BARIATRIC SURGERY METABOLIC EFFECTS IN OBESE INDIVIDUALS ASSOCIATING INSULIN RESISTANCE STATUS

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ABSTRACT

Background and aims. Metabolic syndrome or insulin-resistance syndrome is an obesity related condition that increases the risk of developing type 2 diabetes mellitus over time. In this prospective study, overweight and obese individuals were assessed for insulin-resistance status by the HOMA indexes.
Material and methods. 48 bariatric patients associating metabolic syndrome were assessed before and 6 months after the surgery procedure (gastric sleeve, gastric by-pass). The assessment included the following laboratory blood tests: glucose, insulin, HOMA1 index and HOMA2 index before meal.
Results. There was a significant improvement of insulin resistance status in obese patients who underwent bariatric surgery.
Conclusions. Insulin resistance status in obese individuals improves significantly after bariatric treatment.

Keywords: insulin resistance, HOMA index, obesity, bariatric surgery

BACKGROUND AND AIMS

Obesity is a pathological condition characterized by a mixed disorder of metabolic processes of the organism with a change in its energy balance. In some genetic syndromes, obesity is the phenotypical manifestation of a single gene, but in more than 90% of cases this disease is the result of a multiple pathogenic factors which mainly disrupt the balance between energy intake and energy consumption.

Bariatric surgery is a modern approach in obesity treatment with proven results in rapid and sustained body weight loss. The weight loss itself induces beneficial metabolic effects and improves intestinal hormone secretion [1], but surgical treatment of obesity appears to provide suitabe circumstances for maintaining a long-term downward trend in body weight.

Currently, the body size of an individual is most frequently evaluated by BMI (body mass index or Quetelet index) [2], the ratio between weight (kg) and square of height (m^2).

Therefore, considering BMI values, World Health Organization (WHO) classifies obesity in four categories as follows:

- Overweight: BMI = 25-29.9 kg/m^2, with a mildly increased comorbidity risk associated;
- Obesity Class I: BMI = 30-34.9 kg/m^2, with a moderately increased comorbidity risk;
- Obesity Class II: BMI = 35-39.9 kg/m^2, with an increased comorbidity risk;
- Obesity Class III or morbid obesity: BMI over 40 kg/m^2, associating a very high comorbidity risk [3].

Insulin resistance syndrome or metabolic syndrome

Insulin resistance is a condition of the organism in which a certain amount of insulin concentration induces a suboptimal response in the peripheral tis-

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sues [4]. Insulin resistance manifests primarily in tissues that are insulin-dependent for intracellular glucose transport, namely hepatic, muscular and adipose tissues [5].

The pathophysiological mechanisms involved in insulin resistance syndrome include genetic or primary defects of target cells, anti-insulin antibodies and accelerated insulin catabolism [6]. Mitochondrial dysfunctions also have a significant role in the development of insulin resistance and associated complications [7]. Insulin resistance plays a major role in the pathogenetic development of metabolic syndrome, which may include at least one of the following: hyperinsulinemia, glucose intolerance, type 2 diabetes mellitus, hypertension, elevated levels of serum triglycerides, low HDL-cholesterol, central obesity [8] and pro-coagulant status characterized by elevated PAI-1 levels.

In 2009, the International Diabetes Federation, the International Society of Atherosclerosis, the World Federation of Cardiology and the American Society of Cardiology defined metabolic syndrome by meeting at least three of the following criteria [9]:

- abdominal obesity (abdominal circumference > 80 cm in women and > 94 cm in European males);
- serum triglycerides > 150 mg/dl or patient following a lipid-lowering medication;
- HDL-serum cholesterol < 40 mg/dl in men, < 50 mg/dl in women or patient following a treatment for increasing HDL-cholesterol values;
- systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg or patient following blood presure treatment;
- baseline blood glucose levels > 100 mg/dl or patient previously diagnosed with diabetes mellitus.

Therefore, metabolic syndrome is not a disease in itself, but a combination of metabolic disorders that can identify individuals at high risk for cardiovascular events and/or type 2 diabetes mellitus. The risk of sudden death is estimated to be five times higher in patients with type 2 diabetes mellitus and three times higher in patients with metabolic syndrome. If type 2 diabetes mellitus is not present, metabolic syndrome increases over time the risk of its occurrence up to five times [10].

