Effects of gastric bypass on the GH/IGF-I axis in severe obesity – and a comparison with GH deficiency

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Abstract

Objective: Overfeeding suppresses GH secretion and makes evaluation of a suspected GH deficiency (GHD) difficult. In normal weight subjects, gender is known to influence GH concentrations, which is most apparent in the ambulatory, morning-fasted state. In this study, we examined the GH/IGF-I axis in obese men and women and the effect of surgically induced weight loss.

Design: Sixty-three subjects (body mass index (BMI) 45±6 kg/m²; 54 women, 9 men) were studied prior to, and 6 and 12 months following Roux-en-Y gastric bypass (RYGBP) surgery. Fifty-four patients with classic GHD (BMI 27±6 kg/m²; 35 men, 19 women) were included for comparison.

Methods: Hormones were analysed in fasting morning serum samples.

Results: RYGBP resulted in a decreased BMI to 35±kg/m² at 6 months and 32±6 kg/m² at 12 months. GH and IGF-I increased at 6 months in the women and at 12 months in both sexes by $300$ and 11% respectively. Prior to RYGBP, GH concentrations were low in the obese men and similar to those of GHD men (mean 0.09 mU/l). Obese women had tenfold higher values than obese men and sevenfold higher than GHD women. IGF-I levels were in the low reference range in the obese and below $2$ S.D. for age in 13%.

Conclusions: Surgically induced weight loss partially restores GH secretion. Despite a marked suppression of GH values, a gender influence is maintained in severe obesity. In obese women, single morning GH and IGF-I values seem sufficient to exclude a suspicion of classic GHD.

Introduction

Obesity is associated with reduced 24-h growth hormone (GH) secretion and lowered peak GH levels in response to provocative stimuli (1–3). Although GH secretion may be suppressed as a consequence of increased energy supply, it has nonetheless been speculated that hyposomatropism may further add to maintaining overweight since GH is a potent lipolytic hormone. Serum insulin-like growth factor-I (IGF-I) levels reflect the combined effects of the integrated GH secretion, the tissue responsiveness to GH and other, mainly nutrition-driven, components. Reports regarding IGF-I levels in obesity have shown conflicting results with normal (4, 5), decreased (6) or, in children, even increased levels (7). It has been suggested that insulin may augment intracellular GH signaling and thus promote IGF-I production (8). In patients with GH deficiency (GHD) due to an organic disorder, the IGF-I levels are usually reduced, in particular in younger patients and in adult women with GHD, while a proportion of elderly patients and adult men with GHD may have IGF-I levels in the low reference range (9–13). Since isolated GHD has recently been recognized as the most common endocrine manifestation following traumatic brain injury (14, 15) and cranial irradiation for some malignancies (16), conditions both associated with weight gain (17, 18), it will be a delicate task for endocrinologists to determine if GHD requiring treatment is present in these groups of patients.

In the present study, we took advantage of having a well-characterized group of severely obese patients investigated before and after weight reduction by Roux-en-Y gastric bypass (RYGBP) surgery, and examined their basal levels of GH and IGF-I in relation to body mass index (BMI) and markers of insulin sensitivity. Patients of comparable ages with GHD due to pituitary diseases, usually as a consequence of treatment for a pituitary tumor, were included for comparison. As gender is an important regulator of GH secretion in healthy subjects, in whom premenopausal
women secrete two to three times more than men in spite of having similar IGF-I levels (19–21), an effect of gender was also examined.

Materials and methods

Patients in the gastric bypass surgery study were recruited from the obesity program at Samariterhemmet Hospital in Uppsala, Sweden. Sixty-three patients were included, nine men with a mean age of 38.7±6.54 years (range 30–51) and 54 women with a mean age of 39.0±6.82 years (range 24–50 years). Mean BMI in the men was 46.1±6.54 kg/m² and in the women 44.7±6.50 kg/m². Two of the patients were on medical treatment for type 2 diabetes, one received metformin and the other glipizide and insulin. One woman was taking oral contraceptives. The patients underwent RYGBP at the Department of Surgery, University Hospital, Uppsala. RYGBP excludes the stomach and duodenum from the passage of food. A small pouch (1.5 ml) is created along the lesser curvature that is totally separated from the main stomach. The small bowel is divided 30 cm distal to the ligament of Treitz and a 50 cm long Roux limb is connected to the small gastric pouch directly below the esophagus. The small bowel continuity is maintained by an entero-enterostomy. This creates the Y-shaped junction at which the ingested food via the Roux limb and the gastric acid and bile is mixed. Serum samples were taken after an overnight fast preoperatively and 6 and 12 months postoperatively and analyzed for GH, IGF-I, glucose and insulin. Body height and weight were measured at each time-point to determine BMI.

