

Growth Hormone treatment prevents loss of lean mass after bariatric surgery in morbidly obese patients.

Results of a pilot, open, prospective, randomized, controlled study

SILVIA SAVASTANO¹, CAROLINA DI SOMMA¹, LUIGI ANGRISANI², FRANCESCO ORIO^{1,3},
SALVATORE LONGOBARDI⁴, GAETANO LOMBARDI¹ AND ANNAMARIA COLAO¹

1. Department of Molecular and Clinical Endocrinology and Oncology, Division of Endocrinology, University Federico II of Naples, via S. Pansini 5, 80131 Naples
2. Department of Surgery, S.Giovanni Bosco Hospital of Naples, via F.M. Briganti 255, 80144 Naples Italy
3. Endocrinology University Parthenope Naples, Via Acton 38, 80133 Naples Italy
4. Department of Medical Affairs Merck-Serono Italia, Via Casilina 125, 00176 Rome Italy

Short title GH treatment and weight loss after LASGB

Key words Morbid Obesity, Body Composition, GH treatment, LASGB

Acknowledgements This study has been registered in the ClinicalTrials.Org Database with the number NCT00553852. It was partially supported by an unrestricted grant from MERCK-SERONO, Italy, to the Department of Molecular and Clinical Endocrinology and Oncology, Division of Endocrinology, University Federico II of Naples. We thank dr. Emanuele Nicolai (SDN, Naples) for kindly providing DEXA analyses.

Word count Abstract 250, Text 3595; Tables 2, Figures 5; References 52.

The Disclosure of the manuscript n. 08-1476 version **3** by Authors

SILVIA SAVASTANO, CAROLINA DI SOMMA, LUIGI ANGRISANI, FRANCESCO ORIO,
SALVATORE LONGOBARDI, GAETANO LOMBARDI and ANNAMARIA COLAO

have nothing to declare.

Mailing address

Annamaria Colao, MD, PhD

Department of Molecular & Clinical Endocrinology and Oncology

"Federico II" University of Naples,

via S. Pansini 5, 80131 Naples

ph. +39-081-7462132; fax +39-081-5465443; email colao@unina.it

Abstract

Context: The loss of lean body mass (LBM) negatively influences outcome in bariatric surgery. Impaired Growth Hormone (GH) secretion is frequent in obese patients.

Objective: To investigate if GH treatment prevents LBM loss in the early post-operative period.

Design: Open, prospective, randomized, controlled.

Patients: 24 women (BMI: 44.4 ± 7.6 kg/m², aged 36.8 ± 11.7 yrs) undergoing laparoscopic-adjustable silicone gastric banding (LASGB) and with GH deficiency after LASGB.

Treatment protocol: Group A (n=12): standardized diet regimen and exercise program plus recombinant human GH (0.5 ± 0.13 mg every day); Group B (n=12) standardized diet regimen and exercise program. Follow-up duration 6 months.

Results: Excess of body weight loss did not differ between group A and B after 3 and 6 months. At 3 months, LBM loss was lower ($p < 0.0001$) and FM loss was higher ($p = 0.02$) in group A than in group B. At 3 and 6 months, appendicular skeletal muscle mass (ASMM) loss was lower ($p = 0.000$) in group A than in group B. At 3 ($p = 0.0003$ and 0.0005 , respectively) and 6 months ($p < 0.0001$ and 0.0002 , respectively) the percent changes of FM and FFM were significantly higher in group A than in group B. In both groups fasting and post-glucose AUC insulin significantly reduced. The HOMA and the ISI indexes and total/HDL cholesterol ratio improved only in group A.

Conclusions: GH treatment for 6 months after LASGB reduces loss in LBM and ASMM during a standardized program of low calorie diet and physical exercise program, with improvement of lipid profile and without a deterioration of glucose tolerance.

Introduction

Obesity should be considered an onerous world-wide problem, because of the impressive number of associated complications (1). The subgroup of individuals with Class III or morbid obesity, defined as $BMI > 40 \text{ kg/m}^2$, are a particular concern due to both health risk concerns and resistance to medical therapy (2). In the U.S., it is estimated that 5% of the population currently has Class III obesity.

Bariatric surgery currently provides the only long-term control of obesity, resulting in major weight loss and its long-term maintainance. Consensus recommendations are for consideration of bariatric surgery in adults with $BMI > 35\text{-}40 \text{ kg/m}^2$ with a co-morbidity (Class II obesity) or $> 40 \text{ kg/m}^2$ (Class III obesity) (3).

Laparoscopic-adjustable silicone gastric banding (LASGB) is a purely restrictive operation that induces early satiety by a small gastric pouch and does not, apparently, induce malabsorption (4,5). Along with a significant weight-loss and changes in eating behavior, LASGB is an effective surgical procedure in improving obesity-related co-morbidities (4-6).

Among endocrine changes post-LASGB, those related to the Growth Hormone (GH) and insulin-like growth factor (IGF)-I system have been investigated as importantly related to surgery-associated results. GH and IGF-I have major anabolic and lipolytic actions on muscle, adipose and hepatic tissue (7,8). IGF-I, the mediator of the GH effects, is used as a measure of GH bioactivity as it almost accurately reflects the GH secretory status (9).

However, different factors, primarily age, gender, body composition, nutritional driven components, and glucose homeostasis have been reported to affect IGF-I metabolism (10).

A "functional" GHD was suggested to occur in obese subjects as one of the multiple maladaptative endocrine changes involved in the pathogenesis of both obesity and metabolic syndrome (11-14). The GHD in obesity is, however, generally reversible as massive weight loss is followed by normalization of 24-hour GH release (15).

In analogy with others (14,16,17), we found a relationship between the GH/IGF-I axis and body composition in morbidly obese patients (18). In prospective study conducted in 72 morbidly obese women undergoing LASGB, we found that 6 months after surgery, when the initial catabolic state should have already been overcome, 19.4% of patients were still diagnosed as GH and IGF-I deficient and another 19.4% had IGF-I levels still below normal ranges (19).

To investigate the potential role of GH treatment in determining loss of body weight in morbidly obese patients undergoing LASGB we designed this pilot, open, prospective, randomized, placebo-controlled study. The trial included only patients showing deficient GH and IGF-I secretion one month post-surgery.

Subjects and Methods

Inclusion criteria:

- 1) Functional severe GHD diagnosed by a peak GH ≤ 4.2 $\mu\text{g/L}$ (20) after GHRH+ARG test according to Ghigo et al. (21) performed within 1 month after LASBG;
- 2) Female gender
- 3) Indication of LASGB for the treatment of obesity (3);
- 4) Absence of diabetes mellitus, liver or renal failure, cancer, and acute or chronic inflammatory diseases based on a complete medical examination and laboratory investigations;
- 5) Absence of any other pituitary deficiencies (22).

Exclusion criteria:

- 1) Liver or renal failure, cancer, acute or chronic inflammatory diseases;
- 2) Chronic treatment with any type of medications;
- 3) pituitary deficiency as documented by diagnostic testing (22);
- 4) Bulimia Nervosa of the DSM-IV;
- 5) Ulcers or malignancies excluded by oesophago-gastro-duodenoscopy.

