Obesity, growth hormone and weight loss

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MCE
Molecular and Cellular Endocrinology

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Key words: Obesity, Growth hormone, Weight loss, Insulin-like growth factor

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ABSTRACT

Growth hormone (GH) is the most important hormonal regulator of postnatal longitudinal growth in man. In adults GH is no longer needed for longitudinal growth. Adults with growth hormone deficiency (GHD) are characterised by perturbations in body composition, lipid metabolism, cardiovascular risk profile and bone mineral density. It is well established that adult GHD usually is accompanied by an increase in fat accumulation and GH replacement in adult patients with GHD results in reduction of fat mass and abdominal fat mass in particular. It is also recognized that obesity and abdominal obesity in particular results in a secondary reduction in GH secretion and subnormal insulin-like growth factor-I (IGF-I) levels. The recovery of the GH IGF-I axis after weight loss suggest an acquired defect, however, the pathophysiologic role of GH in obesity is yet to be fully understood. In clinical studies examining the efficacy of GH in obese subjects very little or no effect are observed with respect to weight loss, whereas GH seems to reduce total and abdominal fat mass in obese subjects. The observed reductions in abdominal fat mass are modest and similar to what can be achieved by diet or exercise interventions.

1. Introduction

Human growth hormone (GH) is a mixture of peptides, the major physiologic and bioactive component being a 22 kDa polypeptide chain of 191 amino acids secreted by the anterior pituitary gland (35). In man GH is secreted episodically in a pulsatile fashion. The main regulatory hormones of GH are two hypothalamic peptide hormones: GH releasing hormone (GHRH) a 44 amino-acid peptide required for the initiation of GH pulses and somatostatin an inhibitory peptide which modulates the amplitude of GH pulses. However, several brain transmitter pathways as well as sleep and several other factors seem to be involved in GH regulation, suppressing or stimulating GH release by influencing GHRH or somatostatin (35).

GH exerts biological effects directly on target cells by binding to cell membrane receptors or/and through insulin-like growth factor-I (IGF-I). According to the general somatomedin hypothesis, the effect of GH on the liver is to generate IGF-I, which is secreted into the bloodstream and delivered to the target tissues. Although the liver is believed to be the principal source of circulating IGF-I, IGF-I seems to be synthesized in most organs and released by paracrine as well as autocrine mechanisms (45). GH plays a major role in controlling longitudinal growth in children and is generally regarded as an anabolic factor, yet it has both anabolic and catabolic actions on different tissues in the human body (49,59). For example, GH stimulates protein synthesis in muscle (109a), whereas in fat tissue it promotes lipolysis (49).

Adults with growth hormone deficiency (GHD) are characterised by perturbations in body composition, lipid metabolism, cardiovascular risk profile and bone mineral density (6,18,97) and an increased risk of cardiovascular disease risk has also been reported in young overweight and obese women with impaired GH levels (96). It is well established that adult GHD usually is accompanied by an increase in fat accumulation and GH replacement in adult patients with GHD results in reduction of fat mass and abdominal fat mass in particular (5,7,14,19,33,57,80,83,98). It is

also recognized that abdominal obesity results in a secondary reduction in GH secretion reversible with weight loss (70,98), the reasons for the reduced GH secretion are yet to be fully understood. However, whereas GH replacement in patients with GHD leads to specific depletion of intra-abdominal fat, the administration of GH to obese individuals does not seem to result in a consistent reduction or redistribution in body fat (82). Although the administration of GH to obese subjects has only led to equivocal results (82), it still remains a plausible metabolic candidate according to more recent studies (1,2,4,28,37,66). It is the intention of this review to present the current knowledge on the pathophysiology of the GH-IGF-I axis related to obesity and an overview of clinical studies examining the effect of GH on weight loss and body composition in obese subjects.

2. The GH-Insulin-Like-Growth-Factor-I (IGF-I) Axis in Obesity

In obese subjects the GH secretory response to a variety of stimuli (e.g. insulin-induced hypoglycaemia, arginine, GHRH-arginine, sleep and exercise) is impaired compared to normal subjects (56,69,70,72,74). The spontaneous GH secretion is decreased (70,98) and GH clearance increased (54). It has been reported that an increase in each unit of BMI at a given age reduces the daily GH secretion by 6% (42).

