The impact of bariatric surgery in the levels of IGF-I, glucose, insulin and insulin resistance among patients with morbid obesity

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ABSTRACT: Objective: To identify the influence of bariatric surgery in the levels of IGF-I, glucose, insulin and insulin resistance in patients with morbid obesity. Methodology: The sample was composed of ten eutrophic individuals who had a body mass index (Kg/m²) below 25, as control group, and 10 subjects with morbid obesity who were followed in the 45-day preoperative and postoperative period. This group was submitted to a laparoscopy Roux-en-Y gastric bypass. Statistical analysis was performed using the Wilcoxon and Mann-Whitney tests, adopting a significance level of p<0.05. Results: There were significant decreases in weight and body mass index (BMI) among obese individuals when comparing the pre and postoperative periods. The insulin level decreased significantly after surgery, also reducing insulin resistance. The hormone level returned to the same values to those obtained in the control group. IGF-I levels were reduced on average during the period of 45 days, being statistically significant in comparison to those in the control group. Blood glucose showed no significant difference among groups. Conclusions: It can be concluded that bariatric surgery promotes, in the course of 45 days after surgery, significant reduction in body weight and BMI, a decrease in hyperinsulinemia and in insulin resistance among patients with morbid obesity.

INTRODUCTION

Morbid obesity has been considered one of the great ills of contemporary society. Now seen as a metabolic chronic disease with genetic origins, obesity causes or accelerates the development of many other diseases and causes early death. It is estimated that, in the U.S., 300,000 people die prematurely each year due to obesity and that, in Brazil, this number is between 50,000 and 100,000 people1.2.

It has been noted that there is a tendency of obesity to aggregate in families. Halpern2 explains that this tendency towards obesity in the family is determined by two factors: genetics and the environment. This last one, which often predominates, can be explained by bad habits, particularly poor nutrition, and little or no physical activity.

When the elevation of free fatty acids remains for an extended time-period, they have a direct effect on signaling muscle and liver insulin, reducing the normal responses to insulin, i.e., decreasing the incorporation of glucose by skeletal muscle and increasing gluconeogenesis and the supply of glucose from the liver into the circulation. Excess fat becomes very harmful to the organism, especially when the fat starts to accumulate in tissues that are not intended for this type of accumulation3.

To Bertolami4, insulin resistance means that the circulating insulin does not have its normal function in tissues sensitive to its action, for example, skeletal muscle, fat tissue, liver, and endothelium4. Insulin resistance is usually accompanied by a compensatory increase in insulin secretion by the pancreas to overcome the problematic insulin action in peripheral tissues in order to maintain glucose levels within a normal range4. Bertolami4 also indicates that insulin resistance is concentrated in certain families, being determined by genetic and environmental factors4.

Several studies have shown that reduction in body mass, especially fat, may reflect considerably on lipid profile, change the metabolism of carbohydrates, reduce morbidity and mortality, and improve life quality in morbid obese patients5.

In this sense, excessive intra-abdominal fat – as it occurs in men with central obesity and postmenopausal women – predisposes these individuals to complications of insulin resistance. These complications include an increased risk of cardiovascular disease, as evidenced by the presence of abnormal distribution of lipoproteins (increased triglycerides and decreased HDL - cholesterol), increased plasmatic levels of glucose, fasting insulin, and diabetes type II4.

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As a result, several ways to overcome these problems have been sought, such as: diets, specific drugs, exercise and...
surgical techniques. In this sense, bariatric surgery has proven to be a more effective way for dealing with and preventing complications related to obesity, focusing on reducing the risk of morbidity and mortality, and only secondarily, as a way to lose weight for cosmetic purposes. Therefore, it should not be seen as an esthetics surgery.6.

Because it is a major procedure, performed on subjects with associated morbid conditions, which increase the probability of complications after surgery, obesity surgery carries risks that cannot be ignored7.