Patients:

Of 285 patients coming to our Department with morbid obesity, 72 patients were diagnosed as functional severe GHD. Twenty-four females (BMI: 44.4 ± 7.6 kg/m^2 , aged 36.8 ± 11.7 yrs), fulfilling all inclusion criteria, were enrolled in this study after their written consent had been obtained (Fig.1). Patients were given a standardized interview to obtain information about the duration of obesity, eating patterns, smoking habits and physical exercise. In particular, subjects were also asked to make a daily record of the amount of physical activity (no exercise; ≤ 2 -3 h/week; ≥ 2 -3 h/week). The estimation of dietary intake was assessed by Winfood (Medimatica software medico 1999, Rome, Italy). The daily calorie intake and diet composition were calculated during a personal interview, using a detailed food-frequency questionnaire of 130 foods and beverages (23). All patients were surgically treated at the Department of Surgery, S-Giovanni Bosco Hospital, Naples, Italy. LASGB was performed with the Lap-Band™ System (Inamed Health, Santa Barbara, CA) according to Kuzmak (24). To minimize postoperative vomiting, the band was left completely unfilled at surgery (25,26). At discharge, patients were instructed to follow a solid diet containing an inventory of the

foods permitted and a list of rules specifically developed for patients with gastric restriction (26). The diet was arranged to fit an energy intake of 5.7 MJ/day (55% carbohydrate, 25% fat, 20% protein, 30 g fiber). As also previously reported (19) resting energy expenditure (REE) was indirectly measured at baseline. Physical activity was encouraged; it consisted primarily of 60–90 min/day of moderate–intensity activity (e.g., brisk walking). The band was tightened in case of weight stabilization (<4 kg of weight lost in the last month), providing that a solid food item per meal was ingested and a low vomiting frequency was observed. No more than one adjustment per month was performed and no more than 1.5 ml of sterile saline was added in each step. Band competence was always controlled with a barium swallow before and after the adjustment.

Study design:

This is an open, prospective, randomized controlled study. The study was approved by the Ethical Committee of the University Hospital Federico II and was conducted in accordance with the Helsinki II declaration. The study has been registered in the ClinicalTrials.Org Database (NCT00553852). At study entry, after confirming that all entry criteria were fulfilled and all patients signed the informed consent, the patients were randomized into two groups, one receiving GH therapy and one followed as standard procedures (as detailed below), following a randomization list that was in the hand of AC not included in the patients clinical observation and treatment.

Treatment protocol:

At study entry the 24 patients were randomized in two groups of treatment: Group A= 12 patients received standardized diet regimen and exercise program plus recombinant human GH (Saizen, Merck-Serono, Italy) at a dose of 0.5 ± 0.13 mg every day; Group B= 12 patients received standardized diet regimen and exercise program only without the additional GH treatment. Patients' profile is reported in **Table 1**. The duration of follow-up was 6 months.

Outcome measures:

The primary outcome measures were percent of excess body weight loss (EBWL), decrease of fat mass (FM) and lean body mass (LBM), Secondary outcome measure were BMI, waist circumference, appendicular skeletal muscle mass (ASMM), and glucose tolerance. Insulin resistance (HOMA-R - homeostasis model assessment of insulin resistance) (27) and sensitivity (ISI - Insulin Sensitivity Index) indexes (28), plus lipid profile were assessed. Changes in lipid profile was also analyzed by calculating the total/HDL cholesterol ratio, considered as a major cardiovascular risk factor (29).

Study protocol:

At baseline (within 1 month after LASGB) and 3 and 6 months thereafter, the following parameters were measured:

1. Anthropometric measurements, performed with the subjects wearing only underwear without shoes. Standing height was measured to the nearest cm using a wall-mounted stadiometer. Body weight was determined to the nearest 50 g using a calibrated balance

beam scale. Body mass Index (BMI) was calculated as weight (kg) divided by height squared (m^2) and used as an index for obesity. Measurements of the waist circumference were taken at the mid-point between umbilicus and xiphoid. The ideal body weight (IBW) was calculated according to the Broca's formula (IBW= in men height (cm) -100; in women height (cm) – 104). The EBW was calculated as difference with IBW in kg and as percent. The EBWL was calculated as decrease of EBW during the follow-up and was calculated as difference in kg and as percent value of baseline.

2. LBM and FM were determined using dual-energy X-ray absorptiometry-DEXA. DEXA scans for the whole body (Hologic QDR 4500A S/N 45622) were performed by a trained technician while subjects were in a supine position. Whole-body scan time was less than 2 minutes, and the radiation was 1 milirem. The mean coefficients of variation (CV) for the repeated DEXA analyses were: TBMD, 0.84%; FM, 2.20%; and LBM, 0.86%. Reliability of the DEXA was assessed by phantom scans throughout the duration of the study. All scans were performed by the same DEXA operator blind in respect to patients treatment. LBM was indirectly calculated LBM is indirectly calculated as weight minus BMC minus FM. Body regions (arms, legs, trunk and head) are delineated with the use of specific anatomical landmarks and ASMM was calculated. Soft tissue hydration of individual subjects was evaluated by impedance vector analysis (BIVA) using the BIVA software, as previously reported (18). Resistance (R) and Reactance (X_c) vectors were plotted on RX_c graph. Vectors falling within the reference gender-specific 75th tolerance ellipse indicated normal hydration.

3. The OGTT was performed using 75 g dextrose according to the criteria of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (34). Blood glucose levels were determined by the glucose oxidase method immediately after the OGTT. Serum insulin was measured by a solid-phase chemiluminescent enzyme immunoassay using commercially available kits (Immunolite). Fasting serum total, HDL, and LDL cholesterol and triglycerides were assayed on serum by enzymatic colorimetric methods using commercially available kits (Roche Molecular Biochemicals, Mannheim, Germany). The GHRH (1-29, Geref, Serono, Rome, Italy)+ARG (arginine hydrochloride, Salf, Bergamo, Italy) was performed according to Ghigo et al. (21). The GH response after ARG+GHRH was classified as deficient (GHD) when the GH peak was $\leq 4.2 \mu g/L$ and sufficient (GHS) when the GH peak was $> 4.2 \mu g/L$ (20). Serum GH levels were measured by immunoradiometric assay (IRMA) using commercially available kits (HGH-CTK-IRMA, Sorin, Saluggia, Italy). The sensitivity of the assay was $0.02 \mu g/L$. The intra- and interassay CVs were 4.5 and 7.9%, respectively. Circulating IGF-I levels measured by IRMA after ethanol extraction using Diagnostic System Laboratories Inc. (Webster, Texas, USA). The normal ranges in ≤ 20 , 21-30, 31-40, 41-50 and 51-60 yr old men were 180-625, 118-475, 102-400, 100-306, 95-270 $\mu g/l$, respectively, whereas in women they were 151-530, 118-450, 100-390, 96-288, 90-250 $\mu g/l$, respectively. The sensitivity of the assay was $0.8 \mu g/l$. The intra-assay CVs were 3.4, 3.0 and 1.5% for low, medium and high

points of the standard curve, respectively. The inter-assay CVs were 8.2, 1.5 and 3.7% for low, medium and high points of the standard curve. The standard deviation score (SDS) for age and gender was also calculated. For the purpose of this study, IGF-I levels were classified as normal when higher than -2 SD and deficient when it was lower than -2 SD (9).

4. A questionnaire to investigate eating pattern and physical exercise was administered to all subjects.

Statistical analysis:

Values are given as mean \pm SD unless otherwise specified. Comparison between patients receiving or not GH at baseline, at the 3 and 6 month follow-up was performed by the Mann-Whitney test. Within single groups, the comparison between 3 and 6 month follow-up vs. baseline was performed by Wilcoxon-Signed Rank test. The comparison among baseline, 3 and 6 months results was performed by the Kruskal-Wallis test. The area under the plasma concentration-time curve (AUC) of glucose and insulin above basal during glucose load was calculated using the trapezoidal rule. Statistical significance was set at 5%.

