Effects of Gastric Sleeve Surgery in the Serum Levels of GH, IGF-1 and IGF-binding Protein 2 in Morbidly Obese Patients

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Khalid Al-Regaiey
King Saud University

Suad Alshubrami
King Saud University

Ibrahim Al-Beeshi
King Saud University

Torki Alnasser
King Saud University

Abdulnasser Alwabel
King Saud University

Hassan Al-Beladi
King Saud University

Omar Al-Tujjar
King Saud University

Abdulrahman Alnasser
King Saud University

Assim Alfadda
King Saud University

Muhammad Iqbal
King Saud University

saadhafsa@hotmail.com*Corresponding Author*

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Abstract

Background Bariatric or weight loss surgery is an effective treatment for severe obesity. Reduced calorie intake or malabsorption are not the only mechanism, alterations in the activity of certain hormones and neurotransmitters are also the contributory mechanisms. In this study, we investigated the levels of GH, IGF-1 and IGF-binding protein (IGFBP-2) after bariatric surgery in obese individuals.

Method Plasma GH, IGF-1 and IGFBP-2 levels were measured by ELISA in 33 obese (BMI >38.3) healthy male subjects age ranged from 25 to 50 years before and six months after gastric sleeve surgery. Plasma glucose, BMI, insulin, HOMA-IR and lipid profile were also investigated.

Results Systemic GH (from 12.32±1.3 to 50.97±0.339 ρg/mL, P<0.001) and IGFBP-2 (51.86±11.21 to 68.81±13.36 ρg/mL, P<0.001) levels were elevated after bariatric surgery. However there was no change in IGF-1 levels. BMI (from 52.18±9.86 Kg/m2 to 40.11±8.92 Kg/m2, P<0.001), insulin (19.35±0.304 mIU/L to 8.80±0.181 mIU/L, P<0.001) and Homeostatic model assessment- Insulin resistance (HOMA-IR) index was also reduced from 6.48+0.164 to 2.52 ± 0.061 (p<0.001) were also reduced 6 months after bariatric surgery. Cholesterol, high density lipoproteins (HDL), and low density lipoproteins (LDL) levels were increased after surgery (4.26±0.027 to 5.12±0.026 mmol/L and 0.90±0.007 to 1.55±0.011 mmol/L and 2.62±0.02 to 2.98±0.022 mmol/L, P<0.001) respectively. There was no correlation between GH, IGF-1, IGFBP-2and insulin and lipid parameters.

Conclusions Our study suggests that improved circulating GH and IGFBP-2 levels associated with increased levels cholesterol and triglycerides may be an endocrine response to mediate beneficial effects of bariatric surgery.

Introduction

Obesity remains a continuing global health concern and its prevalence has been doubled since 1980 and according to WHO estimates, in 2016, more than 650 million people are obese and 1.9 billion people are overweight [1]. It is associated with increased risk of many chronic diseases including type 2 diabetes (T2D), hypertension, and cardiovascular disease (CVD).

According to WHO, obesity can be defined simply as abnormal or excessive body fat accumulation to such an extent that health may be adversely affected. Body mass index (BMI) is used to classify body fat measurement but without interpretation for the wide difference in the body fat distribution.

Growth hormone and IGF-1 have major role in metabolic regulation, reproduction and aging. It is produced by anterior pituitary gland in response to growth hormone releasing hormone (GHRH) which is released by hypothalamus as normal reflections to multiple features such as hypoglycaemia, low free fatty acid in the blood, high amino acid, good exercise and sleep [2]. All these features are diminished in adult subjects with high BMI [3]. Following an increase in BMI, GH secretion is reduced that will lead to lipid metabolism disturbance, increases body fat, increases T2D and cardiovascular diseases risk.[4] Binding of GH to its receptor on the liver, and other organs, stimulates the production of IGF-1 which is secreted and delivered to the target tissues [4]. IGF-1 reflect GH levels and mediates the effects of GH while the metabolic effects of GH are induced directly through its receptor [5]. GH secretion is inhibited by IGF-1 and IGF-1 production is stimulated by GH in a negative feedback mechanism [6]. IGF-1 in the circulation binds to IGF-binding proteins (IGFBPs). These IGFBPs act as transporter proteins, modulate IGF actions and regulate the clearance of IGFs [7]. In obesity, non-esterified fatty acids (NEFA) and insulin will inhibit IGFBP production which increase the free IGF-1 in circulation [8]. Serum IGF-1 are reported to be low in young diabetic subjects [9].