Eligibility criteria for bariatric surgery are: obese subjects with a BMI greater than 40 kg/m² or a BMI greater than 35 kg/m² with significant obesity-related illnesses that are difficult to manage without losing weight. The most current technique, considered the "gold standard", is the gastroplasty with gastrojejunal bypass. This technique reduces gastric capacity, also restricting, in a minor degree, food absorption8.

As surgical techniques have been reassessed and improved, a similar process occurs to the system to analyze the efficiency of such procedures. Thus, new versions of the surgery or minor changes arise. In this context, this research aims to examine the levels of IGF-I, insulin, glucose and insulin resistance in patients with morbid obesity compared to non-obese subjects, as well as to examine whether there are differences between these levels measured before and after bariatric surgery.

METHODOLOGY

The present research it is a prospective analytical study with morbidly obese patients from the Integrated Service of Gastroenterology and Obesity in the State of Sergipe (SIGO). This research project was submitted to the Ethics in Research with Human Subjects (CEP/UFS) Committee, and the performance of the study followed the guidelines of resolution 196/96 of the National Health Council.

The sample consisted of individuals of both sexes (10M: 10F) and of various ages, without significant difference (p = 0.1043) between the mean ages of groups. The samples were placed in three groups:

- Control Group: comprising 10 eutrophic subjects (5M: 5F), i.e., with a BMI<25Kg/m², with an average age of 29 ± 12.11 years old.
- Preoperative Group: comprising 10 morbidly obese subjects (5M: 5F), with a mean age of 37.5 ± 8.6 years old, and with indication of bariatric surgery, i.e., a BMI above 40Kg/m² or BMI above 35Kg/m², with associated co morbidities.
- Postoperative Group: comprising the same group of 10 obese patients from the preoperative group, who had undergone bariatric surgery, with a 45-day postoperative follow-up period.

Inclusion criteria applied were: individuals of both sexes aged between 18 and 60 years, with a BMI below 25Kg/m² (control group) and a BMI above 40Kg/m² or 35Kg/m², with co morbidities (pre and postoperative groups).

The exclusion criteria were: individuals that had a disease or associated clinical condition correlated with: cancer, coma, neurological damage, serious or terminal illness, individuals with disabling cardiopulmonary or osteoarticular disease, or even the presence of mental confusion or dialogue and understanding difficulties. Another criterion was the patient’s refusal to participate in the research.

After the patients were placed in the study groups, body weight values and other measurements were taken and laboratory exams to diagnose IGF-I (somatomedin C), basal insulin and fasting glucose were performed. For individuals in the preoperative group, apart from these examinations, routine preoperative exams were also requested.

For this study, we standardized the IGF-I dosage using the methodology of immunoradiometric assay (IRMA); to measure blood glucose, the glucose oxidase method; and for insulin dosage, the methodology of automated electrochemiluminescence, from 1mL of serum9.

From the baseline levels of blood glucose and insulin, the HOMA-IR index was calculated as the product of the fasting plasma insulin level (micro U/cc), and the fasting plasma glucose level (m mol/L), divided by 22.5.10,11 A laparoscopy Roux-en-Y gastric bypass (LRYGBP) was the chosen surgical approach. This combined procedure is composed of restrictive and mal absorptive components. For statistical analysis, we considered the mean and standard deviation. In the comparison of different groups, as in the case of non-obese subjects compared with obese patients “pre and post-operated”, the Mann-Whitney test was applied to two independent samples and in order to compare the same group of obese patients before and after bariatric surgery, the paired Wilcoxon test was applied. In order to detect statistically significant differences between the values obtained, we adopted the significance level of p<0.05.

RESULTS

There was a significant difference between the mean weight and BMI among obese individuals when compared to the control group (p = 0.0001), as well as among patients in both pre and postoperative groups. Even with weight and BMI reductions, patients in the postoperative period remained different from control subjects.