Results

In all the patients no post-operative complications occurred. The composition of the diet corresponded to dietary prescriptions in all cases. None of the patients reported to exercise regularly. Of the 24 patients only one patient of group B did not complete the study protocol after 2 months due to the scarce compliance of patient to dietetic regimen. In both group A and B, either before and after surgery, the soft tissue hydration, according to the RXc graph method, showed that no subject vectors were below the boundary line threshold discriminating between the obese and the oedematous, indicating a normal hydration. All vectors fell in the lower left quadrant, out of the boundary line of 75th tolerance ellipse, as expected in morbidly obese patients with normal hydration. After randomization, the two groups were comparable for all parameters, except for LBM (Table 1).

ASMM also were not significantly different between the two groups (Group A: 28.1 \pm 1.8 Kg vs. Group B: 29.6 \pm 2.0; p=0.069).

Study results are summarized in Table 2. In GH treated patients, IGF-I levels significantly increased (Fig.2).

Main outcome measures (Table 2)

As for EBWL calculated as percent value of baseline, there was no difference between group A and B after 3 and 6 months (Fig.3). After 3 months, the loss of LBM was lower

($p < 0.0001$) and the loss of FM were higher ($p = 0.02$) in patients of group A than in those of group B, and were not evident after 6 months ($p = 0.34$ and $p = 0.69$, respectively). Both after 3 ($p = 0.0003$ and 0.0005 , respectively) and 6 months ($p < 0.0001$ and 0.0002 , respectively) the percent changes of FM and LBM were significantly higher in patients of group A than in those of group B.

Secondary outcome measures (Table 2)

BMI significantly reduced in both groups and weight decrement was slightly but significantly higher in group B than in group A ($p = 0.046$). Waist circumference decreased significantly in both groups with a similar extent, while the loss of ASMM was lower in group A than in group B ($p = 0.09$, $p = 0.01$ at 3 and 6 months respectively). In both groups, fasting and post-glucose AUC levels of glucose did not change while fasting and post-glucose AUC levels of insulin significantly reduced (Fig.5). The HOMA and the ISI indexes, however, improved only in group A patients. Similarly, the total/HDL cholesterol ratio, significantly reduced only in group A patients.

Discussion

This study demonstrate that GH treatment for 6 months in a selected group of functional GHD obese females undergoing LASGB was followed by a significant decrease of FM and increase in LBM and ASMM, with improvement of lipid profile and no deterioration of glucose tolerance. Instead, insulin resistance and sensitivity indexes improved only in GH-treated patients though insulin levels reduced in all patients. These effects were noticed even if the amount of weight loss and waist circumference was similar in the two groups.

The golden goal of every ideal weight-reducing interventions for obesity is to selectively lose body fat while retaining lean body mass. No pharmacological agents are currently available to achieve this goal and caloric restriction is usually accompanied by catabolism of body proteins with negative nitrogen balance (31,32). Bariatric surgery is an option for people who are morbidly obese and cannot lose weight by traditional means or who suffer from serious obesity-related health problems (4-6). However, apart from the effectiveness of bariatric procedures in reducing body weight and obesity-related diseases, the maintenance of LBM is of particular concern in obese patients after bariatric surgery because of the serious complications associated with rapid and sustained weight loss (6).

In a recently published meta-analysis to identify the proportion of weight loss as LBM by various weight loss interventions, both malabsorptive and mixed restrictive and malabsorptive procedures, such as biliopancreatic diversion and gastric bypass, respectively, result in greater LBM loss than LASGB (33). In particular, especially associated with a well balanced low-calorie diet, LASGB seems to achieve satisfactory weight losses mainly due to decreased fat mass, while sufficiently sparing LBM (34). In this context, however, we recently observed that after LASGB the percentage of LBM was lower in the subgroups of morbidly obese patients with persistent obesity-related deficiency in the GH/IGF-I axis, with post-operative IGF-I levels as the strongest determinant of the percent changes of FM, fat-free mass and EBWL (19).

GH has anabolic and lipolytic properties (7,8,35). Clinical studies evidenced that GH therapy in adult patients with GHD resulted in decreased fat mass, C-reactive protein, carotid intima-media thickness, truncal and visceral adiposity, and in improving lipid profile (36). Despite these evidence, an *in vivo* role for GH in human fat balance has not been completely defined, and trials of GH therapy in obesity have given equivocal results (37-40). Some studies have shown that insulin resistance and glucose concentrations transiently worsen during the first few weeks of GH treatment and that these deleterious effects can persist even after visceral adipose tissue reduction has occurred (38). Moreover, it should also be noted that IGF-I may have adipogenic effects, particularly in the presence of insulin-induced reduction of the IGF-I inhibitory binding protein, IGFBP-1 (39). Conversely, in other studies, a combination of GH administration and caloric restriction has been proved to be effective in obese and/or abdominally obese men in reducing total body fat, abdominal fat, diastolic blood pressure, LBM, daily nitrogen balance, and REE, and in improving glucose and lipoprotein metabolism (40-42). GH treatment was responsible for the restored insulin sensitivity through the decrease in visceral tissue mass, followed by a decrease in free fatty acid exposure to the liver, counteracting the insulin-antagonistic effect of GH. Alternatively, it might be hypothesized an increased glucose transport in the skeletal muscle, the major site of glucose disposal, mediated through the IGF-I receptor, an increased proportion of insulin-sensitive type I muscle fibres, or increased capillarization in the skeletal muscle (43). Subsequently, the striking lipolytic effect of GH on visceral adipose tissue has been associated with a GH-induced reduction in the anti-lipolytic effects of insulin, which has been reported to be markedly different in different adipose tissue regions (44). This is consistent with more recent data obtained in healthy women with visceral adiposity in absence of generalized obesity in that one year of GH replacement therapy resulted in decreasing both visceral

adiposity, insulin sensitivity, and cardiovascular risk markers in this study population (45). In a double-blind, placebo-controlled 6-month intervention trial followed by a blinded follow-up period of 6 months of 30 non diabetic middle-aged men with central adiposity, Pasarica et al. (46) have also shown an increase in weight and lean body mass and 8.8% reduction in visceral adiposity. They have also reported fasting insulin, glucose, and the quantitative insulin sensitivity check index for insulin resistance increased during GH therapy. However, the effects of GH on fatness and visceral adiposity disappeared shortly after GH withdrawal. In this context, in our study group we found that the post-operative percent changes of FM were significantly higher in GH treated than in non GH treated patients, both after 3 and 6 months.

GH therapy has been also shown to preserve LBM in catabolic conditions (e.g. hypocaloric diets, wasting conditions, glucocorticoid therapy). Since hypocaloric diets are commonly recommended post-bariatric surgery, GH supplementation could theoretically help to conserve lean mass during this period, with increase in resting energy expenditure. Studies related to GH treatment of bariatric surgery patients with obesity-related abnormalities of GH/IGF-I axis have not been published. In the present study, apart from any weight loss adjunctive effects, we evaluated the possible favourable influence of the GH replacement treatment during the early post-operative period in preventing loss of LBM, a crucial event to ensure an optimal outcome of surgery in terms of long-lasting body weight loss. Indeed, at the end of the study we found a same amount of EBWL in patients treated with GH than in those who did not, but in the former the weight loss was mainly due to FM loss while LBM and ASMM were reduced. The BIVA analysis allows us to evidence a normal hydration in both groups, either at baseline or during the follow up, thus excluding any interference on LMB calculation by DEXA due the possible fluid retentive effects of GH replacement treatment. Conversely, as REE was evaluated only at baseline, it is not possible to evidence any possible role of GH treatment not only in FFM sparing but also in increasing REE as an adjunctive advantage for GH treatment during weight loss, as previously reported by Tagliaferri et al., 1998 (41). The beneficial effects of GH treatment were also accompanied by an improvement of lipid profile without a deterioration of glucose tolerance. In contrast, GH treated patients achieved improved insulin sensitivity and reduced insulin resistance as compared to those who did not receive GH treatment. Clearly, 6 months of treatment with GH could be considered not sufficient to respond to the requirement of optimal body weight loss: in our series EBW was still 37.2 ± 15.3 and 37.4 ± 19.3 kg in GH treated and untreated patients, respectively.