IGFBP-2 is considered to be second most abundant of all and is responsible for several cellular processes like cell proliferation, migration, and adhesion, which play a significant role in the cancer establishment and its succession [10–11]. It is secreted by the differentiation of pre-adipocytes. Plasma IGFBP-2 levels can be used as a biomarker of insulin sensitivity as it helps in glucose metabolism by improving insulin sensitivity [12]. Increased levels of IGFBP2 had strong inverse association with risk of T2DM body mass index [13–14].

Bariatric surgery is an effective treatment for severe obesity that leads to improvement and remission of many obesity-related comorbidities, sustained weight loss over time, improvement in quality of life and prolonged survival [15–16]. Bariatric surgery reduces body weight and improves glycaemic control through reduced nutrient intake and malabsorption. However, there are other mechanisms like changes in the secretion and activity of hormones and neurotransmitters involved in appetite, energy expenditure and glucose metabolism also add to the beneficial effects of bariatric surgery

[17–18].

As yet, the underlying mechanisms of how bariatric surgery is influencing the physiological metabolic process pre and post-surgery are not fully understood. Therefore, the aim of this study was to assess the GH/IGF-1 axis and IGFBP-2 levels in obese patients before and after gastric sleeve surgery and correlation with other anthropometric parameters and lipid profile.

Material And Methods

1. Subjects

This study was conducted in the Departments of Physiology and Surgery, College of Medicine and Obesity Research Centre (ORC), King Khalid University Hospital, King Saud University. In this study, 33 male subjects age ranged from 25 to 50 years with obesity grade II & III, undergoing gastric sleeve surgery were enrolled and written consent was signed by all the participants.

2. Clinical Examinations and Blood collection

All patients were clinically examined by a physician, a psychologist and a nutritionist before surgery and attended surgery and nutrition clinics at 3, 6 and 12 months after surgery. The patients were not on medication for kidneys, thyroid, or liver disorders and were taking oral vitamins. BMI was recorded at each visit and patients were classified according to their BMI results. Blood was taken from patients in the fasting state on day of surgery and 6 months later. Serum was separated following centrifugation at 1500 × g for 10 minutes, and stored at -80^{o}C in aliquots within 30 minutes of collection. Other parameters such as routine CBC, lipid profile, glucose, insulin, and liver function test results were retrieved from the hospital files.

3. Enzyme-Linked Immunosorbent Assay (ELISA)

GH, IGF-1 and IGFBP-2 levels were analysed by indirect Simple Step Human ELISA kits (GH Ab190811, IGF-1 Ab100545 and IGFBP-2 Ab100540) following the manufactures instructions (abcam, Cambridge, UK). Briefly, patient samples (33 pre- and 33 post-bariatric surgery) and standards were reacted with specific antibodies coated in the microplates for each protein under investigation and incubated at room temperature (18–25 °C) for 1 hour on a plate shaker. Next, the cocktail of antibodies (capture and detector antibodies) were added and incubated as before. One hundred microliter TMB substrate was added to the microplate and incubated at room temperature (18–25 °C) on plate shaker for 30 minutes. The reactions were stopped by adding 100 µl stop solution in each well and absorbance was read by microplate reader (EL 800, BioTek Instruments, USA) at 450 nm.

Statistical analysis

Data was analysed using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Categorical data were expressed as absolute numbers and percentages. Numerical data were expressed as mean, median, standard error of mean (SEM) and range. Student's t-test was used in both distributions the data pre & post-surgery, p value < 0.05 was considered statistically significant.

Results

1. Anthropometric and biochemical assessments

Anthropometric measurements of 33 obese male subjects are shown in Table 1. BMI was deceased after bariatric surgery (from 52.18±9.86 Kg/m^2 before surgery to 40.11±8.92 Kg/m^2 [mean±SEM], 6-12 months after surgery, P<0.001).

Cholesterol (CHOL) and high density lipoproteins (HDL) levels were increased post-bariatric surgery (CHOL from 4.26±0.027 mmol/L to 5.12±0.026 mmol/L and HDL form 0.90±0.007 mmol/L to 1.55±0.011 mmol/L), P<0.001). There was also a significant increase in low density lipoprotein (LDL) levels post-bariatric surgery (from 2.62 ± 0.026 mmol/L to 2.98 ± 0.022 mmol/L, p < 0.031). Triglyceride (TGL) levels were decreased after bariatric surgery (from 1.62±0.038 mmol/L to 1.05±0.012 mmol/L, p = 0.028) (Table 2). Insulin levels were decreased from 19.35±0.304 mIU/L to 8.80±0.181 mIU/L, P<0.001, and Homeostatic Model Assessment-Insulin resistance (HOMA-IR) index was also reduced from 6.48+0.164 to 2.52 ± 0.061 (p<0.001). Glucose levels were not changed in patients before and after bariatric surgery.