HOMA index

Matthews et al. described in 1985 a method which easily evaluates the insulin resistance status of an organism, namely HOMA index („Homeostasis model assessment") [11]. Under basal conditions, the relationship between glucose and insulin serum levels reflects the balance between liver glucose synthesis and insulin secretion of β pancreatic cells maintained through a feed-back loop established between the liver and endocrine pancreas.

HOMA1 index, the initial model, was calibrated to give a normal 100% pancreatic cell function and a normal insulin resistance of 1. Increased insulin resistance associates increased basal blood insulin level and suboptimal secretion of pancreatic β cells by increasing blood sugar levels. Considering this glucose-insulin interrelation, any pair of basal sugar and insulin blood levels can be used to quantify insulin resistance (IR) and pancreatic β cell function (% B) using the following formula:

HOMA1-IR = (IB (μU/l) x GB (mmol/l)) / 22.5,

where IB represents basal blood insulin levels before meal, and GB basal blood glucose levels before meal. For basal glucose in mg/dL, the denominator is 405.

HOMA index is considered a lab test which has a predictive value in the cardiovascular risk [12]. Furthermore, detection of insulin resistance in non-diabetic subjects using HOMA index test was associated with an increased risk of stroke [13].

Recommendations to determine HOMA index include the following: assessment of patients with BMI over 28 kg/m^2; suspicion of insulin resistance status (metabolic syndrome, type 2 diabetes mellitus); polycystic ovary syndrome [14].

HOMA1 index does not take into account the differences between insulin and hepatic sensitivity, increased insulin secretion and decreased hepatic gluconeogenesis to blood glucose levels above 180 mg/dl, glycosuria and circulating proinsulin. Therefore, the improved model index HOMA 2 was also calculated in the present study by accessing the website *https://www.dtu.ox.ac.uk/homacalculator/download.php.* HOMA2 calculator automatically calculates the insulin resistance after introducing glucose and insulin serum levels, and also reveals the percentage of functional β-pancreatic cells.

Insulin levels were determined using chemiluminescence detection method (CLIA) and as for glucose, the spectrophotometric method [15].

HOMA index reference values are [16]:

< 2 – normal;

> 2 – possible resistance to insulin;

> 2.5 – increased probability of insulin resistance;

> 5 – the mean value in type 2 diabetes mellitus.

MATERIAL AND METHOD

The present prospective clinical trial was conducted from January 2017 to September 2018, at the Laboratory Department of Bethany Medical

Clinic Oradea over the patients who underwent bariatric surgery at MedLife Genesys Hyperclinic Arad, Bariatric Surgery Department.

Study design and patients

The laboratory blood tests for the eligible subjects were performed in Oradea at Bethany Private Medical Center. The patients included in the study were overweight and obese individuals associating metabolic syndrome assessed in order to receive a bariatric treatment, namely gastric sleeve or gastric by-pass. The following flowchart (Figure 1) presents the selection algorithm for the eligible patients.

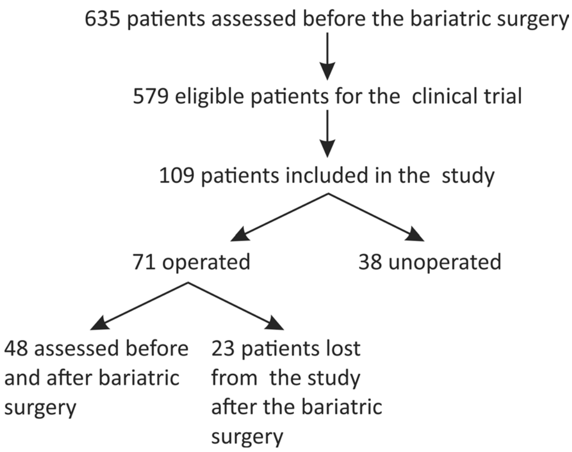

FIGURE 1. *The selection algorithm of eligible patients*

Laboratory, anthropometric and clinical data collection

Before bariatric surgery and 6 months thereafter, the patients enrolled in the study were assessed for the following laboratory tests: insulin, glucose serum levels and HOMA indexes before meal.

The clinical evaluation included the following: weight, height, body mass index (BMI), abdominal circumference, blood pressure, family history of overweight/obesity and comorbidities.

Statistical analysis

In terms of followed trend in time, comparison of mean values was performed using the Student pair test for normal distribution variables and the Wilcoxon test for those with asymmetric distribution. The statistical significance limit was 0.05.