Finally, an increased endogenous GH secretion and the recovery of all components of the ghrelin/GH/IGF axis have been noted in a number of studies 6-12 months after bariatric surgery (47-50). In this context, the exogenous administration of GH could be considered to have a detrimental effect on this recovery by suppressing endogenous recovery of secretion. Nevertheless, our previous observations at 6 months after LASGB clearly evidenced the presence of a discrepancy between the GH response to the pharmacological stimulus and low IGF-I levels (19), as also observed in catabolic conditions (51) and after malabsorptive bariatric surgical procedures (52).

Conclusion

GH treatment for 6 months is able to reduce loss in LBM and ASMM during a standardized program of low calorie diet and physical exercise program in a group of morbidly obese female patients undergone LASGB with persistent GH response in the range of severe GHD diagnosis and with low IGF-I levels. This evidence opens a new frontier for GH therapy in the management of morbid obese patients and might allow a better understanding of the physiological relevance of GH the pathogenesis of the multiple maladaptative endocrine changes involved in the pathogenesis of obesity and the metabolic syndrome. However, in consideration of the costs of rhGH replacement therapy, a careful cost-benefit analysis is required taking into account also the cost of a commonly used therapy for management of morbidly obese patients and the significant improvement in well-being, quality of life, energy level, and work capacity demonstrated after GH replacement in adult hypopituitary GHD.

References

1. **Malnick SDH, Knobler H** 2006 The medical complications of obesity. *Q J Med* 99:565–579
2. **Hensrud DD, Klein S** 2006 Extreme obesity: A new medical crisis in the United States. *Mayo Clin Proc* 81:S5-S10
3. **National Institutes of Health Consensus Development Conference 1992** Gastrointestinal surgery for severe obesity. *Am J Clin Nutr* 55:615s–619s
4. **O'Brien PE, Dixon JB, Laurie C, Skinner S, Proietto J, McNeil J, Strauss B, Marks S, Schachter L, Chapman L, Anderson M** 2006 Treatment of mild to moderate obesity with laparoscopic adjustable gastric banding or an intensive medical program: a randomized trial. *Ann Intern Med* 144:625-633
5. **Kral JG, Näslund E** 2007 Surgical treatment of obesity. *Nat Clin Pract Endocrinol Metab* 3:574-583
6. **Shah M, Simha V, Garg A** 2006 Long-Term Impact of Bariatric Surgery on Body Weight, Co-Morbidities, and Nutritional Status: A Review. *J Clin Endocrinol Metab* 91:4223-4231
7. **Russell-Jones DL, Weissberger AJ, Bowes SB, Kelly JM, Thomason M, Umpleby AM, Jones RH, Sonksen PH** 1993 The effects of growth hormone on protein metabolism in adult growth hormone deficient patients. *Clin Endocrinol (Oxf)* 38:427–431
8. **Møller N, Jorgensen JO, Møller J, Orskov L, Ovesen P, Schmitz O, Christiansen JS, Orskov H** 1995 Metabolic effects of growth hormone in humans. *Metabolism* 44 (10 Suppl 4):33-36
9. **Growth Hormone Research Society (GRS)** 1998 Consensus guidelines for the diagnosis and treatment of adults with growth hormone deficiency: summary statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency *J Clin Endocrinol Metab* 83:379–381
10. **Frystyk J** 2004 Free insulin-like growth factors: measurements and relationships to growth hormone secretion and glucose homeostasis. *Growth Horm IGF Res* 14:337-375
11. **Maccario M, Valetto MR, Savio P, Aimaretti G, Baffoni C, Procopio M, Grottoli S, Oleandri SE, Arvat E, Ghigo E** 1997 Maximal secretory capacity of somatotrope cells in obesity: comparison with GH deficiency. *Int J Obes Relat Metab Disord* 21:27-32
12. **Scacchi M, Pincelli AI, Cavagnini F** 1999 Growth hormone in obesity. *Int J Obesity* 23: 262-271
13. **Savastano S, Di Somma C, Mentone A, Savanelli MC, De Leo M, Lombardi G, Colao A** 2006 GH insufficiency in obese patients. *J Endocrinol Invest (Suppl. 5):*42-53
14. **Franco C, Bengtsson BA, Johannsson G** 2001 Visceral obesity and the role of the somatotrophic axis in the development of metabolic complications. *Growth Horm IGF Res* 11:S97-S102
15. **Rasmussen MH, Hvidberg A, Juul A, Main KM, Gotfredsen A, Skakkebae NE, Hilsted J** 1995 Massive weight loss restores 24-hour growth hormone release profiles and serum insulin-like growth factor-I levels in obese subjects. *J Clin Endocrinol Metab* 80:1407–1415
16. **Maccario M, Ramunni J, Oleandri SE, Procopio M, Grottoli S, Rossetto R, Savio P, Aimaretti G, Camanni F, Ghigo E** 1999 Relationships between IGF-I and age, gender, body mass, fat distribution, metabolic and hormonal variables in obese patients. *Int J Obes Relat Metab Disord* 23:612-618
17. **Voorhoeve PG, van Rossum EF, Te Velde SJ, Koper JW, Kemper HC, Lamberts SW, de Waal HA** 2006 Association between an IGF-I gene polymorphism and body fatness: differences between generations. *Eur J Endocrinol* 154:379-388
18. **Savastano S, Di Somma C, Belfiore A, Guida B, Orio Jr F, Rota F, Savanelli MC, Cascella T, Mentone A, Angrisani L, Lombardi G, Colao A** 2006 Growth hormone status in morbidly obese subjects and correlation with body composition. *J Endocrinol Invest* 29:536-543
19. **Di Somma C, Angrisani L., Rota F, Savanelli MC, Cascella T, Belfiore A, Orio F, Lombardi G, Colao A, Savastano S** 2008 Growth Hormone and Insulin-Like Growth Factor-I deficiency are associated with reduced loss of fat mass after laparoscopic- adjustable silicone gastric banding. *Clin Endocrinol (Oxf)* Jan 10; [Epub ahead of print]