2. Analysis of GH, IGF-1 and IGFBP-2 levels in serum before and after bariatric surgery

GH levels were increased post-bariatric surgery (GH from 12.32 ±1.3 to 50.97±0.339 ρg/mL, P<0.001), while IGF-1 levels did not change (4414.38 ± 58.81 before surgery vs. 3730.74 ±43.649 ng/mL after surgery). IGFPB2 levels increased after surgery from 51.86 ±0.34 to 68.81 ± 0.405 ρg/mL, P<0.001) after surgery (Figure 1). Analysis of serum levels of GH (Fig.1-A), IGF-1 (Fig.1-B) and IGFBP-2 (Fig.1-C) in patients before and after bariatric surgery. Growth hormone and IGFBP-2 levels were statistically significant whereas IGF-1 levels did not show any change.

Table 1. Anthropometric baseline characteristics of study subjects.

Variable	Mean	SEM
Age (years)	35.12	0.249

Height (cm)	170.97	0.005
Weight (Kg)	150.16	0.77

Table 2. Demographical and clinical measurements before and after surgery

Parameters	Pre-Surgery Mean±SEM	Post-Surgery Mean±SEM	P value
BMI (kg/m^2)	52.18±0.299	40.11±0.270	0.001
GLUC (mmol/L)	7.08±0.085	6.27±0.031	0.681
TGL (mmol/L)	1.62±0.038	1.05±0.012	0.028
CHOL (mmol/L)	4.26±0.027	5.12±0.026	<0.001
HDL (mmol/L)	0.90±0.007	1.55±0.011	<0.001
LDL (mmol/L)	2.62±0.026	2.98±0.022	0.031
HOMA-IR index	6.48±0.164	2.52±0.061	<0.001
Insulin (mIU/L)	19.35±0.304	8.80±0.181	<0.001

Discussion

Bariatric surgery is an effective options for long-term obesity treatment to obtain sustained weight loss, substantial improvement of comorbidities and quality of life. Reduced stomach volume and malabsorption are not the only means by which bariatric surgery improves insulin action and associated parameters, alterations in endocrine response are thought to play important roles in the beneficial effects of bariatric surgery [19].

In this study, GH levels were increased after gastric sleeve surgery while IGF-1 levels were not changed. IGF-1 has important role in GH activity and relate to its serum levels. Increased IGF-1 levels in obesity have negative effect and cause GH suppression [20–21]. High, low and normal levels of IGF-1 have been reported in obese population [20, 22]. In obese children, reduced GH is not associated with decreased levels of IGF-1 and reduced somatic growth [21]. In our study, cholesterol, high density lipoproteins (HDL) and low density lipoprotein were increased after bariatric surgery. This can be explained by the fact that GH is lipolytic and releases free fatty acids from visceral adipose tissue and to a lesser extent from subcutaneous fat by increasing hormone sensitive lipase (HSL). Furthermore, GH maintains triglyceride storage in liver by either inhibiting triglyceride lipolysis via HSL or oxidation by PPARγ [2, 23]. GH also stimulates triglyceride uptake into skeletal muscle to be used for energy or stored as intra-myocellular lipid [24]. This explains, at least partially, the increased levels of cholesterol, LDL and HDL and reduced TG observed in the current study. Furthermore, as a result of bariatric surgery, calorie intake is reduced which might lead to increased GH levels since its secretion is stimulated by hypoglycaemia [25].

IGFBP-2 is the main IGF binding protein secreted by differentiating white adipocytes and is associated in regulating body weight and homeostasis. It is reported to protect from obesity and insulin resistance [10, 26–28]. In our study, insulin levels and HOMA-IR score and BMI were reduced after bariatric surgery. These findings are in agreement with a recent 20-year longitudinal study of aging where IGFBP-2 levels were found positively correlated with insulin sensitivity and inversely with BMI at baseline and follow up [29]. In obese children circulating levels of IGFBP-2 correlate inversely with body mass and positively with insulin sensitivity [30]. It has been suggested that the obesity-related hyperinsulinemia may increase IGF-1 and inhibit IGFBP-2 secretion [31]. An earlier study reported that obesity-related hyperinsulinemia increased IGF-1 and inhibited IGFBP-2 secretion [31]. A recent animal study has shown that metformin upregulates IGFBP-2 production through activation of AMPK-Sirt1-PPARα signaling pathway. Metformin-treated patients have increased IGFBP-2 levels and reduced serum IGF1 levels compared to untreated diabetic patients [32]. This highlights IGFBP-2 a novel target for metformin action and AMPK-Sirt1-PPARα a novel pathway to control metabolic syndrome. IGFBP-2 has also been shown to be regulated by leptin and may mediate some of leptin's antidiabetic effects. Thus, it is possible that in our study elevated levels of IGFBP-2 in healthy male population after surgery played a role in improving insulin sensitivity and increased levels of GH. A previous study showed an increase in IGFBP-2 levels after bariatric surgery in women [33].