The mechanism responsible for the altered GH secretion in obesity is largely unsettled. It has been hypothesized that a relatively increased amount of free IGF-I could be responsible for an enhanced feedback inhibition of GH release in obese subjects which could be a simple mechanism by which GH secretion is diminished in obesity (see below). Several other mechanisms have been proposed explaining the impaired GH release. For example, FFA may influence GH release negatively; however, a causal relationship between FFA and decreased GH secretion in obesity has not been proven. Elevated insulin levels seem capable of reducing GH release and the hyperinsulinemia which is a frequent finding in obesity could be related to the

impaired GH secretion (15). Further, it has been proposed that the reduced GH secretion in obesity may be due to diminished GH pituitary reserves. However, this hypothesis seems unlikely by the observation of a massive GHRH and GH-releasing peptide-6 induced GH release in obese subjects (17) suggesting a marked somatoroph secretory capacity in obesity and arguing against reduced stores of GH, as the explanation of the impaired GH secretion in obesity. The cause for the increased GH clearance is also puzzling, especially seen in the light of increased growth hormone GH-binding protein (GHBP) observed in obesity (see below). To what extent subnormal GH secretion and increased clearance may contribute to preserve the obese state is unknown. However, as described previously GH plays an important role in the maintenance of normal body composition in as much as GHD adults have increased adiposity which can be corrected by GH administration.

GH is bound to a high affinity circulating GHBP. In man, there is evidence that GHBP is derived from proteolytical cleavage of the extracellular domain of the GH receptor and may reflect GH receptor status (55). Several studies have reported that GHBP levels are increased in obesity (27,41,71) and a direct relationship between abdominal adiposity and GHBP concentration has been observed (71). The physiological significance of increased GHBP in obesity is presently unknown. It would be reasonable to speculate that the increased GHBP levels in obesity serve to prolong the biological t½ of GH. However, deconvolution analysis of concentration profiles reveals that the clearance of GH is accelerated in obesity and might contribute to the hyposomatropism in this condition (98). If circulating levels of GHBP reflect GH receptor density, an alternative explanation might be that the greater density of tissue receptors acts to sequester GH more avidly from the circulation, and this phenomenon might represent tissue adaptation to reduced GH output in obesity. However, if this is so, then increased GH sensitivity and increased adipose tissue responsiveness to GH would be expected. This seems not to be the case, as the lipolytic action of GH is similar in abdominally obese and normal weight subjects. Thus, the alternative hypothesis is

that the reduced GH levels, given normal adipose tissue responsiveness, blunts lipolysis in abdominally obese subjects and therefore contributes to the development of an increased amount of abdominal fat which then again increase the risk of developing abdominal obesity associated diseases. In favour of this hypothesis is that abdominally obese subjects have numerous metabolic features in common with GHD patients. For example, both conditions are associated with insulin resistance, hypercholesterolemia, reduced HDL and hypertension.

IGF-I is a GH dependent polypeptide, which mediates some of the actions of GH. Despite the reduced levels of GH in obesity, studies have reported conflicting data with regards to the levels of IGF-I. However, the majority of studies report IGF-I to be low-normal or low (47) in obese subjects compared to lean normal subjects. In accordance with this an inverse relationship between IGF-I and indices of fat mass distribution has been demonstrated (68). The IGF-axis is of increasing interest due to recent reports suggesting that low IGF-I levels are closely linked to the pathogenesis of T2DM and cardiovascular disease (44,46,81).

Free (biologically active) IGF-I accounts for less than 1% of the total circulating amount of IGF-I. However, free IGF-I is believed to be responsible for the bioactivity on target tissue (31,45). It has been hypothesized that a relatively increased amount of free IGF-I could be responsible for an enhanced feedback inhibition of GH release in obese subjects and thereby be a simple mechanism by which GH secretion is diminished in obesity (29,70). Free IGF-I has been reported to be relatively increased in one group of obese men and women (30) and two studies have reported increased free IGF-I levels in obese men (29,61). In contrast, other studies have observed normal (63,75) to low (34) free IGF-I levels in obese men and women. It could be argued that these discrepancies can be accounted for by methodological differences as free IGF-I determinations are technically difficult and the observed between-study heterogeneity could be a result of differences in the assay used. However, both ultrafiltrated free IGF-I as well as dissociated free IGF-I levels

have been measured and both found to be significantly decreased in obese women (73). This is in accordance with the previous reported decreased IGF-I/IGFBP-3 molar ratio, a rough estimate of free, biologically active IGF-I, in obesity (26,70) and the normalisation after diet-induced or surgical-induced weight loss consistent with the transient GH-deficient state (26,70). The previous observed differences in measured values of fasting free IGF-I could be due to diurnal induced variations in free IGF-I, IGFBP-1 levels, fasting induced or other hour-to-hour factors influencing the amount of free IGF-I. Thus, in a recent study both 24-h diurnal mean free IGF-I and basal free IGF-I levels were measured and both were found to be decreased in the obese women compared to non-obese women (73). Therefore, it seems very unlikely that circulating free IGF-I should mediate the impaired 24-hour GH release as previously hypothesized.