Fifty-four patients with GHD were also included in the study. 35 men, mean age 40.6±8.46 years (range 20–51) and 19 women, mean age 41.2±6.96 years (range 26–51). All had GHD confirmed by stimulation tests (peak GH < 3 μg/l – generally at an insulin tolerance test). BMI in the men was 27.9±5.73 kg/m² and in the women 25.4±4.87 kg/m². Most of the patients had panhypopituitarism (47 out of 54). Thirty-four of the 35 men had replacement therapy with testosterone, 31 with cortisone acetate and 33 with levothyroxine. Fourteen of the 19 men had replacement therapy with estrogen (12 oral and two transdermal delivery), 15 with cortisone acetate and 17 with levothyroxine. Serum samples were taken fasting in the morning before the start of GH therapy and analysed for GH, IGF-I, glucose and insulin.

GH was measured with a non-competitive sandwich time-resolved fluoroimmunoassay (AutoDELFIA hGH kit; Wallac Oy, Turku, Finland) specific for the pituitary 22 kDa GH isoform. The results are expressed in mIU/l. The minimal detection limit was 0.009 mIU/l. The within- and between-assay coefficients of variation (CV) were 1.1 and 2.3% respectively. IGF-I was measured by a non-extraction IGF-I immunoradio-

metric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA) using two region-restricted affinity-purified polyclonal antibodies. The within- and between-assay CV values were 5.6 and 14.6% respectively. Serum insulin was measured with an AutoDELFIA automatic immunoassay system (Wallac Oy). Fasting plasma glucose was measured with a routine clinical chemistry laboratory technique at the Department of Clinical Chemistry, University of Uppsala. Homeostatic model of assessment (HOMA) index was calculated according to Matthews et al. (22).

Serum values for GH were transformed into logarithms before analysis and are represented as geometric means (±S.D.). Values for BMI, IGF-I, IGF-I standard deviation score (SDS), glucose, insulin and HOMA indices are presented as means (±S.D.). Unpaired two-tailed Student’s t-test was used for differences amongst groups and paired two-tailed Student’s t-test for statistical comparisons within the same group.

Results

Effects of gastric bypass on BMI, GH, IGF-I and glucose homeostasis

The gastric bypass surgery caused a marked reduction in body weight, with decreases in BMI from 45±6 kg/m² to 35±6 kg/m² and 32±6 kg/m² at 6 and 12 months respectively (Table 1). After 6 months, the GH values had increased significantly in the women (Table 1), and at 12 months the GH values were higher than preoperatively in both men (P < 0.01) and women (P < 0.001) (Table 1 and Fig. 1). After 12 months, mean IGF-I values were increased compared with baseline (P < 0.05 in both men and women) (Table 1 and Fig. 2) and, in the women, also compared with 6 months after surgery (P < 0.05) (Table 1). Also age-adjusted mean IGF-I SDS increased after 12 months (Table 1). However, 10% of the patients (five out of 54 women and one out of nine men) still had IGF-I levels below −2 S.D. of the normal mean. Men and women with severe obesity had comparable levels of insulin, glucose and HOMA indices. All values were higher than in patients with GHD (Table 1). Twelve months after gastric bypass surgery, insulin decreased by 59±26% (P < 0.001), glucose by 17±14% (P < 0.001) and HOMA index by 65±17% (P < 0.001). At this time-point, only glucose remained higher in the obese than in the GHD subjects (Table 1). Among the 63 morbidly obese subjects prior to gastric bypass, 41 had normal fasting plasma glucose levels (FPG: <5.6 mmol/l), 14 had impaired FPG (5.6–6.9 mmol/l) and eight had a diagnosis of diabetes (FPG ≥7.0 mmol/l) according to American Diabetes Association criteria (23). At 6 and 12 months postoperatively, corresponding figures were 57, 5 and 1, and 60, 2 and 1 subjects respectively.

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Measurements of metabolic markers in 54 women and nine men before and 6 and 12 months after gastric bypass surgery and in 35 men and 19 women with GHD.

