This difference, however, was attenuated or lost after 4 to 5 weeks of treatment in some studies (16,17). We view this as a considerable limitation in light of the short duration and the lack of long-term follow-up in most studies.

Effects on Fat Distribution

All four studies that used computed tomography or magnetic resonance imaging to assess changes in fat distribution in response to GH treatment reported decreases in intra-abdominal fat of 7% to 18% (1,5,14,27). Münzer et al., authors of the largest study (111 volunteers) (1), found that elderly men, but not women, had a

Table 2. Metabolic effects of GH administration in obesity

Authors (Ref. no.)	*n*	FFA	f-insulin		f-glucose		f-C-peptide		Miscellaneous	Complications
			GH	plac	GH	plac	GH	plac		
Clemmons (25)	8	NR	*		*		NR		No glucosuria	Mild edema 62%
Drent et al. (18)	15	NR	GH > plac		GH = plac		NR		GH: Glucagon ↑ (cf plac)†	↑ BP (GH)‡; otherwise NR
Johansson et al. (5)	30	*	↑	*	*	*	↑	*	↓ GDR§	CTS 3%; FR 27%; Muscle stiffness 6%¶
Kim et al. (4)	24	↓‡	NR						Insulin AUC during OGTT ↓, plac more than GH	Edema 13%
Münzer et al. (1)	110		NR							CTS, arthralgia
Nam et al. (27)	18	↓**	↓	↓	↓	↓	NR		GDR ↑ (GH)	3 edema, 2 arthralgia
Norrelund et al. (3)	15	↑**	↑	↓	*	*	↑††	↓††	↓ glu turnover and oxidation**	NR
Skaggs and Crist (20)	12	NR	NR							NR
Richelsen et al. (14)	9‡‡	↑	↑↑	§§	↑	§§	↑	§§		CTS 5/9; edema
Richelsen et al. (14)	18	↑**	↑	↓	NR					NR
Snyder et al. (16)	8	↑¶¶	GH ⩾ plac‡‡		GH ⩾ plac‖‖		GH > plac		GH: ↑ Cp excretion GH: Pp glu + ins > plac	NR
Snyder et al. (17)	11‡‡	Similar	GH ⩾ plac		GH > plac		GH > plac			Fluid retention
Snyder et al. (19)	20	GH > plac††	GH = plac		GH > plac		NR		Cp excretion GH = plac	FR, edema
Snyder et al. (26)	11	↑††	*	§§	↑***	§§	NR		Cp excretion GH > plac‖‖	FR; edema
Thompson et al. (21)	33	NR	NR							89% edema†††; hand numbness 44%; fatigue 56%
Tagliaferri et al. (15)	20	↑**	↑	↓	*	*	NR			NR

Studies were placebo controlled unless indicated otherwise.
AUC, area under the curve; BP, blood pressure; CP, C-peptide; CTS, carpal tunnel syndrome; f, fasted; FR, fluid retention; GDR, glucose disposal rate; glu, glucose; ins, insulin; NR, not reported; OGTT, oral glucose-tolerance test; pp, post-prandial; ↑, concentration increased; ↓, concentration decreased; plac, placebo.
* No change.
† GH and placebo equally.
‡ Despite weight loss/exercise.
§ Except at final time point.
¶ These caused average dose reduction of 0.17 mg/d.
‖ Area under the curve during OGTT; decreases more than in placebo; fasted not mentioned but is higher than placebo too.
** GH and placebo equally.
†† Not significant.
‡‡ Placebo crossover.
§§ Initial placebo values are NR.
¶¶ Four hours after GH injection; fasted was unchanged.
‖‖ Quantity unclear.
*** In high carbohydrate diet only.
††† Five of 33 dropped out (intolerable edema).

statistically significant (3.9%) loss of visceral fat. Interpreting this finding by itself is impossible because almost any intervention resulting in body fat loss also results in a disproportionate loss of visceral fat compared with subcutaneous fat. To assess confidently whether GH treatment specifically enhances visceral fat loss, one must match GH-treated groups with placebo-treated groups with equal fat loss. Unfortunately, most studies in which placebo-treated volunteers lost equal amounts of fat compared with GH-treated volunteers did not assess

regional fat loss. The one study that did report these results (4) found similar visceral fat loss (centimeters squared) in placebo- and GH-treated groups. We conclude that the observed fat redistribution reported in some studies cannot confidently be attributed to GH administration.