20. **Corneli G, Di Somma C, Baldelli R, Rovere S, Gasco V, Croce CG, Grottoli S, Maccario M, Colao A, Lombardi G, Ghigo E, Camanni F, Aimaretti G** 2005 The cut-off limits of the GH response to GH-releasing hormone-arginine test related to body mass index. *Eur J Endocrinol* 153:257-264
21. **Ghigo E, Aimaretti G, Gianotti L, Bellone J, Arvat E, Camanni F** 1996 New approach to the diagnosis of growth hormone deficiency in adults. *Eur J Endocrinol* 134:352-356
22. **Lamberts SW, de Herder WW, van der Lely AJ** 2008 Pituitary insufficiency. *Lancet* 352:127-134
23. **Hu FB, Rimm E, S Smith-Warner A, Feskanich D, Stampfer MJ, Ascherio A, Sampson L, Willett WC** 1999 Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire. *Am J Clin Nutr* 69:243-249
24. **Kuzmak LI** 1991 A review of seven years' experience with silicone gastric banding. *Obes Surg* 1:403-408
25. **Angrisani L, Lorenzo M, Esposito G, Romano G, Puzziello A, Belfiore A, Santoro T, Roina G, Petito A, Falconi C, Tesouro B** 1997 Laparoscopic adjustable silicone gastric banding: preliminary results of Naples experience. *Obes Surg* 7:19-21
26. **Busetto L, Pisent C, Segato G, De Marchi F, Favretti F, Lise M, Enzi G** 1997 The influence of a new timing strategy of band adjustment on the vomiting frequency and the food consumption of obese women operated with laparoscopic adjustable silicone gastric banding (LAP-BAND®). *Obes Surg* 7:505-512
27. **Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC** 1985 Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412-419
28. **Matsuda M, DeFronzo RA** 1999 Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 22:1462-1470
29. **Castelli WP** 1996 Lipids, risk factors and ischaemic heart disease. *Atherosclerosis* 124 Suppl:S1-S9
30. **Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus** 1997 *Diabetes Care* 20:1183-1197.
31. **Van Gaal LF, Vansant GA, De Leeuw IH** 1992 Factors determining energy expenditure during very-low-calorie diets. *Am J Clin Nutr* 56 (1 Suppl):224S-229S
32. **Anderson JW, Konz EC, Frederich RC, Wood CL** 2001 Long-term weight-loss maintenance: a meta-analysis of US studies. *Am J Clin Nutr* 74:579-5784
33. **Chaston TB, Dixon JB, O'Brien PE** 2006 Changes in fat-free mass during significant weight loss: a systematic review. *Int J Obes (Lond)* 31:743-750
34. **Coupaye M, Bouillot JL, Poitou C, Schutz Y, Basdevant A, Oppert JM** 2007 Is lean body mass decreased after obesity treatment by adjustable gastric banding ? *Obes Surg* 17:427-433
35. **Møller N, Gjedsted J, Gormsen L, Fuglsang J, Djurhuus C** 2003 Effects of growth hormone on lipid metabolism in humans. *Growth Horm IGF Res* 13:S18-S21
36. **Colao A, Di Somma C, Savanelli MC, De Leo M, Lombardi G** 2006 Beginning to end: cardiovascular implications of growth hormone (GH) deficiency and GH therapy. *Growth Horm IGF Res*:S41-S48
37. **Johannsson G, Marin P, Lonn L, Ottosson M, Stenlof K, Bjorntorp P, Sjostrom L, Bengtsson BA** 1997 Growth hormone treatment of abdominally obese men reduces abdominal fat mass, improves glucose and lipoprotein metabolism, and reduces diastolic blood pressure. *J Clin Endocrinol Metab* 82:727-734
38. **Shadid S, Jensen MD** 2003 Review. Effects of growth hormone administration in human obesity. *Obes Res* 11:170-175
39. **Albert SG, Mooradian D** 2004 Low-Dose Recombinant Human Growth Hormone as Adjuvant Therapy to Lifestyle Modifications in the Management of Obesity. *J Clin Endocrinol Metab* 89:695-701
40. **Attallah H, Friedlander AL, HoLBMAn AR** 2006 Visceral obesity, impaired glucose tolerance, metabolic syndrome, and growth hormone therapy. *Growth Horm IGF Res* 16:S62-S67

41. **Tagliaferri M, Scacchi M, Pincelli AI, Berselli ME, Silvestri P, Montesano A, Ortolani S, Dubini A, Cavagnini F** 1998 Metabolic effects of biosynthetic growth hormone treatment in severely energy-restricted obese women. *Int J Obes Relat Metab Disord* 22:836-841
42. **Laron Z, Ginsberg S, Lilos P, Arbiv M, Vaisman N** 2006 Long-term IGF-I treatment of children with Laron syndrome increases adiposity. *Growth Horm IGF Res* 16:61-64
43. **Lund S, Flyvbjerg A, Holman GD, Larsen FS, Pedersen O, Schmitz O** 1994 Comparative effects of IGF-I and insulin on the glucose transporter system in rat muscle. *Am J Physiol* 267(3 Pt 1):E461-E466
44. **Rosenbaum M, Gertner JM, Leibel RL** 1989 Effects of systemic growth hormone (GH) administration on regional adipose tissue distribution and metabolism in GH-deficient children. *J Clin Endocrinol Metab* 69:1274-1281
45. **Franco C, Brandberg J, Lönn L, Andersson B, Bengtsson BA, Johannsson G** 2005 Growth hormone treatment reduces abdominal visceral fat in postmenopausal women with abdominal obesity: a 12-month placebo-controlled trial. *J Clin Endocrinol Metab* 90:1466-1474
46. **Pasarica M, Zachwieja JJ, Dejonge L, Redman S, Smith SR** 2007 Effect of growth hormone on body composition and visceral adiposity in middle-aged men with visceral obesity. *J Clin Endocrinol Metab* 92:4265-4270
47. **Holdstock C, Engström BE, Ohrvall M, Lind L, Sundbom M, Karlsson FA** 2003 Ghrelin and adipose tissue regulatory peptides: effect of gastric bypass surgery in obese humans *J Clin Endocrinol Metab*.88:3177-83
48. **Mancini MC, Costa AP, de Melo ME, Cercato C, Giannella-Neto D, Garrido AB Jr, Rosberg S, Albertsson-Wikland K, Villares SM, Halpern A** 2006 Effect of gastric bypass on spontaneous growth hormone and ghrelin release profiles. *Obesity* 14: 383-387
49. **Ram E, Vishna T, Diker D, Gal-Ad I, Maayan R, Lerner I, Dreznik Z, Seror D, Vardi P, Weizman A** 2005 Impact of gastric banding on plasma ghrelin, growth hormone, cortisol, DHEA and DHEA-S levels. *Obes Surg* 15:1115-1123
50. **Engström BE, Burman P, Holdstock C** 2006 Effects of gastric bypass on the GH/IGF-I axis in severe obesity and a comparison with GH deficiency. *Eur J Endocrinol* 154: 53-59
51. **Mauras N and Haymond, MW** 2005 Are the metabolic effects of GH and IGF-I separable? *Growth Hormone & IGF Research* 15:19-27
52. **De Marinis L, Bianchi A, Mancini A, Gentilella R, Perrelli M, Giampietro A, Porcelli T, Tilaro L, Fusco A, Valle D, Tacchino RM** 2004 Growth hormone secretion and leptin in morbid obesity before and after biliopancreatic diversion: Relationships with insulin and body composition. *J Clin Endocrinol Metab* 89:174-180

Legends to figures

Figure 1: Patients enrollment.

Figure 2: Circulating IGF-I levels during the study. Group A: GH treated; Group B= non GH treated.

Figure 3: Excess body weight loss expressed as percent of baseline. Group A: GH treated; Group B= non GH treated.

Figure 4: Changes of Lean Body Mass (LBM) measured by DEXA during the study. Group A: GH treated; Group B= non GH treated.

Figure 5: Glucose tolerance during the study expressed as response after glucose load of glucose (left panels) and insulin (right panels) at baseline and after 6 months in GH treated (top) and untreated (bottom) patients

Table 1: Patients' profile at study entry.