The mean values of anthropometric and laboratory evaluation from the studied subjects are available in Table 1. There was no significant difference (p = 0.14) in glucose levels between the control group (mean 80 mg/dl ± 5.71) and the preoperative group (mean ± 95mg/dL 27.38), nor was there a significant statistical difference (p = 0.8) between the pre and post-operative groups, when in the postoperative period the group presented a mean of 86mg/dL ± 8.76.

During the analysis of the variable insulin, a significant difference in hormone levels was observed between the control (10uU/cc ± 4.92) and preoperative (41uU/cc ± 37.12; p = 0.01) groups. For the same variable, a significant
reduction was also noted when comparing the groups of obese patients in the preoperative (mean 41uU/cc ± 37.12) and postoperative period (mean 11uU/cc ± 5.01; p = 0.02). In relation to insulin levels, there was no significant difference between the control (11uU/cc ± 4.92) and postoperative groups (11uU/cc ± 5.02; p = 0.74).

Among studied patients, a reduction in the levels of insulin resistance among control group subjects was observed (1.96uU/cc ± 0.94), when compared with the preoperative group (10.14uU/cc ± 9.99; p=0.03). After bariatric surgery, a significant statistic reduction of the insulin resistance was observed (p = 0.02). It was noted that the obese subjects during the preoperative period had a mean HOMA-IR of 10.14 uU/cc ± 9.99, and the postoperative group an average of 2.26 uU /cc ± 1.16. There was no significant difference between the control (1.96 uU / cc ± 0.94) and postoperative groups (2.26 uU / cc ± 1.16; p = 1.0), due to HOMA-IR values.

About the IGF-I variable, there was a decrease with a significant statistic difference between preoperative (194ng/ cc ± 59.48) and control groups (358ng/cc ± 109; p = 0.01). We also observed a reduction in the IGF-I levels within the obese group in the period after surgery (140ng/ cc ± 90.94), when compared to the obese group in the preoperative period (194ng/cc ± 59.48; p = 0.01). Concerning this variable, out of the ten patients evaluated in the postoperative period, only two patients had an increase in the level of this peptide during the 45 days follow-up after the bariatric surgery. There was a significant statistic difference (p = 0.0005) between the control group (358ng/cc ± 109) and the postoperative group (140ng/cc ± 90.94).

Table 1: Anthropometric and metabolic characteristics of the studied population (values in mean ± standard deviation).

<table>
<thead>
<tr>
<th>Units</th>
<th>Control</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years old)</td>
<td>29 ± 12.11</td>
<td>38 ± 8.60</td>
<td>38 ± 8.60</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>64 ± 10 (*)</td>
<td>126 ± 23.45 (+)</td>
<td>107 ± 18.57(*)</td>
</tr>
<tr>
<td>Hight (m²)</td>
<td>1.67 ± 0.09</td>
<td>1.68 ± 0.00</td>
<td>1.68 ± 0.08</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>22.7 ± 1.94(*)</td>
<td>44.36 ± 4.82 (+)</td>
<td>38 ± 4.13(*)</td>
</tr>
<tr>
<td>IGF-I (nanog/mL)</td>
<td>358 ± 109(*)</td>
<td>194 ± 59.4</td>
<td>140 ± 90.94(*)</td>
</tr>
<tr>
<td>Insulin (uU/mL)</td>
<td>0 ± 4.92</td>
<td>41 ± 37.12</td>
<td>11 ± 5.02</td>
</tr>
<tr>
<td>Glucose (mg/DL)</td>
<td>80 ± 5.71</td>
<td>95 ± 27.38</td>
<td>86 ± 8.76</td>
</tr>
<tr>
<td>HOMA-IR (uU/mL)</td>
<td>1.96 ± 0.94</td>
<td>10.14 ± 9.99</td>
<td>2.26 ± 1.16</td>
</tr>
</tbody>
</table>

Significance level: p 0.0001

(*) Significant difference between control and preoperative
(+ ) Significant difference between pre and postoperative
(#) Significant difference between control and postoperative
G1. Graphic representation of average plasma glucose level of all three groups: control, pre and postoperative (not statistically significant).