One possible explanation for the different free IGF-I levels observed in obese subjects might be the type of fat distribution, since visceral fat mass, rather than adiposity per se, has been reported to correlate inversely to circulating total IGF-I levels (21,53,60,68,70), and free IGF-I levels could also vary across categories of indices of adiposity. Free IGF-I levels correlate inversely with different measures of obesity and body composition and with the strongest relationship to waist circumference and visceral fat mass. Thus, it seems that obesity, and visceral obesity in particular, is interlinked to decreased free IGF-I levels in alignment with the previously reported decreased total IGF-I levels. The mechanism subserving this link is presently not known. Recent data suggest that inflammatory mediators may play a role in inducing reduced IGF-I bioactivity (90) and in recent years adipose tissue has emerged as an important source of pro-inflammatory mediators (51). The question of whether these mediators play a role in the IGF-I/IGF-binding protein system in obesity requires future study. However, the finding of low circulating free IGF-I in visceral obesity (73) is of dual interest because visceral fat mass plays a crucial role in the

development of obesity-related diseases and recent reports suggest that low IGF-I levels are further linked to the pathogenesis of T2DM and cardiovascular disease (44,45,81).

3. Effect of caloric restriction and weight loss on the GH-IGF-I axis in obesity

Caloric restriction applied for a relatively short-term usually increases the GH release significantly in normal weight subjects (38); however, this is significantly abolished in obese subjects (36,69). The lack of stimulation of GH release in obese subjects by diet may promote retention of fat mass. However, studies have demonstrated that apparently all the defects in the GH IGF-I axis in obesity are reversible with diet-induced and surgical induced large weight loss (20,56,70). The recovery of the GH IGF-I axis after weight loss suggest an acquired defect, rather than a pre-existing disorder. The impaired GH IGF-I axis may, however, act toward expansion and maintenance of fat mass and contribute to perpetuation of the obese state.

4. Obesity, Growth Hormone Deficiency and Body Composition

Obesity as such is a serious health hazard, and the various risks associated with obesity seem related to abdominal fat accumulation in particular (10). The heterogeneity of obesity may explain why not every obese subject is characterized by chronic complications. In this regard, body fat distribution, especially intra-abdominal adipose tissue accumulation, has been found to be a key factor of diabetogenic, atherogenic and inflammatory metabolic abnormalities increasing the risk of T2DM and cardiovascular disease (10). It has recently been demonstrated that abdominal obesity was independently associated with an increased risk of coronary heart disease and T2DM independently of overall adiposity (12,22,23).

The fact that GH induces lipolysis in humans has been known for many years (67).

Children with GHD have increased levels of body fat which is more pronounced on the trunk than on the limbs. When GHD children are treated with GH, body fat returns to normal after a few months of treatment. Adults with GHD have abnormal body composition with increased amounts of body fat, especially abdominal body fat. GH treatment in GHD adults has consistently been shown to promote growth of lean tissue while reducing fat mass (48,80,83,100). The reduction of fat mass is a consistent finding in GH treated GHD adults and independent of the methodologies used. However, the magnitude of the change in fat mass varies considerably according to the different methods applied (9). These encouraging effects of GH have generated interest in the efficacy of using GH in the treatment of obesity.

5. Effect of growth hormone therapy on body weight and body composition

In a literature search 19 randomised controlled studies investigating GH therapy in obese subjects were identified (Table 1). Two trials (79,89) were excluded due to lack of placebo control and five trials were excluded as they fell outside the category of obese subjects (8,11,32,58,91). In addition, three non-controlled studies (16,87,88) and three trials investigating GH treatment of obese children were excluded for further analysis (3,25,50). In only two of the studies pre- vs. post-treatment changes in body weight were observed to be greater than placebo (Table 1). Thus, in the vast majority of the investigations no significant effect on body weight was reported and based on these results significant decreases in body weight cannot be expected during GH treatment in obese subjects. The evidence from the studies support to some extent GH as being effective in reducing fat mass and abdominal/visceral fat mass in obese subjects in as much as 11 of the 19 significant pre- vs. post-treatment reductions in total fat mass and/or abdominal/ visceral fat mass. However, it has to be acknowledged that only seven of these studies reported significant reductions when compared to placebo (Table 1).