No.	Age (yrs)	Body Mass Index (Kg/m ²)	Waist Circumference (cm)	Peak GH after GHRH+ARG test (µg/liter)	IGF levels (SDS)	Fat Mass (Kg)	Fat Mass (%)	Lean Body Mass (Kg)	Lean Body Mass (%)	GH dosage (mg•day)
1.	18	47,3	114	4,0	-0,51	61,4	47,2	65,8	52,8	0,584
2.	24	36,1	125	1,8	-0,30	41,1	39,9	59,6	60,1	0,466
3.	28	41,1	106	0,3	-0,45	58,5	50,5	55,1	49,6	0,584
4.	30	39,5	109	0,5	-0,47	41,4	43,6	51,1	56,4	0,292
5.	35	40,8	127	1,3	-0,52	49,7	44,8	59,2	55,2	0,584
6.	40	35,5	123	2,1	-1,00	40,7	45,3	54,8	54,7	0,584
7.	40	37,1	116	2,5	-1,10	47,5	41,3	54,8	58,7	0,349
8.	41	62,8	118	1,7	-0,66	75,1	54,6	60,1	45,4	0,699
9.	49	45,2	119	0,6	-0,77	60,0	48,8	61,0	51,2	0,466
10.	50	50,6	134	0,3	-0,08	64,4	54,3	52,0	45,7	0,583
11.	52	40,3	111	2,2	-0,60	44,6	44,3	54,1	55,7	0,292
12.	56	42,5	138	0,2	-0,93	58,5	52,5	51,1	47,5	0,466
Mean±SD	38.6±11.9	43.2±7.6	120±10	1.4±1.1	-0.61±0.29	53.6±11	47.2±4.9	56.5±4.6	52.7±4.9	0.49±0.13
13.	21	65,1	131	1,2	-0,23	56,2	54,6	66,8	45,5	0,0
14.	21	43,7	125	3,9	-0,19	81,0	44,5	65,0	55,5	0,0
15.	26	40,2	126	1,9	-0,33	62,4	50,7	57,8	49,4	0,0
16.	26	43,7	109	2,3	-1,00	48,3	40,1	70,3	59,9	0,0
17.	33	51,0	131	0,9	-0,44	57,3	43,9	70,8	56,1	0,0
18.	37	41,7	127	1,9	-1,30	49,1	45,4	56,5	54,6	0,0
19.	37	43,7	116	2,1	-1,30	56,2	44,5	67,8	55,5	0,0
20.	38	45,2	128	1,6	-0,47	60,0	48,8	60,7	51,2	0,0
21.	41	38,9	115	1,1	0,29	53,8	47,9	56,3	52,1	0,0
22.	55	44,0	128	1,5	-0,06	54,3	46,4	60,7	53,6	0,0
23.	57	53,7	122	2,1	0,67	69,7	55,5	53,0	44,5	0,0
Mean±SD	35.6±12.2	46.4±7.6	123±7	1.9±0.8	-0.40±0.61	58.9±9.5	47.5±4.7	62.3±6.1	52.5±4.7	0.0
P*	0.54	0.17	0.28	0.37	0.18	0.23	0.79	0.02	0.79	

* comparison between group A and B by Mann-Whitney test.

Table 2: Results of primary and secondary outcome measures.

	Group A				Group B			
	Baseline	GH treated (n=12)		P	baseline	GH not treated (n=11)		P
		3 months	6 months			3 months	6 months	
Peak GH after GHRH+ARG ($\mu\text{g/l}$)	1.5 \pm 1.1	-	-		1.9 \pm 0.8	-	-	
IGF-I (SDS)	-0.61 \pm 0.30	0.85 \pm 1.05	0.96 \pm 0.60	<0.0001	-0.40 \pm 0.62	-0.89 \pm 0.43	-0.80 \pm 0.50	0.099
Primary Outcome Measures								
Excess Body Weight Loss (%)	-	23.3 \pm 10.1	32.6 \pm 12.0	0.053	-	23.2 \pm 15.2	42.9 \pm 17.8	0.011
Fat Mass (%)	47.2 \pm 4.9	43.7 \pm 4.6	37.6 \pm 4.2	0.005	47.5 \pm 4.5	51.2 \pm 3.7	47.6 \pm 5.2	0.103
Fat Mass changes (Kg)	-	-9.3 \pm 5.8	-7.9 \pm 8.6	0.645	-	-3.1 \pm 5.4	-9.4 \pm 9.6	0.070
Fat Mass changes (%)	-	-7.3 \pm 8.0	-20.7 \pm 9.3	0.001	-	8.6 \pm 9.2	0.8 \pm 13.7	0.014
Lean Body Mass (%)	52.7 \pm 4.9	56.3 \pm 4.6	63.1 \pm 7.2	0.005	52.5 \pm 4.7	48.7 \pm 3.7	54.7 \pm 7.2	0.061
Lean Body Mass changes (Kg)	-	-2.8 \pm 3.8	2.6 \pm 4.1	0.004	-	-12.0 \pm 5.9	0.4 \pm 6.5	<0.0001
Lean Body Mass changes (%)	-	7.2 \pm 8.0	18.2 \pm 7.9	0.002	-	-6.8 \pm 8.6	4.1 \pm 8.3	0.024
Secondary Outcome Measures								
Weight decrement (Kg)	-	-10.7 \pm 4.2	-15.2 \pm 5.7	0.005	-	-12.0 \pm 7.9	-21.3 \pm 8.0	0.006
Waist circumference decrement (cm)	-	11.5 \pm 16.7	16.7 \pm 8.0	0.032	-	13.3 \pm 9.6	16.6 \pm 8.4	0.074
Appendicular Skeletal Muscle Mass changes (Kg)		-2.1 \pm 0.8	-1.9 \pm 0.8	0.547		-5.7 \pm 1.7	-6.3 \pm 3.3	0.598
Fasting glucose levels (mg/dL)	83.9 \pm 6.0	82.7 \pm 5.8	81.6 \pm 6.0	0.43	84.6 \pm 14.8	87.3 \pm 9.9	90.1 \pm 6.6	0.24
Fasting insulin levels (mU/L)	13.1 \pm 4.0	10.2 \pm 3.7	8.8 \pm 3.1	0.016	11.5 \pm 3.5	10.8 \pm 2.9	10.1 \pm 2.6	0.037
Insulin resistance and Insulin sensitivity indexes								
HOMA index	2.7 \pm 0.9	2.1 \pm 1.0	1.8 \pm 0.8	0.019	2.6 \pm 1.3	2.3 \pm 1.8	2.2 \pm 0.6	0.28
ISI index	3.5 \pm 1.4	-	5.4 \pm 1.2	0.007	4.2 \pm 1.1	-	5.3 \pm 2.3	0.21
Glucose tolerance								
Glucose AUC during glucose load (mg/dL*120min)	17532 \pm 1116	-	16751 \pm 620	0.077	16289 \pm 1572	-	15840 \pm 727	0.18
Insulin AUC during glucose load (mg/dL*120min)	10215 \pm 5138	-	5539 \pm 1097	0.007	8143 \pm 3966	-	5540 \pm 857	0.019
Total/HDL cholesterol ratio	5.4 \pm 0.8	4.2 \pm 0.5	3.8 \pm 0.4	<0.0001	5.3 \pm 0.9	4.8 \pm 0.6	4.6 \pm 0.6	0.10