G2. Graphic representation of insulin levels of all three groups: control, pre and postoperative.
Graphic 03. Graphic representation of HOMAR-IR mean of all three groups: control, pre and postoperative.

Graphic 04. Graphic representation of IGF-I levels of all three groups: control, pre and postoperative.
DISCUSSION

Several studies have shown that obesity has increased significantly in both sexes and in all ages, races, and socioeconomic and educational status. Francisco (2002) showed that, in developed countries such as the United States and Sweden, obesity and overweight affect nearly half the adult population, accounting for between 8-10% of the total costs spent on health. In developing countries like Brazil, the situation is not much different and a significant increase in the prevalence of obesity in these last decades has been observed. A map of obesity rates, made in 2007 by the Brazilian Society for Bariatric and Metabolic Surgery, showed that 51% of the Brazilian population is overweight and 12% is obese. In a study about the costs of hospitalizations related to overweight and obesity, Sichieri et al. (2001) estimated values obtained from data of hospitalized people aged between 20 to 60, from the Hospital Information System of Unified Health System, showing a total cost varying from 6.8% to 9.3%, compared to other reasons for hospitalizations, excluding pregnant women.

Due to this growing number of obese people, there is also an increase in the number of people with insulin resistance, type II diabetes mellitus, and cardiovascular disease. Carneiro stated that the higher prevalence of hypertension in obesity has been attributed to hyperinsulinemia resulting from insulin resistance, present in these individuals, especially those with excess fat in the dorsal region. Hyperinsulinemia promotes activation of the sympathetic nervous system and tubular re absorption of sodium, which contributes to increased peripheral vascular resistance and blood pressure.

Studies have shown that, when conventional treatments to reduce body weight and to control obesity in the long term were ineffective, surgical treatment represented the most effective therapy, promoting significant and sustained weight loss, as well as resolution of co morbidities associated with this condition.

In this study, we evaluated the effects of bariatric surgery in the levels of insulin, glucose, and IGF-I, to better understand the role of each element involved in the pathophysiology of obesity and, thus, to provide subsidies for the treatment and the prevention of insulin resistance and obesity, which are predisposing factors to cardiovascular diseases.

BMI values obtained in this casuistry are in agreement with most published studies regarding the candidate patients and those who underwent bariatric surgery.

The surgical technique chosen for this study was a LRYGBP, which is a surgical procedure that combines a restrictive component with a decline of intestinal absorption. This technique has been recognized, in several studies, as the "gold standard" among the bariatric surgical techniques, due to good results promoted in terms of weight loss and good management of complications in late post-surgery follow-up. We observed, in the segment studied, a significant reduction in body weight for patients who underwent the referred surgical technique.

Greater importance has been given to the role of insulin and insulin resistance in obesity (a condition where the cell receptors become insulin resistant). Insulin resistance may be a genetic or an acquired condition that leads to a subnormal glucose uptake by cells, especially muscle and fat cells, despite the normal levels of insulin concentrations. Harrell (2002) asserted that the hiperinsulinemia and insulin resistance are the major factors in the pathogenesis of cardiovascular disease and that most of the time they are silent.

According to Geloneze & Pareja, morbid obesity is a condition that causes insulin resistance. These authors stated that, in this condition, there is always excessive visceral fat and that insulin resistance and visceral adiposity contribute to the prevalence of metabolic syndrome in almost all patients with morbid obesity or stage III obesity. Cesaretti & Kohlmann (2006), studying experimental models of insulin resistance and obesity, stated that the pancreas starts producing more insulin due to decreased glucose uptake, seeking the maintenance of normal glucose levels, thus leading the body to a state of hyperinsulinaemia. Such metabolic inefficiency forces the liver to produce more glucose, the muscle to a poor use of the circulating glucose, and the fatty tissue to increase lipolysis. Caramel showed in his study on obesity that this inefficiency in the metabolism in obesity maybe, at the same time, a cause and a consequence, reporting that hyperinsulinaemia is a compensatory state which leads to a change in the membrane receptors for insulin, but this condition is correctable with weight loss and exercise.