RESULTS

Distribution by gender

109 patients were enrolled in the study, of which 83 (76.1%) were female and 26 (23.9%) male: $p < 0.0001$, Chi-Square test (Figure 2).

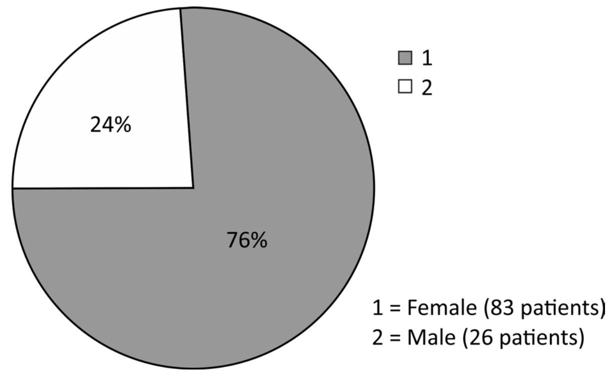

FIGURE 2. *Distribution by gender of the enrolled group (percentage%)*

Considering only the patients who came for the 6th month follow-up assessment, the ratio becomes even more unequal: out of 48 patients, 41 (85.4%) were women and only 7 (14.6%) men ($p < 0.0001$, Chi-Square test).

By comparing these data with the gender distribution in the group that didn't show up at the post-operative assessment, we obtain the following data:

TABLE 1. *Gender distribution in the lost group and the enrolled group*

Gender	Lost group (n = 61)	Enrolled group (n = 48)
Female nr. (%)	42 (68.9)	41 (85.4)
Male nr. (%)	19 (31.1)	7 (14.6)

There is a higher ratio in women among controls, but the difference does not reach the statistical significance: $p = 0.0738$, Yates correction (Figure 3).

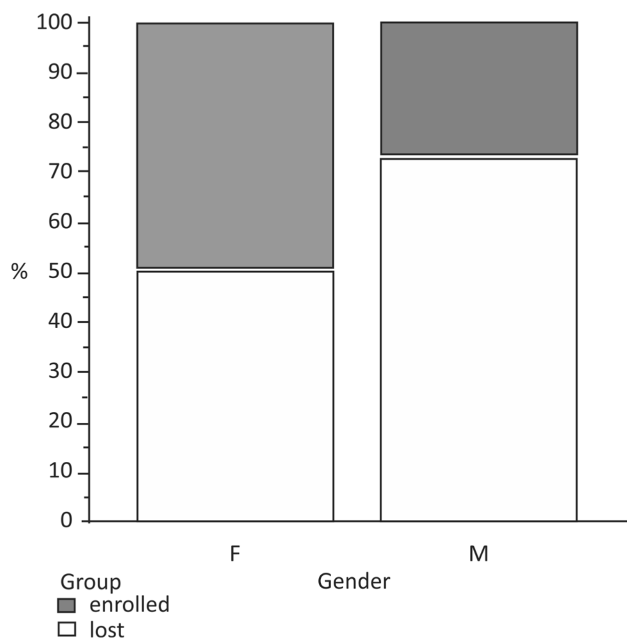

FIGURE 3. *Distribution of the lost group and the enrolled group by gender (percentage%)*
M = male, F = female