Figure 1

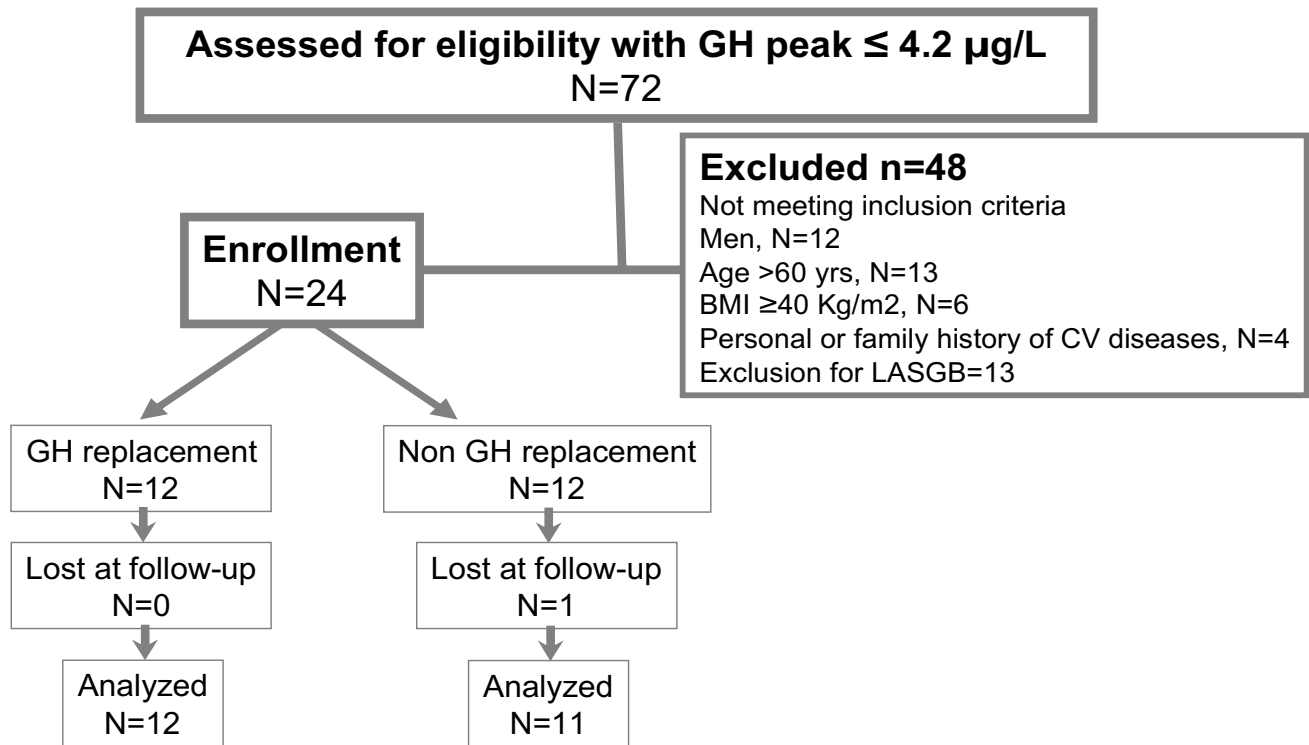


Figure 2

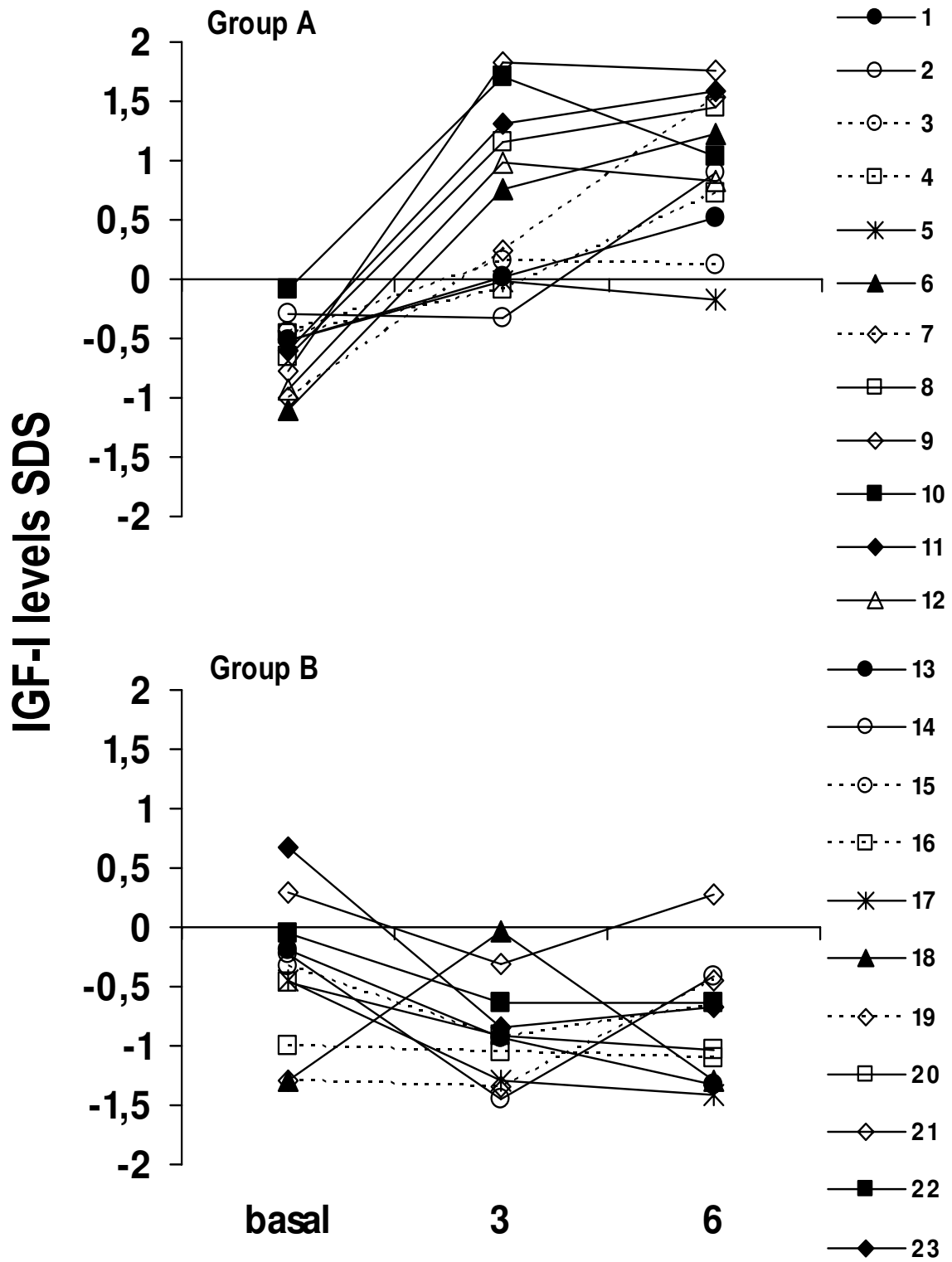
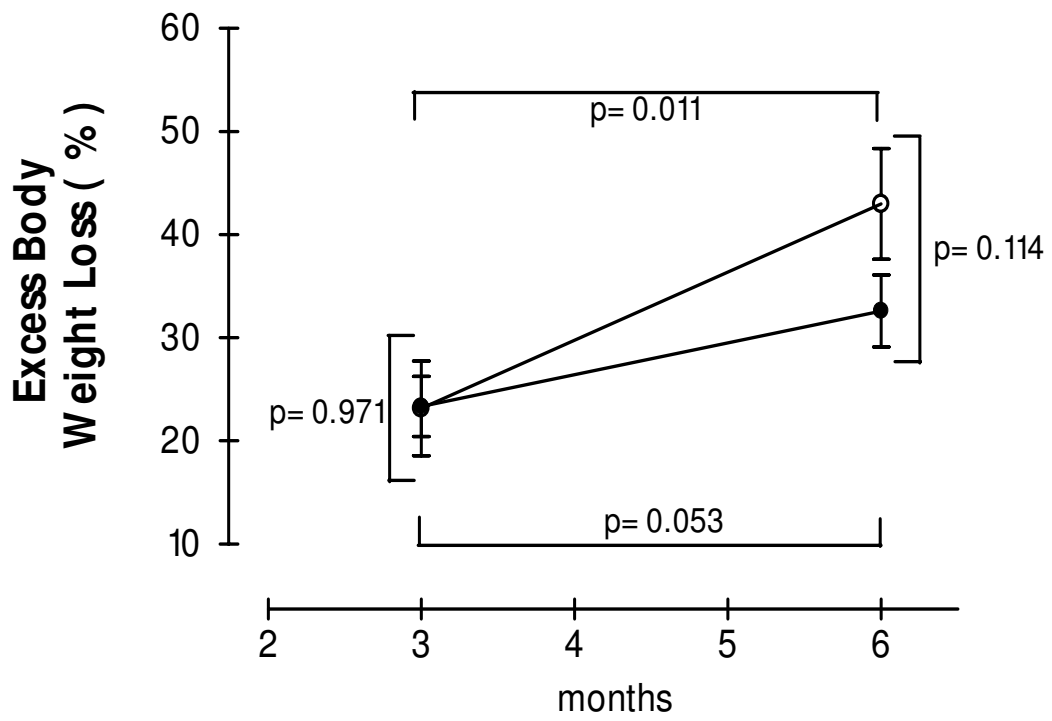