Metabolic Effects

If rhGH therapy preferentially reduced visceral fat, would the expected improvements in metabolic health appear? Apparently not. When reported, insulin resistance worsens, plasma FFA concentrations increase, and serum high-density lipoprotein-cholesterol concentrations (7) decrease. Despite reassuring statements, in all studies we reviewed except one (27), even small amounts of GH decreased insulin-stimulated glucose disposal rates and/or increased levels of glucose, insulin, C-peptide, and 24-hour urinary C-peptide excretion (3,5,7,14–18,27). This was especially prominent in, but not limited to, studies in which rhGH was combined with an isoenergetic diet. In several studies, the adverse effects on glucose metabolism were either not reported (1,20,21) or did not reach statistical significance. In other studies, insulin sensitivity was claimed to remain unchanged or even to improve, based on criteria that do not describe the full picture. For example, Figure 3 in the study by Johansson et al. (5) shows similar glucose disposal rates and glucose and insulin concentrations at the end of 9 months of GH vs. placebo treatment, but marked worsening in the GH group in all time-points measured in between. This is not a reassuring result.

Nam et al. (27) reported an improvement of insulin action and fat distribution in a 12-week placebo-controlled study of 18 type 2 diabetic volunteers. Nevertheless, some potential limitations of this study should be considered. Body fat and lean tissue were assessed using bioelectrical impedance analysis, a method notoriously sensitive to changes in extracellular fluid. The changes in lean body mass and visceral fat are not convincingly significant when the SD and the sample size are considered. In addition, although visceral fat is reported to be more reduced in the GH group, the means of data analysis (visceral fat area change divided by body fat change) has not been validated as an appropriate index of visceral fat loss (see comments above). Although glucose disposal was found to increase more and FFA to decrease more in GH-treated patients, these results are discordant with all other above-mentioned studies. The results may relate to a unique study population or may represent a type 1 statistical error. These results should be reproduced in larger diverse populations before GH therapy should be considered for type 2 diabetes.

In summary, the vast majority of the studies describing metabolic parameters show a clear trend toward metabolic deterioration with GH administration to adults with visceral obesity.

Adverse Effects

In addition to the metabolic side effects, ~20% to 40% of the volunteers receiving GH developed fluid retention, arthralgias, or carpal tunnel syndrome (5,14,16,17,21). Furthermore, in children, the induction of sleep apnea is reported (28).

Conclusions

In summary, we found no evidence for metabolic benefits of GH administration in obesity in the absence of true GH deficiency. On the contrary, almost all studies reporting the effects of GH administration on glucose metabolism in obesity show trends toward worsening of insulin resistance. Thus, if visceral fat loss were truly achieved, its possible benefits (a primary incentive for GH administration) could be lost; however, any demonstrable effects on body composition were minimal, not necessarily attributable to the GH administration, and present only when isocaloric diets were given. Although GH administration attenuated nitrogen loss, this effect was lost after a few weeks, whereas it did not convincingly affect other measures of lean body mass. Troublesome nonmetabolic side effects of GH include fluid retention, arthralgia, and carpal tunnel syndrome.

Perhaps not surprisingly, GH returns to normal after weight reduction in obesity (2). This finding strongly suggests that low GH is a consequence, not a cause, of central obesity. Considering the high costs and the lack of understanding of the long-term consequences of GH treatment of obesity, we argue against its use for this purpose.

Acknowledgments

This work was supported by Grant DK40484 from the U.S. Public Health Service and by the Mayo Foundation. S. Shadid was partially supported by Novo Nordisk.

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