OBES SURG
DOI 10.1007/s11695-012-0669-1

CLINICAL RESEARCH

Serum Insulin-Like Growth Factor-1 Concentrations Are Reduced in Severely Obese Women and Raise After Weight Loss Induced by Laparoscopic Adjustable Gastric Banding

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Abstract

Background Obesity is associated with abnormalities of the growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis. The role of serum IGF-1 measurement for recognition of hypothalamic–pituitary diseases in obesity is still a matter of debate.

Methods This study evaluated the serum levels of IGF-1 in a population of severely obese women before and after long-term weight loss obtained by laparoscopic adjustable gastric banding (LAGB). Eighty obese women with body mass index (BMI) of more than 34 kg/m^2 and 80 unrelated age-matched lean controls were enrolled. IGF-1 serum levels were measured together with BMI, liver volume, and intra-abdominal fat thickness assessed by ultrasound. Evaluation was repeated 2 years after LAGB.

Results Our results showed that mean IGF-1 levels in obese subjects before LAGB were significantly lower ($p<0.001$) than that observed in age-matched controls. Age and BMI were independent predictors of serum IGF-1 values, overall accounting for 39 % of IGF-1 variability. The mean IGF-1 concentration significantly increased 2 years after LAGB. BMI reduction was independently associated with IGF-1 increase ($r=-0.29$, $p<0.001$). For each point of BMI reduction, the mean increase of serum IGF-1 was 4.39 ng/mL.

Conclusions (1) Severely obese women have low IGF-1 serum levels with respect to normal weight age-matched controls; (2) the extent of IGF-1 deficiency is proportional to increased BMI; (3) after LAGB a spontaneous raise of serum IGF-1 occurs, proportional to the extent of weight reduction; and (4) serum IGF-1 in severely obese subjects may have a limited value for detection of hypothalamic–pituitary diseases.

Keywords Insulin-like growth factor-1 · Obesity · Laparoscopic adjustable gastric banding

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Published online: 18 May 2012

Introduction

Obesity is associated with abnormalities of the growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis. Both GH secretion rate and burst frequency are reduced in obese as compared to lean subjects [1]. Furthermore, morbidly obese patients show reduced GH secretion after pharmacological stimulation, with serum peak GH levels frequently comparable to those found in adult patients with organic GH deficiency [2–4]. Serum concentrations of IGF-1 reflect the combined effects of integrated GH secretion and tissue responsiveness to GH. Normal, decreased, or, in children, even increased serum levels of IGF-1 have been described in unselected obese subjects, while in severe obesity low serum concentrations have been consistently reported [5–8]. The frequent occurrence of an improvement of GH/IGF-1 activity after weight loss [9, 10] but not after a short-term hypocaloric diet [11], suggests a reversible defect of this axis strictly related to body weight. Treatment of obesity by conservative means is often disappointing. Several surgical procedures have been developed which have proven to be effective in achieving stable weight loss, reducing the mortality rate, and ameliorating co-morbidities [12, 13]. Laparoscopic adjustable gastric banding (LAGB) is one of the most popular restrictive bariatric surgical approaches worldwide that, without major alterations in the anatomy and physiology of the gastro-intestinal tract, produces sustained weight loss [14, 15]. Few studies with a 6-month follow-up have demonstrated that impairment of the GH/IGF-1 axis in severely obese patients is associated with a less effective surgical outcome [16–18], and that GH administration prevents loss of lean mass after LAGB [17]. Objective of this study was to evaluate the serum levels of IGF-1 in a population of severely obese women before and after a long-term follow-up of weight loss obtained by LAGB.