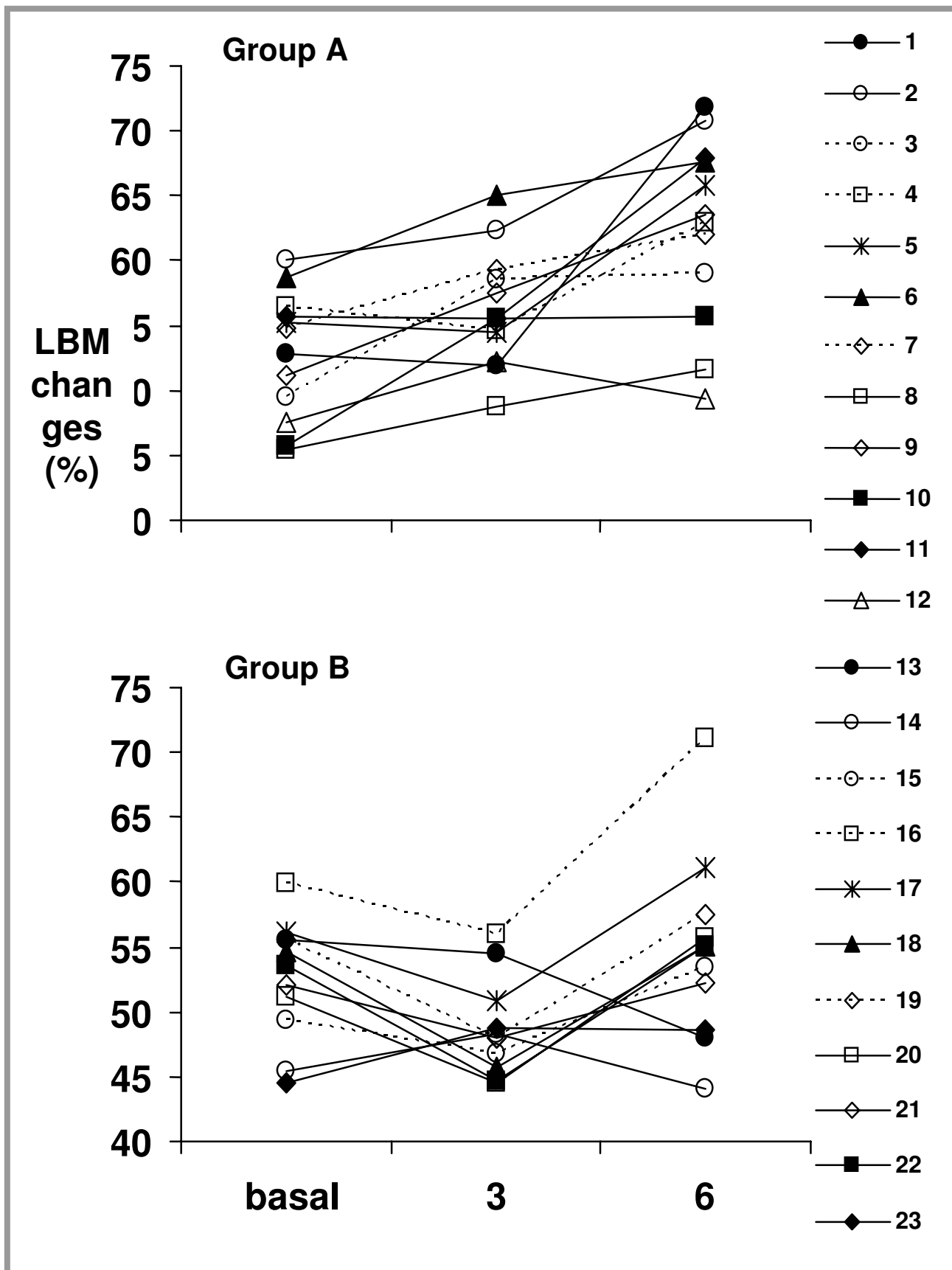
Figure 3



○ treated

● not treated

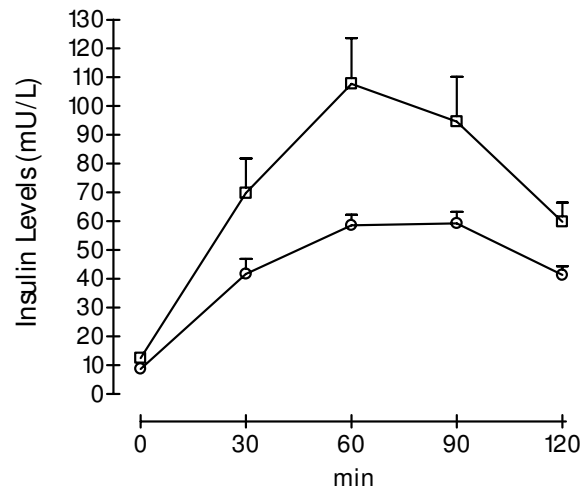
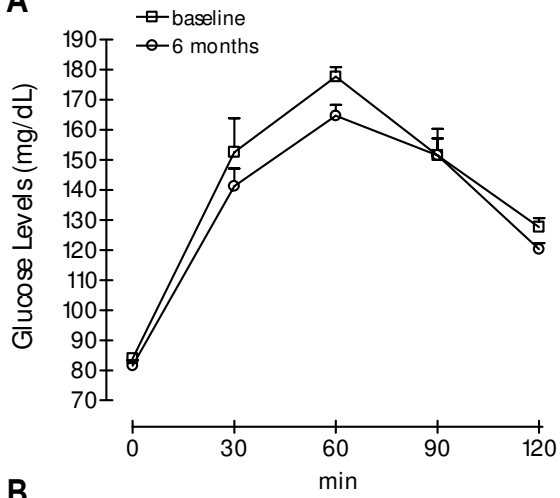
Figure 4



Group A: GH treated; Group B: non GH treated.

Figure 5

Group A



Group B