In conclusion, our study suggests that improved circulating GH and IGFBP-2 levels associated with increased levels cholesterol and triglycerides may be an endocrine response to mediate beneficial effects of gastric sleeve surgery.

Limitation and Recommendation

Our study subjects were small homogenous males without medical complications. Future studies should be conducted in a larger sample size including women and control lean subjects undergoing non-bariatric laparoscopic surgery to compare. Other relevant metabolic molecular pathways and molecules in different fat depots should also be explored.

Declarations

Acknowledgment

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Conflict of interest

The authors declare that they have no conflict of interests.

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Ethical Approval

This study was approved by Institutional Review Board, Ethics Committee, College of Medicine Research Centre (E-17-2652).

Authors' contributions

KA and MI conceived the idea, designed the proposal, performed the experiment, analysed the data, writing and editing of the manuscript. AA conceived the idea, designed the proposal, provided the samples and contributed to final concept and design. SA, IA, TA, AA, HA, OA, AA performed data collection, statistical analysis, results write-up, formatting and editing of the manuscript. All authors approved and read the manuscript in its current state.

Availability of data and materials

The data used and analysed during the current study are available from the corresponding author on reasonable request.

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Figures

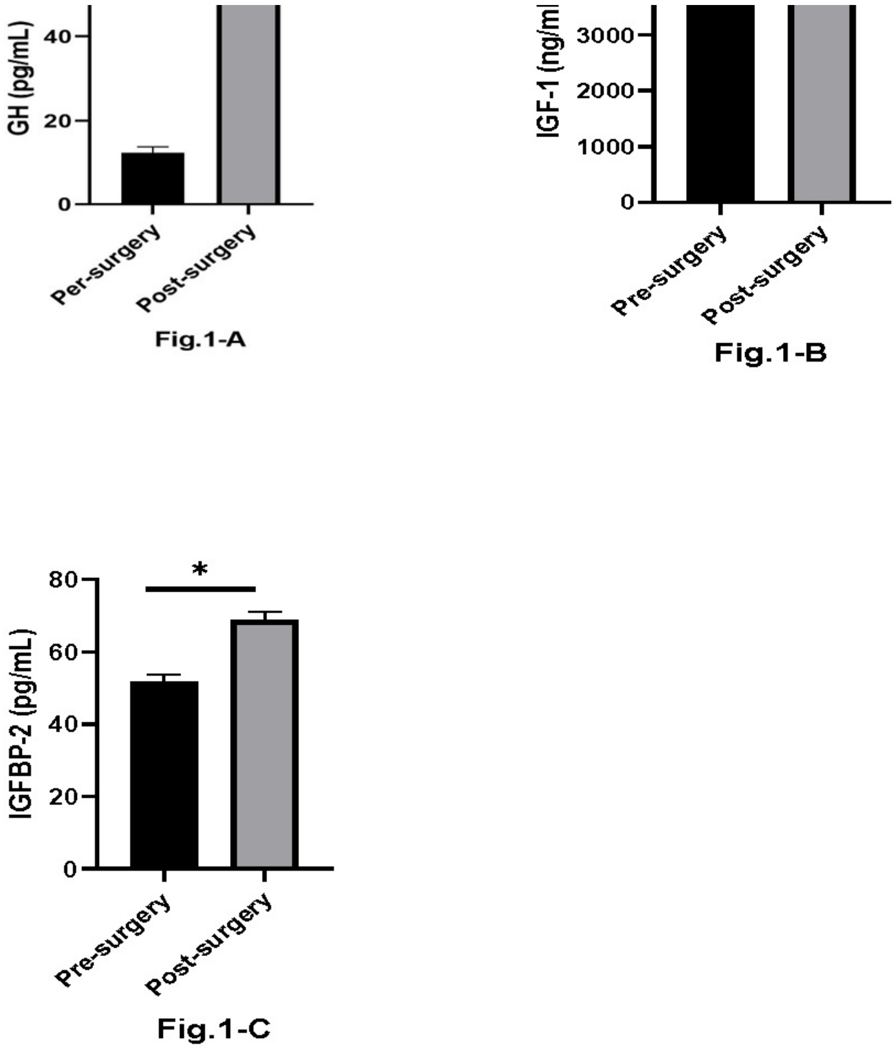

Figure 1

(A-C). Assessment of serum levels of GH, IGF-1 and IGFBP-2 in patients before and after bariatric surgery. (P<0.001).