Patients and Methods

This was a historical prospective study. Eighty consecutive unrelated women with body mass index (BMI) of more than 34 kg/m^2, who were referred to our obesity clinic for evaluation before bariatric surgery, were included in this study. None of the patients was taking hypoglycemic agents. Additional exclusion criteria were: history of hypothalamic–pituitary disease, self-reported alcohol consumption >20 g daily, use of illicit drugs or hepatotoxic medications, viral hepatitis, and pregnancy or breast feeding within the 12-month period before enrolment and 2 years after it. Clinical, biochemical, and instrumental examinations of each patient were performed following the Italian guidelines for obesity, and each patient was treated according to appropriate protocols for her condition. Body weight was measured to the nearest kilogram while body height and abdominal circumference were determined to the nearest centimeter. Venous blood samples were obtained after an overnight fasting for measurement of serum IGF-1, glucose, and insulin. Serum IGF-1 was measured by a radioimmunoassay technique (SM-C-RIA-CT by DIAsource ImmunoAssay S.A., Nivelles, Belgium). GH stimulation test was not performed, based on current recommendations stating that patients who should be tested for GH deficiency are those who show evidence of hypothalamic–pituitary disease [19]. The homeostasis model of insulin resistance (HOMA) was calculated based on fasting serum glucose and insulin concentrations [20]. Ultrasound examination for determination of hepatic left lobe volume, subcutaneous, and intra-abdominal fat was performed as previously described [21, 22]. All patients underwent LAGB (Swedish Adjustable Gastric Band by Ethicon Endosurgery, Johnson and Johnson, New Brunswick, NJ, USA). Clinical, biochemical, and instrumental examinations were repeated (mean ± SD) 24.5±6.0 months after surgery. Anthropometric and serological data before and after LAGB are shown in Table 1.

Table 1 Population features before and 24 (±6)months after LAGB

	Before LAGB	After LAGB	Mean variation (%)
Age (years)	42.4±10.5	44.1±10.7	+2.0±0.4 (+4.8 %)*
Body weight (kg)	110.1±14.6	84.7±12.1	−25.4±11.8 (−23.1 %)*
BMI (kg/m^2)	42.8±5.2	32.9±4.2	−9.9±4.6 (−23.1 %)*
Insulin-like growth factor-1 (IGF-1; ng/mL)	133.3±48.1	177.1±73.2	+43.8±69.8 (+32.8 %)*
Subcutaneous adipose tissue (SAT; mm)	40.9±11.0	34.9±11.7	−6.0±12.4 (−14.7 %)*
Intra-abdominal fat (IAF; mm)	80.2±20.8	48.0±20.5	−32.2±24.2 (−40.1 %)*
Hepatic left lobe volume (HLLV; cm^3)	398.4±183.6	238.5±89.6	−159.9±155.7 (−40.1 %)*
Serum glucose (mg/dL)	98.0±18.7	84.3±8.1	−13.7±15.7 (−14 %)*
Insulin (μU/mL)	18.3±9.5	7.5±4.4	−10.9±9.9 (−59.3 %)*
HOMA index	4.5±2.7	1.6±1.0	−3.0±2.8 (−65.5 %)*

Data are reported as mean ± SD; mean variations after LAGB are also expressed as percentage of pre-operative values

*p<0.001

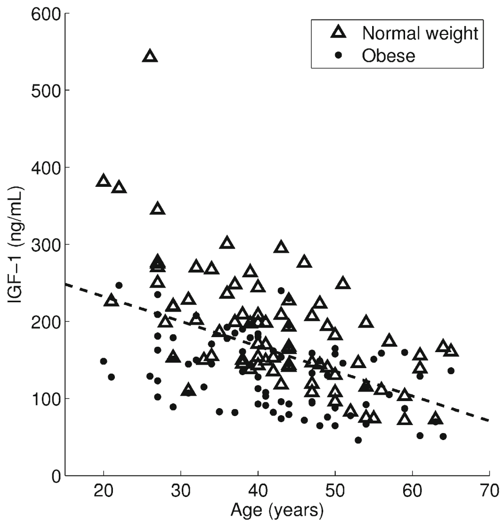

Fig. 1 Inverse relationship between age and serum IGF-1 values in the entire study group (160 subjects, *dotted* best fit line, $r=-0.48$, $p<0.001$), consisting of 80 obese patients before LAGB (*black circles*, best fit line not shown, $r=-0.42$, $p<0.001$), and 80 normal weight age-matched controls (*white triangles*, best fit line not shown, $r=-0.62$, $p<0.001$)

Eighty unrelated, age-matched, lean (BMI less than 25 kg/m^2) women, selected among a cohort of 442 healthy women, were included as controls (BMI 22.1±1.5).