A simple comparison revealed that in the studies reporting a significant effect on loss of fat mass the mean duration of GH treatment was considerably longer compared to the studies showing no significant effect. Thus, the impact of GH on fat mass seems to depend on treatment duration of 12 weeks or more as only few studies with less than 12 weeks treatment duration reported reduction in fat mass. When analysing the studies of medium to long-term duration separately, reductions in total fat mass and or abdominal fat mass were observed and occurred in studies covering a broad dose range. Although the GH dose that may be more efficacious in obese subjects has not been established, the studies of more than 12 weeks duration indicate that a dose in the range of the current average dose for GH replacement in GHD adults or even lower may be suitable. In future studies rather lower doses than excessively high GH doses should be considered in order to minimize the GH induced hyperinsulinemia which may oppose the lipolytic effect of GH in obese subjects. It has been suggested that the mechanism behind this is that lower GH doses exert insulin-like effects (101), whereas a high dose of GH is more likely to be associated with deterioration in insulin sensitivity. It could also be speculated that titration and a lower dose may increase compliance due to reduction in the number of dose-related side-effects.

If exclusively analysing the studies with treatment duration of a minimum of 12 weeks, nine out of 11 studies reported significant pre- vs. post-treatment reductions in total fat mass and/or abdominal/visceral fat mass and six of these studies reported significant reductions when compared to placebo (Table 2). In six of these studies a significant reduction in visceral adipose tissue ranging from 5-34% as measured by CT were observed (Table 2). In comparison other interventions that reduce body weight in obese subjects, such as caloric restriction, very-low calorie diet, or exercise produced reduction in visceral adiposity ranging from 9-49% (85). Seven of the nine studies with a treatment duration of minimum 12 weeks showed that changes in body fat mass

and abdominal fat mass can occur with GH treatment compared to placebo in the absence of significant reduction in body weight (Table 2).

It is of interest that also smaller GH fragments stimulate energy expenditure and induce weight loss in animals (39). Intact GH may induce insulin resistance, at least initially. It is possible that the development of GH fragments (with predominant activity directed at fat) may potentially improve body composition without adversely affecting glucose metabolism. This is of potential interest in the treatment of obese subjects and in subjects with metabolic syndrome. AOD9604, a growth hormone fragment developed to selectively stimulate prolipid mobilizing and lipid oxidation portions, has shown promise in animal (39) and early clinical phase 1 studies (40). The clinical study, a 12-week phase II study, showed that 34 patients treated with low-dose oral AOD9604 experienced significant weight loss and improvement in glucose tolerance compared with the 37 placebo-treated patients (40).

Traditionally, in the management of obesity the primary goal is weight loss. However, from a medical point of view measures of GH induced body composition changes are more meaningful than weight loss since abdominal/visceral obesity in particular are related to the risk of increased morbidity and mortality in obese subjects than obesity per see (65). Abdominal/visceral fat is more important than peripheral fat depots for the adverse consequences of obesity (10,13). It is important to recognize that it is the amount of adipose tissue, especially visceral adipose tissue that confers the negative impact of obesity on health risk factors, whereas peripheral adipose tissue might have a protective role against arteriosclerosis (94). It is a fact that among equally overweight/obese subjects carefully matched for their level of total body fat, patients with a selective excess of visceral adipose tissue are at a substantially increased risk of showing the well-described abnormalities of insulin resistance. For this reason, the reduction in abdominal/visceral fat

depots and increased/unchanged lean body mass could be considered beneficial, even though no major weight loss was achieved.

6. Conclusions

There is now sufficient evidence to conclude that the GH-IGF-I axis in obesity is impaired with decreased GH secretion and subnormal IGF-I levels. The recovery of the GH IGF-I axis after weight loss suggest an acquired defect, however, the fully understanding of the mechanisms subserving the obese state of hyposomatotropism remain yet to be revealed in further investigation. The clinical studies examining the efficacy of GH in obese subjects demonstrated very little or no evidence with respect to weight loss by GH therapy of obese subjects. More evidence exists with respect to the effect in reducing total and abdominal fat mass in obese subjects. The observed reductions in abdominal fat mass were modest and similar to what can be achieved by diet or exercise interventions. It is unproven whether the GH induced reductions in fat mass are beneficial for obese subjects in the long-term.