In accordance with the referred works, among the studied population, normoglycemic obese patients were evaluated, and they, on average, did not present hyperglycemia in the preoperative period. However, they presented a state of hiperinsulinemia and, after bariatric surgery, despite the reductions on body weight and BMI; there was no significant change in blood glucose levels, as there was in the insulin levels. We could also observe that, in the postoperative follow-up, insulin resistance (IR) was reduced. This reduction can be proven by the HOMA-IR calculation, with a postoperative mean value that approached the average value of the control group, although the BMI mean is still within the range for obesity class II, i.e., BMI > 35.

Pereira (2003) also evaluated obese patients who underwent bariatric surgery by the technique of Roux-en-Y bypass. The patients were insulin resistant and hiperinsulinemia in fasting state, and after a year of surgery, although showing a weight loss of approximately 40% regarding initial BMI, remained obese (BMI>35). They stated that, in these patients, the insulin levels only normalized completely through the improvement of insulin resistance, concluding that glucose storage took place, once fasting lipid oxidation remained high. Mingnore quoted by Pereira showed that insulin sensitivity after two years of a bilio pancreatic bypass, which induces predominant fat mal absorption, was still low, although observing that the final BMI reached a normal value in that study. These authors also asserted that despite the persisting insulin resistance, insulin secretion was normalized after weight reduction.

Geloneze & Pareja, after studying the effect of bariatric
surgery on metabolic syndrome, showed that there was a reduction in insulin levels of about 54% with the Roux-en-Y gastric bypass when compared with the gastric band operation, which was around 25% in a 10-year follow-up, confirming that the combination procedures (a combination of restrictive and mal absorptive) is more effective in reducing insulin levels. The effectiveness of a combination procedure was confirmed among the groups in this research, which revealed a significant reduction (p = 0.0189) in insulin levels among the obese population in the pre and postoperative, along with the reduction of weight and BMI.

This study supports the hypothesis of Gagliardi that affirmed that there are not necessarily elevated blood glucose levels when the peripheral tissues become resistant to the metabolic action of insulin, since beta cells have a great capacity to increase production and secretion of insulin, which maintains, for a long time, a metabolic situation of chronic hyperinsulinemia associated with normoglycemia. This study showed that, although obese patients presented a HOMA-IR elevated, these patients were normoglycemic. Our findings are also in agreement with Silverthorn which showed that moderate weight loss improves glycemic control and reduces hyperinsulinemia in about 5% to 10%. With the advent of surgical procedures to treat obesity, several studies have been dedicated to the physiological mechanisms associated with such procedures. It is noticed that, in surgeries that shorten the food transit, causing a rapid arrival of nutrients in the distal small intestine, there is an increased rate of incretins in the bloodstream. The incretins, gastrointestinal hormones that are part of the enteroinsular axis, potentiate glucose-dependent insulin action, i.e., they stimulate postprandial insulin secretion. The main released incretin is GLP-1, mainly secreted by L cells of the ileum and colon. GLP-1, besides stimulating insulin secretion, increases the population of beta cells and maintains their function, suppresses glucagon release, slows gastric emptying and reduces food intake. Studies also report that the high rate of GLP-1 in the blood contributes to a significant increase in insulin sensitivity. It is likely that such mechanisms are involved in the observed improvement in insulin sensitivity in patients from the postoperative group of this research.