Statistical Analysis

Univariate statistical analyses were performed using simple linear regression and Student's *t* test for paired or unpaired data. Spearman's rank correlation along with Mann–Whitney *U* and Wilcoxon tests were used as appropriate when the sample distribution was not Gaussian (normal distribution assessed by Kolmogorov–Smirnov test). For selected parameters (dependent variables), multiple linear regression analysis using a forward selection algorithm was employed to determine the significant predictors among the independent variables (p value<0.05). The R^2 statistic was employed to quantify the percent of variance explained by each predictor in the multivariate model. Statistical analyses were performed using Matlab (Mathworks, Natick, MA, USA). Statistical significance was considered for p values<0.05. Data are presented as mean ± SD. The variation of anthropometric and biochemical values after LAGB compared to pre-operative values is expressed as delta (Δ).

Table 2 Results of multiple regression analysis for identifying the major determinants of IGF-1 variability in the obese population before LAGB

	Explained R^2	β coefficient (95 % CI)	Std. β coef.	*t* value	Sig.
Age	24 %	−3.126 (−3.946 to −2.306)	−0.472	−7.531	$p<0.001$
BMI	Additional 15 %	−2.436 (−3.225 to −1.647)	−0.383	−6.100	$p<0.001$

Both age and BMI were independently and inversely related to IGF-1 values, explaining together 39 % of its variability

Results

Serum IGF-1 Levels in Obese Women Before LAGB and in Normal Weight Controls

Mean IGF-1 levels in the obese population before LAGB (Table 1) were significantly lower than that observed in age-matched controls (189.2±78.0 ng/mL, $p<0.001$). Serum IGF-1 values were inversely related to age ($p<0.001$), both in obese subjects before LAGB and in normal weight controls (Fig. 1). When obese and normal weight subjects were grouped, both age (explained $R^2=24$ %) and BMI (additional explained $R^2=15$ %) were found as independent predictors of serum IGF-1 concentrations (inverse correlations), overall accounting for 39 % of total IGF-1 variability (Table 2).

Serum IGF-1 Changes After LAGB: Relationships with Changes of Various Parameters

As expected, a marked reduction of mean body weight was observed in our cohort of 80 obese women after LAGB intervention (Table 1). However, there was a large difference in weight loss among patients, ranging from minimal weight loss to almost complete weight normalization (range, −1.9 to −21 %). The mean IGF-1 concentration significantly increased 2 years after LAGB and approached the levels measured in age-matched controls (Fig. 2, Table 1). A large

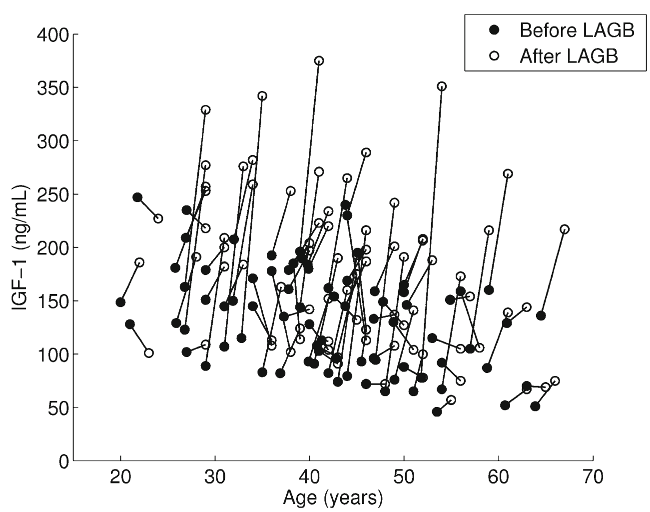

Fig. 2 Individual variations of serum IGF-1 before and after LAGB. On average, serum IGF-1 concentrations significantly increased 2 years after LAGB

inter-individual variation of serum IGF-I concentrations was observed, with some women showing a large increase while others exhibited only minimal or no changes. To identify the predictors of IGF-1 recovery after weight loss, a multivariate analysis was performed. Among various anthropometric and serologic measures, only ΔBMI was independently associated with ΔIGF-1 ($r=-0.29$, $p<0.001$). For each kilogram of weight reduction the mean increase of serum IGF-1 was 1.66 ng/mL, and for each point of BMI reduction the mean increase of serum IGF-1 was 4.39 ng/mL.