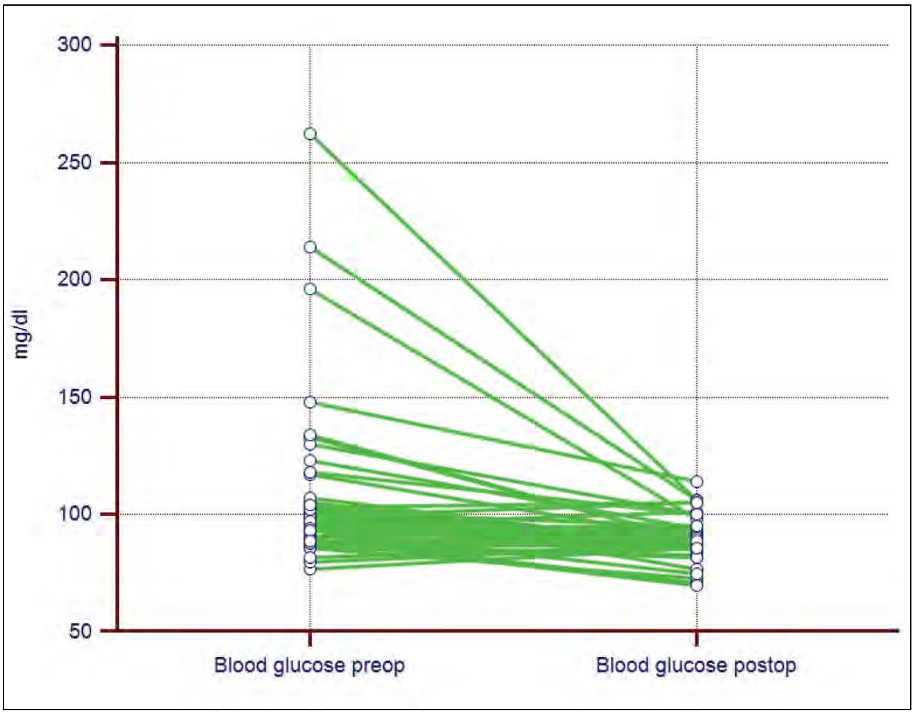

FIGURE 4. *Glucose serum levels before bariatric surgery and at 6 months thereafter*

Glucose serum levels pre- and postoperative

Glucose levels before meal registered a decreasing trend of marked significance: the median preoperative value was 98 mg/dl and postoperatively 89 mg/dl ($p < 0.0001$, Wilcoxon test) (Figure 4).

Insulin serum levels pre- and postoperative

The insulin level also registered a significant decrease: from the mean value of 20.6 µU/ml (± 14.0) to mean values of 6.64 µU/ml (± 3.8) ($p < 0.0001$, the Student test for dependent batches) (Figure 5).

HOMA 1 and HOMA 2 indexes pre- and postoperative

The following table reveals the geometrical mean values for HOMA 1 and HOMA 2 risk indexes.

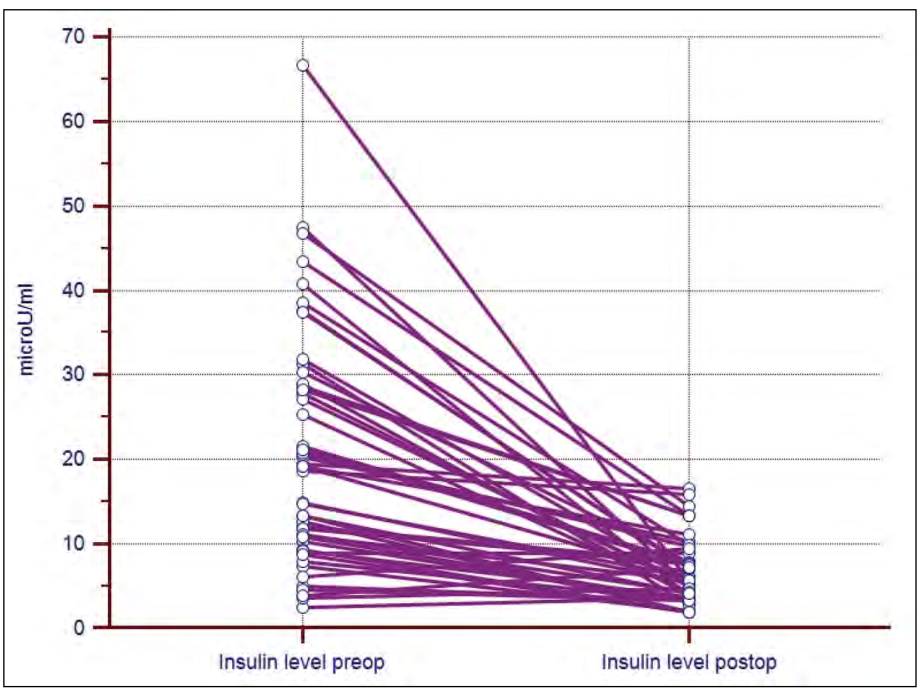

FIGURE 5. *Insulin serum levels before bariatric surgery and at 6 months thereafter*

TABLE 2. *Geometrical mean values for HOMA 1 and HOMA 2 risk indexes*

Index	Preoperative (n=48)	Postoperative (n=48)	Statistic significance (p)
HOMA 1 – geometrical mean value	4.3 (3.2-5.6)	1.2 (1.0-1.5)	< 0.0001
HOMA 2 – geometrical mean value	2.3 (1.8-3.0)	0.76 (0.65-0.85)	< 0.0001

After studying the results shown in this table, the decrease of HOMA indexes after bariatric surgery becomes obvious. The Figure 6 and Figure 7 further emphasizes these differences.