Table 1

| Measurements of metabolic markers in 54 women and nine men before and 6 and 12 months after gastric bypass surgery and in 35 men and 19 women with GHD. |
|---|---|---|---|---|---|---|---|---|
| 0 months | 6 months | 12 months |
| Men | Women | Men | Women | Men | Women |
| GH (mU/l) | 0.004 (0.00–0.02) | 0.139 (0.03–0.057) | 0.09 (0.04–0.20) | 0.89 (0.24–3.38) | 0.22 (0.08–0.58) | 2.57 (0.58–11.3) | 0.36 (0.13–1.00) | 2.71 (0.63–11.5) | 0.36 (0.02–0.33) | 0.139 (0.03–0.057) | 0.09 (0.04–0.20) | 0.89 (0.24–3.38) | 0.22 (0.08–0.58) | 2.57 (0.58–11.3) | 0.36 (0.13–1.00) | 2.71 (0.63–11.5) |
| IGF-I (μg/l) | 152.4 (44.9) | 157.3 (44.9) | 152.4 (44.9) | 157.3 (44.9) | 152.4 (44.9) | 157.3 (44.9) | 152.4 (44.9) | 157.3 (44.9) | 152.4 (44.9) | 157.3 (44.9) | 152.4 (44.9) | 157.3 (44.9) | 152.4 (44.9) | 157.3 (44.9) | 152.4 (44.9) | 157.3 (44.9) | 152.4 (44.9) | 157.3 (44.9) |
| BMI (kg/m²) | 46.3 (17.0) | 173.2 (17.0) | 89.4 (17.0) | 26.4 (17.0) | 86.7 (17.0) | 21.1 (17.0) | 86.7 (17.0) | 21.1 (17.0) | 86.7 (17.0) | 21.1 (17.0) |
| Insulin (mU/l) | 18.9 (7.1) | 18.9 (7.1) | 18.9 (7.1) | 18.9 (7.1) | 18.9 (7.1) | 18.9 (7.1) | 18.9 (7.1) | 18.9 (7.1) | 18.9 (7.1) | 18.9 (7.1) |
| Glucose (mmol/l) | 5.57 (1.2) | 4.99 (1.2) | 2.68 (1.2) | 1.72 (1.2) | 2.03 (1.2) | 1.80 (1.2) | 2.03 (1.2) | 1.80 (1.2) | 2.03 (1.2) | 1.80 (1.2) |
| HOMA index | 4.72 (2.6) | 6.29 (2.6) | 2.40 (2.6) | 1.72 (2.6) | 2.40 (2.6) | 1.72 (2.6) | 2.40 (2.6) | 1.72 (2.6) | 2.40 (2.6) | 1.72 (2.6) |

GH and IGF-I levels in obese individuals compared with patients with GHD

The GH levels in the severely obese women were sevenfold higher ($P < 0.001$) than in GHD women, whereas obese men and men with GHD had similar levels (Table 1 and Fig. 1). The IGF-I levels were in the low–normal reference range in most of the obese subjects (Table 1 and Fig. 2), and in 13% (six out of 54 women and two out of nine men) below $-2$ S.D. of the normal mean for their age. There were no differences in GH levels, HOMA index or BMI between those with the lowest IGF-I and those with IGF-I within the reference range. The IGF-I levels among the GHD subjects were below $-2$ S.D. of the normal mean for their age in 84% of the women and in 40% of the men. As can be seen in Fig. 2, IGF-I values within the reference range were most common among GHD men above 40 years of age.

Discussion

In the present study, gastric bypass surgery of the severely obese patients resulted in a similar reduction in BMI in men and women after 6 months and a further reduction after 12 months. In parallel, GH and IGF-I secretion increased in both men and women and resulted in a partial restoration of the GH/IGF-I axis. Metabolic markers such as lipids and glucose/insulin levels have been extensively studied, while there are only two reports (24, 25) examining the GH/IGF-I axis after massive weight loss (in nine and 15 subjects before and after massive weight loss respectively). The present findings based on 63 subjects seem to be in line with other studies regarding GH secretion in obese, fasting and anorectic states (26, 27). A positive effect of gastric bypass on glucose homeostasis was clearly demonstrated by a marked improvement in glucose metabolism postoperatively, with normalization of fasting glucose levels in all but one of the patients with diabetes and in 11 of 14 patients with impaired FPG. These findings confirm the large benefit of surgical weight loss on glucose metabolism.

Thirteen percent of the obese subjects had IGF-I levels below $-2$ S.D. of the age-related normal mean for age and gender. Since glucose homeostasis and IGF-I are inter-related and reciprocally dependent, in that insulin stimulates liver GH receptor expression (28) and acts to maintain systemic IGF-I levels and, conversely, deletion of IGF-I leads to muscle insulin insensitivity (29), we examined whether the ‘low IGF-I group’ of patients was characterized by a lower insulin sensitivity. No differences with respect to fasting glucose, insulin or HOMA index were found, and these patients also had BMI and GH levels similar to the ‘normal IGF-I group’. Given that the GH levels were analysed as fasting ambulatory levels we cannot, however, exclude differences in 24-h integrated levels. It may be hypothesized that obese patients with low IGF-I should be more intensely monitored for future...
cardiovascular diseases, as IGF-I levels within the normal reference range seem to protect against heart failure, ischemic heart disease (30–32) and diabetes (33), in particular if accompanied by low IGF-binding protein (IGFBP)-I (32, 33) or high IGFBP-3 levels (30).