Discussion

An association between GH deficiency and obesity has been demonstrated in several studies. For this reason, a lower cutoff of GH peak after GHRH plus arginine has been advocated to detect GH deficiency in obese patients [23, 24]. Yet, in obese subjects the prevalence of GH deficiency established with adjusted cutoff remains as high as 33 % [3] and there is evidence suggesting that a BMI>25 may prevent an accurate distinction between a normal GH response and an inadequate one, resulting in the erroneous classification of overweight and obese patients as GH deficient [25]. Although conflicting data on IGF-1 levels in obesity before and after weight loss induced by caloric restriction [9–11] or LAGB bariatric surgery [16–18] have been reported, there is now sufficient evidence to conclude that decreased GH secretion is accompanied with subnormal IGF-1 levels [8].

Indeed, in our cohort of severely obese women serum IGF-1 levels were manifestly lower with respect to a carefully age-matched normal-weight population. Beside the well-established influence of age on IGF-1 levels (explaining 24 % of the total hormonal changes), in this study we demonstrate that the extent of IGF-1 deficiency was proportional to increased BMI that accounted for an additional 15 % of IGF-1 variability. The improvement of IGF-1 levels that we observed after weight loss further confirms that the obesity-related IGF-1 deficiency is an acquired condition, secondary to weight gain. Consistent with this conclusion, the increase of serum IGF-1 levels observed after LAGB was proportional to weight loss. Overall, these observations indicate that, beside age, body weight is a major determinant of serum IGF-1 levels in severely obese women. Yet, to fully understand this relationship serum IGF-1 binding proteins and body composition could be analyzed.

A careful endocrinological evaluation of obese subjects scheduled for bariatric surgery may reveal undiagnosed dysfunctions that require specific therapy and/or contraindicate the surgical treatment [26]. Among these, pituitary dysfunction has been detected in sporadic cases and no isolated GH deficiency could be demonstrated. Single IGF-1 measurements may be useful for selecting pituitary patients to be submitted to the GHRH-arginine test, thus reducing the need for a stimulatory test in many subjects [27]. Data from the current study indicate that low IGF-1 values may occur secondarily to the obese state, and therefore serum IGF-1 in severely obese subjects may have a limited value for detection of hypothalamic–pituitary diseases, since it may represent an adaptation of the GH/IGF-1 axis to the obese state.

Recombinant GH administration has been advocated for the treatment of obesity [28], and it has been recently tested to prevent loss of lean mass after bariatric surgery, with improvement of lipid profile and without affecting glucose tolerance [17]. Interestingly, while a significant increase of IGF-1 values was observed in the treated group, there was no evidence of IGF-1 improvement at 3 and at 6 months after LAGB in the control group. The results of our study suggest that the increase of serum IGF-1 levels occurs at a later time point, between 6 months and 2 years, when most likely a “critical” bulk of weight loss has been achieved.

In conclusion, the results of our study demonstrate that: (1) severely obese women have low IGF-1 serum levels with respect to age-matched normal weight controls; (2) the extent of IGF-1 deficiency is proportional to increased BMI that accounts for approximately 15 % of IGF-1 variability; (3) after LAGB, a spontaneous raise of serum IGF-1 occurs, proportional to the extent of weight loss; and (4) serum IGF-1 in severely obese subjects may have a limited value for detection of hypothalamic–pituitary diseases.

Acknowledgments This work was supported by the following research grants: “Pathogenetic mechanisms determining the obese phenotype and influencing the response to treatment” Ministero dell’Università e della Ricerca, Programmi di Ricerca Scientifica 2007; “Obesity: development of new strategies for prevention of obesity and its complications” Ministero del Lavoro, della Salute e delle Politiche Sociali, CCM 2008.

Conflict of Interest The authors declare no conflict of interest.

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