Percentage of functional β pancreatic cells pre- and postoperative

As for the percentage of functional β pancreatic cells, we noticed a statistically significant decrease: the preoperative arithmetic mean is 144.2 (± 74.9) and the postoperative, 86.0 (± 34.9) ($p < 0.0001$, Student test for dependent batches) (Figure 8).

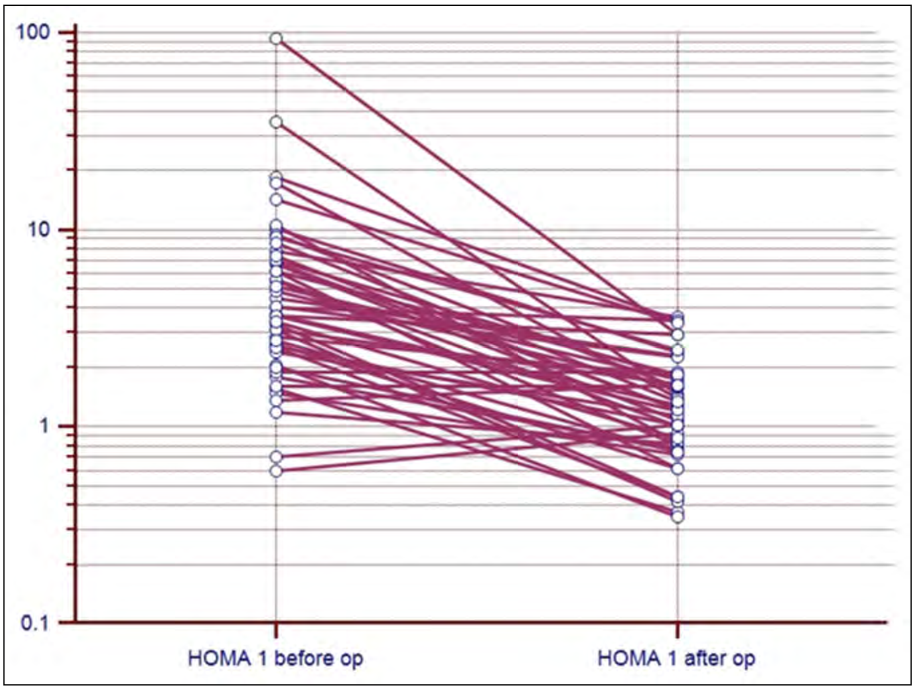

FIGURE 6. *HOMA1 index values before and after bariatric surgery*

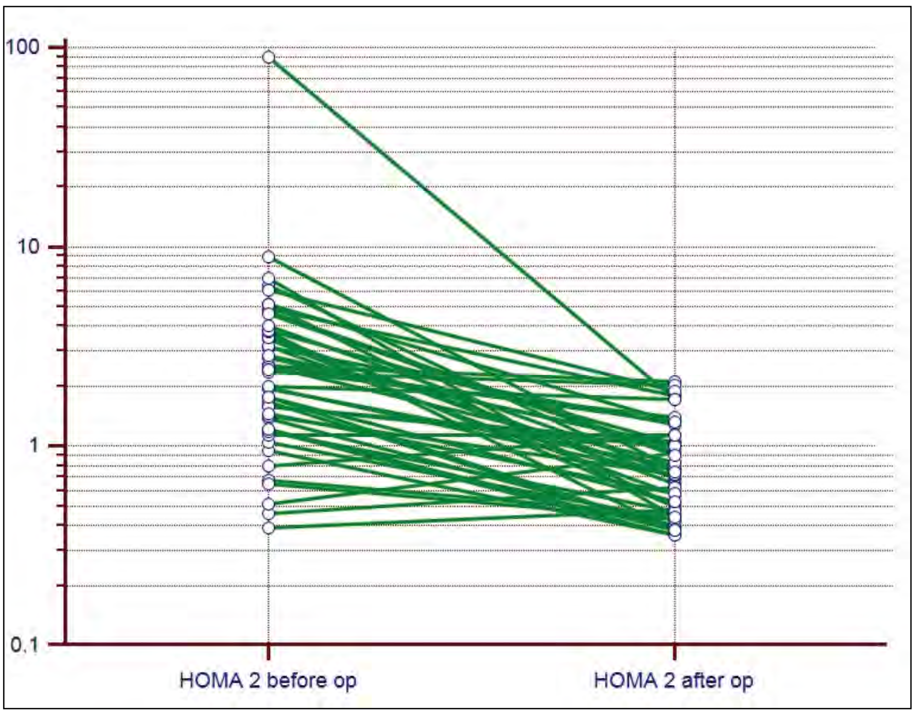

FIGURE 7. *HOMA2 index values before and after bariatric surgery*

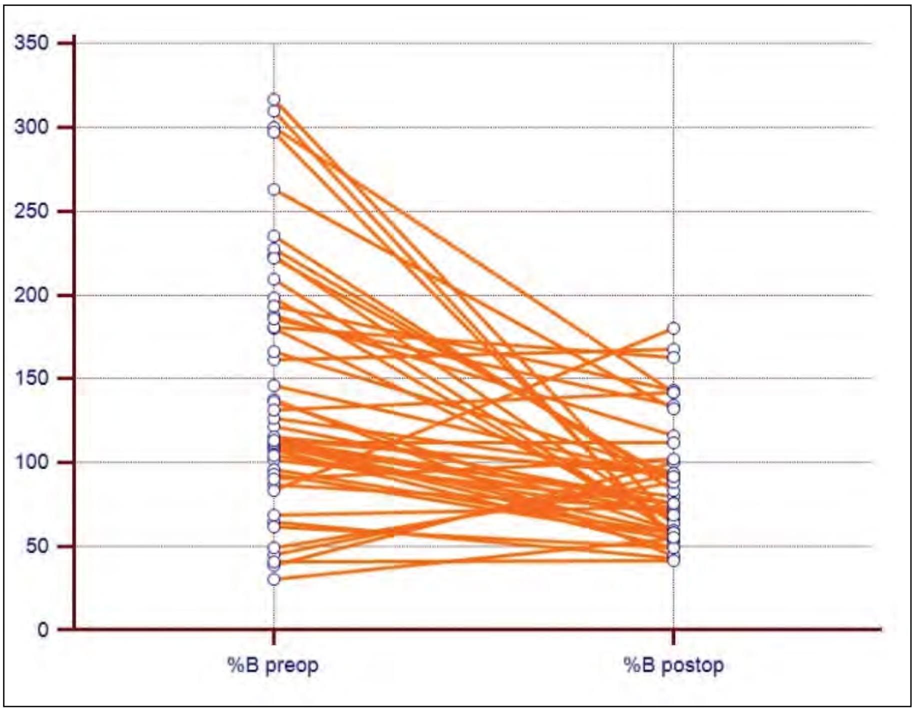

__FIGURE 8.__ Percentage of functional β pancreatic cells pre- and postoperative

DISCUSSIONS

The gender distribution results of this study fall within the limits observed in the literature [17]. Thus, the ratio between genders, clear-cut suitable for the feminine gender, follows the trend observed in similar studies. Both the percentage of preoperative group (76.1%) and study group (85.4%) remain in the range of these studies indicating a female percentage of 60 to 90%.

The results regarding the levels of serum insulin and blood glucose obtained in this study are consistent with other similar studies [18,19].The incidence of elevated blood glucose levels before meal decreased significantly 6 months after the bariatric procedures (gastric sleeve, gastric by-pass). For the patients with a short history of diabetes, insulin resistance may be the major cause of the disease and not β pancreatic cell dysfunction [20,21]. Thus, increasing insulin sensitivity is an effective treatment for type 2 diabetes mellitus. The decrease trend of HOMA1 and HOMA2 indexes along with the optimized functionality of β pancreatic cells indicates an improvement in insulin resistance status with a good long-term prognosis for the individual. Postoperative HOMA1 index is considered an independent predictor factor for the complete remission response of diabetes mellitus [22]. The results of our study regarding the decrease of HOMA1 index fall within the variability observed in the specialty literature.

CONCLUSIONS

Excess adipose tissue has a baneful effect on carbohydrate and lipid metabolisms. One of the bariatric surgery beneficial effects is a quick significant improvement in the insulin resistance status in obese individuals, registering a decreasing risk of developing type 2 diabetes mellitus over time. Thus, bariatric procedures should be considered first therapeutic option in obese patients associating metabolic syndrome and/or type 2 diabetes mellitus.

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