Among the hormone mechanisms involved in the metabolic syndrome, the involvement of IGF-I deserves special attention, given to the fact that IGF-I is the most potent growth factor. It has an insulin-like action and presents important and complex endocrine-metabolic repercussions, along with insulin. The insulin-like growth factor 1 (IGF-I), mainly produced in the liver under the action of GH, participates in the growth and in the function of almost all organs, including adipose tissue. IGF-I is peptide hormones, which promote growth and tissues differentiation, besides having insulin-like metabolic effects. According to Guadarrama et al. (2003), Lima et al. (2004) and Menezes, there is very little free IGF, usually found in the circulation associated with proteins (IGFBP-1 to IGFBP-6), with unknown functions. Among the normal weight subjects and the obese ones studied in this research, a significant difference was found in serum levels of IGF-I, with a lower level in obese subjects compared to the levels found in normal weight individuals. In the 45-day follow-up period, a greater reduction in IGF-I was found when compared with normal individuals.

Britt studied the GH/IGF-I axis in obese patients followed for six and twelve months after bariatric surgery using Capella’s technique, and compared them with individuals diagnosed with GH deficiency. They concluded that GH is decreased in obese and behaves as in GH deficiency (GHD). In that period of study, they observed a reduction in BMI and an increase in GH and IGF-I in women by the sixth month, and in both sexes within twelve months after surgery. These authors also reported that the values of GH / IGF-I, found in men before surgery, were similar to those found in subjects with GHD, and these levels in women, although lower, were higher than the levels found in men, but still below in comparison with the reference value for the ages. Thus, they concluded that surgery reduces weight and restores the levels of GH. The normalization of IGF-I levels within 12 months found on that referred study and not found on a 45-day postoperative period in this research, raises the necessity of new research in order to determine IGF-I levels in the late postoperative period.

According to Matos, GH is one of the main components of the somatotropic axis and its primary action is to regulate peripheral IGF-I. GH has a direct action in most human cells and, thus, its deficiency or excess leads not only to changes in growth, but also to a wide variety of metabolic disorders. Halpern, studying the effects of growth hormone on anthropometric and metabolic parameters in android obesity, also states that obese patients present decreased GH plasma levels, and a decreased response to various stimuli.

We expected, in this casuistic, to find lower levels of IGF-I among obese patients in the preoperative period compared to the levels found in the control group, and to find similar normal IGF-I levels (control group’s levels) in the obese patients 45 days after the bariatric surgery, with reduction in body weight. We found, instead, that despite a substantial weight reduction occurred during the study, IGF-I levels kept decreasing.

Guadarrama suggested that one of the functions of IGF-I is to control growth hormone secretion and that, when the concentration of IGF-I is low, there is a stimulus for GH secretion. This suggests that the period of 45 days postoperative of bariatric surgery, used in this study, may not have been enough to a normalization of GH levels, thus justifying the low IGF-I values found in this casuistic, since previous studies show that the concentration of IGF-I correlates with the concentration of GH. Moreover, Barreto Filho emphasized that hyperinsulinemia inhibits GH release, and also blocks the synthesis of IGFBPs in the liver, causing increase in the free fraction of IGF-I. Different from the findings showed in previous studies, in the present study we observed that insulin levels were higher in the preoperative period and IGF-I levels reduced. Reductions in
weight and BMI after bariatric surgery was registered, the insulin levels decreased, and a even greater reduction of the IGF-I levels in the postoperative period was found.

Further studies, with a larger sample, and a longer follow-up period after surgery are necessary, so we can have a better understanding of the metabolic behavior of patients after weight loss induced by bariatric surgery using the Roux-en-Y gastric bypass procedure.

In conclusion, bariatric surgery using the Roux-en-Y gastric bypass procedure was able to induce the reduction of weight and BMI in a short-term, and also the reduction of insulin plasma levels and insulin resistance in the present study, reaching similar values in the postoperative group when compared to the group control. However, such facts do not compromise normal blood glucose levels in the preoperative period, which remained normal in the postoperative.

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