Table 1: The effect of GH on weight and body composition

Reference	Age Mean ± SD (range)	Body Composition Method	Total FM	Abdominal FM	LBM	Body Weight	Duration/ Dose
Albert et al. 2004	35.0±6.0	DEXA	↓*	↓*	→	↓*	6 months/ 3.8/6.0 µg/kg/d
Ahn et al 2006	53.1±7.2	CT	↓	↓*	↑	→	12 weeks/ ~500 µg/d
Attallah et al. 2005	55.1+10.5	CT		↓*		→	40 weeks/ 8.0 µg/kg/d
Drent et al. 1995	39.1±7.9	BIA, TBP	→		→		8 weeks/ 2000 µg/d
Franco et al. 2005	58 (51-63)	CT	→	↓*	→	→	12 months/ 670 µg/d
Halpern et al. 2006	35.9±7.5	DEXA	↓		→	↓*	13 weeks/ 50 µg/kg/d
Johannsson et al. 1997	58 (48-66)	CT	↓	↓	→	→	39 weeks/ 9.5 µg/kg/d
Jørgensen et al. 1994	30.4±2.4	DEXA	↓*				5 weeks/ 30 µg/kg/d
Kim et al. 1998	37.5±9.0	BIA, CT	↓	↓	→	→	12 weeks/ 10 µg/kg/d
Nam et al. 2001	47.3±6.2	BIA, CT	↓*	↓*	↑	→	12 weeks/ 10 µg/kg/d
Nørrelund et al. 2000	36±4.2	DEXA	→		→		4 weeks/ 10–27 µg/kg/d
Richelsen et al. 1994	32.0±3.1	CT, DEXA	↓	↓	↑	↑	5 weeks/ 30 µg/kg/d
Richelsen et al. 2000	35.3±3.8	DEXA	→				4 weeks/ 10–27 µg/kg/d
Pasarica et al. 2007	50±7	DEXA	↓*	↓*	↑	↑	26 weeks/ 10 µg/kg/d
Skaggs et al. 1991	34 (29-50)	UW	↓		→	→	4 weeks/ 240 µg/kg/week
Snyder et al. 1988	20-54	UW	→			→	10 weeks/ 50 µg/kg/d
Tagliaferri et al. 1998	25.4±1.1	DEXA	→		→	→	4 weeks/ 50 µg/kg/d
Thompson et al. 1998	67 (59-79)	DEXA	→		↑	→	12 weeks/ 50 µg/kg/d
Taaffe et al. 2000	67.1±5.2	DEXA		→			12 weeks/ 50 µg/kg/d

*Significant change compared to placebo

Table 2: The clinical studies with a duration of treatment of at least 12 weeks. Effects of GH on weight and body composition

Reference	Subjects M	Subjects F	Body Composition Method	Total FM mean±SD	Abdominal FM mean±SD	LBM	Body Weight	Duration (Dose)
Albert et al. 2004	12	27	DEXA	↓* 2.89 kg ±3.76	↓* 1.5 kg** ≈ **8%**	→	↓* 2.4 kg** ≈ **2.4**	6 months (3.8/6.0 µg/kg/d)
Ahn et al 2006	12	12	CT	↓ 4.0% ±3.2	↓* 16.4 cm² ±19.2 ≈ **10%**	↑	→	12 weeks (~500 µg/d)
Attallah et al. 2005/7	51	30	CT		↓* 23.9 cm² ±7.4 ≈ **13%**		→	40 weeks (8.0 µg/kg/d)
Franco et al. 2005		40	CT	→	↓* 6.6 cm²** ≈ **6%**	→	→	12 months (670 µg/d)
Halpern et al. 2006	40		DEXA	↓ 9.5% ±7.9		→	↓* 3.5 kg** ≈ **2.9**	13 weeks (50.0 µg/kg/d)
Johannsson et al. 1997	30		CT	↓ 9.2% ±2.4***	↓ **14.5%** ±3.8***	→	→	39 weeks (9.5 µg/kg/d)
Kim et al. 1998	2	22	BIA, CT	↓ 1.0 kg ±0.5	↓ 31.5 cm² ±2.3 ≈ **34%**	→	→	12 weeks (10.0 µg/kg/d)
Nam et al. 2001	10	8	BIA, CT	↓* 1.0 kg ±0.4	↓* 39.5 cm² ±3.3 ≈ **28%**	↑	→	12 weeks (9.0 µg/kg/d)
Pasarica et al. 2007	30		CT, DEXA	↓* 1.8% ±0.3	↓* 0.6 kg ±0.13 ≈ **5%**	↑	↑ 2 kg** ≈ **1.9%**	26 weeks 10 mg/kg/d
Thompson et al. 1998		16	DEXA	→		↑	→	12 weeks (50 µg/kg/d)
Taaffe et al. 2000		14	DEXA		→			12 weeks (50 µg/kg/d)

*Significant change compared to placebo

**No range provided

***mean ± SEM

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