Most of the obese subjects rather had high IGF-I levels for their GH status. This could indicate that clearance of circulating GH is reduced or tissue sensitivity to GH is enhanced in the obese state. Abdominal fat mass determines circulating levels of GH-binding protein (GHBP) (34), a protein which protects GH from degradation and elimination. The levels were elevated in severely obese subjects (5, 35) and this has been suggested to compensate for the low GH secretion (34). Others have found levels of GHBP to be similar in obese and lean subjects (36). IGFBP-1 levels are known to be inversely related to insulin levels and thus lower in obese subjects (37). Frystyk et al. (38) found free IGF-I to be increased in obese subjects, and suggested that the observed hyposecretion of GH would represent a stage of pseudohyposomatropism. However, since some effects of GH are independent of IGF-I it seems likely that, for instance, fat mobilization is truly attenuated in obesity due to low GH levels. Few studies have addressed tissue responsiveness to GH in morbid obesity. By using IGF-I generation tests, Maccario et al. (36) found a more prominent response in obese women compared with lean women. Among the obese subjects, a subgroup with Cushing’s disease had the most marked response, leading the authors to conclude that both hyperinsulinemia and hypercortisolism enhance sensitivity to GH. Gianotti et al. (39) observed a tendency for a more marked IGF-I response to GH in obese men compared with lean men. Buijs et al. (40) found no differences between obese and normal weight women with respect to adipose tissue responsiveness to GH, determined as glycerol rate of appearance per kg fat mass. This is in keeping with

Figure 1 (a) GH values (mU/l) in obese men before (Preop) and 12 months after gastric bypass compared with GHD men. The dashed lines indicate mean values. (b) GH values (mU/l) in obese women before (Preop) and 12 months after gastric bypass compared with GHD women. The dashed lines indicate mean values.

Figure 2 (a) IGF-I values (µg/l) in obese men and women before gastric bypass, (b) IGF-I values (µg/l) in obese men and women 12 months after gastric bypass and (c) IGF-I values (µg/l) in GHD men and women. Reference ranges (shaded area) for age (±2 S.D.) were obtained from the manufacturer.
another study (41) where no differences in plasma free fatty acid, glycerol, glucose and insulin were found in obese and lean subjects after a single intramuscular dose of GH. Taken together, these observations may indicate a tissue-specific adaptation to GH in severe obesity with an enhanced sensitivity to the anabolic effects, but not to the energy-mobilizing actions of GH. The existence of normal longitudinal growth in some obese children with clearly low GH levels, for instance after surgery for craniopharyngioma (42), may support the notion of an enhanced GH effect with respect to anabolism in states of severe obesity.

In the present study, 44% of the patients with GHD had IGF levels above −2 S.D. of the reference age despite having clearly low GH peaks (below 3 μg/l) at an insulin tolerance test. Most of the patients had complete pituitary insufficiency supporting the likelihood of having a true GHD (43). Normal IGF-I levels within the reference range were, in particular, seen in men above the age of 40. Our data corroborate previous observations in GHD patients (12, 13) where 51 and 34% respectively had normal IGF-I values. The reason for normal IGF-I levels in patients with GHD is poorly understood. Nutritional factors, hyperinsulinemia due to visceral obesity and differences in GH sensitivity have all been implicated. Since GH secretion declines approximately 14% every decade above the age of 20 years (44), is influenced by gender (19–21, 45–47) and by obesity (48, 49), and the definition of GHD is based on results of an insulin tolerance test in middle-aged healthy subjects (50, 51), any defined single GH cut-off level must be regarded as arbitrary. The recent findings of a close relationship between BMI and GH response to both an arginine–GH-releasing hormone (GHRH) stimulation test (49, 52) and a GHRH/GHRP-6 test (53) underline the necessity for fine tuning the diagnostic measures. It may well be that the criteria used today are too strict for younger women but too broad for elderly men.

A finding in this study that warrants further investigation is that a single serum sample of GH and IGF-I in the fasting, ambulatory state appears helpful in differentiating hyposomatropism of obesity from ‘true’ GHD in women. This is explained by the maintained gender difference in GH secretion in hyposomatropism of obesity, but not in classic GHD, in combination with the lower responsiveness to GH in women compared with men (54, 55).

In conclusion, the results in the present study have shown a marked impact of morbid obesity on the GH/IGF-I axis and have demonstrated the ability of surgical weight loss to restore GH secretion. Since the influence of gender on GH secretion is preserved in hyposomatropism of obesity, but not in classic GHD, it appears that, in women, single fasting, morning GH and IGF-I values could be helpful in selecting those subjects who will need further work-up of their GH secretory status.

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