,,VICTOR BABEŞ" UNIVERSITY OF MEDICINE AND PHARMACY TIMIŞOARA
FACULTY OF MEDICINE
DEPARTAMENT X SURGERY II

PHD CANDIDATE
STOICA LAURIAN FELIX

SUMMARY OF THE PHD THESIS

THERAPEUTICAL OPTIONS IN THE SURGICAL TREATMENT OF OBESITY: SLEEVE GASTRECTOMY, GASTRIC PLICATION OF THE GREATER CURVATURE, MINI-GASTRIC BY-PASS.

Thesis Advisor
PROF. DR. LAZĂR FULGER

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Key words: obesity, gastric sleeve, gastric plication, mini-gastric by-pass, adipokines

INTRODUCTION

Physical appearance and especially body fat is a subject with intense psychosocial impact debated over time.

Overweight and obesity are associated with various chronic heart conditions, depression, diabetes mellitus or even neoplasia. Although many people consider unhealthy eating habits as playing an important role in the appearance of obesity, obesity actually is a multifactorial condition.

Being a critical subject, I chose to delve deeper into the surgical procedures (sleeve gastrectomy, gastric plication of the greater curvature and mini-gastric bypass) for treating obesity, the mechanisms involved in the remission of obesity and also part of the hormonal changes that occur.

GENERAL PART

1. General aspects regarding obesity

Overweight and obesity are defined as an excessive accumulation of adipose tissue, which can affect health. One method of assessing obesity is the use of the body mass index, calculated according to the formula: weight divided by the square of height.

Worldwide, the prevalence of overweight and obesity has almost doubled since 1980. Globally, from 1980 to 2015, the proportion of men with BMI ≥ 25 kg/m^2 increased from 25.4% to 38.5%, and in in the case of women, from 27.8% to 39.4%. The non-communicable diseases (NCD) Risk Factor Collaboration estimates that by 2025, the prevalence of obesity will reach 18% in men and 21% in women.

Obesity is a multifactorial disease, now endemic in most of the world. Understanding the contribution of different causes is essential for its successful management.

A small proportion of obesity cases are due to genetic mutations, but the increased prevalence of common, multifactorial obesity is mainly due to complex of interactions between changes in environmental factors (obesogenic environment) and an individual genetic predisposition.

Epigenetic mechanisms are pre- or post-translational changes in gene regulatory activity without altering the genomic sequence.

Obesity is a multifactorial disease that is caused by biological, genetic, social, environmental and behavioral causes.

The prevalence of obesity varies with unique individual characteristics such as age, sex, race, ethnicity, and socioeconomic status. It grows throughout life. It is not fully understood why race and ethnicity play such an important role in the prevalence of obesity, but genetic factors affecting body composition and adiposity distribution appear to be involved, in addition to different cultural standards of body image.

Rural areas are associated with a 1.36 fold increase in obesity compared to urban areas. Rural areas usually have greater distances between residences and supermarkets, hospitals or recreation halls, a fact that prevents healthy behaviors that would lead to obesity prevention

Numerous infectious agents cause obesity in various experimental animal models, a phenomenon called infectious obesity, adenovirus -36 infection alters carbohydrate and lipid metabolism by decreasing fatty acid oxidation, increasing glucose absorption and conversion to fatty acids, resulting in adipocyte hypertrophy.

The human body is host to a large variety of microorganisms that are part of the microbiome. Recent research suggests that changes in the specific phylum of the enteral microbiome may be an indicator for obesity in children. A study that examined the involvement of the microbiome in the development of obesity was carried out in rodents, showing that the transfer of the microbiome from obese to lean animals induced obesity, whereas the transfer of the microbiome from lean animals did not.

Breastfeeding appears to have a protective role on the development of obesity by promoting the development of healthy microbiome bacteria, while milk formula has the opposite effect. The effect of the fiber-rich diet due to the abundance of Bifidobacteria and Lactobacillus on weight loss is also well-known.

The diagnosis of obesity, its assessment, is not strictly based on weighing, as an assessment of body composition, especially of adipose tissue, is necessary. The term "adiposopathy" defines the pathogenic role of adipose tissue, tissue involved in lipid and carbohydrate metabolism, through the secretion of bioactive proteins called adipokines. Due to the endocrine and inflammatory role of adipose tissue, obesity is also classified according to the percentage of adipose tissue in the body and its distribution. Waist and hip circumference are two necessary measurements when assessing the distribution of adipose tissue. The ratio of the two measurements is increased in android obesity and decreased in gynoid type. Increased values of BMI and waist circumference are associated with increases in some parameters involved in the evaluation of cardiovascular diseases:

2. The surgical treatment of obesity

The modern era of bariatric procedures involving the stomach started from the observational studies on patients who underwent ulcer surgery that subsequently lost weight.
Sleeve gastrectomy has become a distinct operation, although it was originally described in 1988 as part of biliopancreatic diversion with duodenal switch, with the intention of removing most of the stomach, preserving the pylorus, and minimizing dumping syndrome.

2.1 Laparoscopic sleeve gastrectomy

The surgical technique described by Jorge Daes uses 5 trocars. The goal is to devascularize the greater gastric curvature but also to section the stomach, parallel to the greater gastric curvature by means of the linear stapler.

2.2 Laparoscopic gastric plication of the greater curvature

The surgical technique was described by Talebpour

The purpose of the plication is to restrict as much as possible the space inside the stomach by means of the folds. The plication is performed by invaginating three sections of the gastric wall corresponding to the perimeter of the greater curvature. By the end of this process three longitudinal folds of the gastric wall will result.

2.3 Laparoscopic mini-gastric bypass

The classic Rutledge technique involves placing five "diamond-shaped" trocars into the upper abdomen. The purpose of the gastric reservoir resulting from the MGB is to remove the reservoir function of the stomach and transform the stomach into a non-obstructive extension of the esophagus, in which food does not stay, but slides into the jejunal lumen.

RESEARCH

1. Ghrelin, adiponectin and leptin levels in obese rats with type 2 diabetes mellitus after gastric sleeve and gastric plication

The aim of the study is to analyze the changes in serum ghrelin, adiponectin and leptin levels in an experimental model based on obese rats with type 2 diabetes mellitus, which undergo gastric sleeve and gastric plication.

We carried out an experimental study, in which we included 18 Wistar rats, aged 9 weeks, all male, obtained from the biobase of the "Pius Brânzeu" Center for Laparoscopy and Microsurgery of the “Victor Babeș” University of Medicine and Pharmacy in Timisoara. During the first 36 weeks, the rats were fed ad libitum with obesity-inducing food (Bio Serv F3282, food containing lipids 60%) and fresh water. After obesity was induced, at the end of 36 weeks, the rats were divided into three groups: the gastric sleeve group (6 rats), the gastric plication group (six rats), and the control group (six rats). At the end of the surgical procedures, the rats were given a normal diet (Bio Serv F4031) until the end of the study. All animal experiments were carried out with the consent of the ethics committee of SCJUT, in accordance with the laws of the European Union, regarding the protection of animals (86/609 /EC).

To perform the longitudinal gastrectomy, we performed a median laparotomy of approximately 4 cm. Later we mobilized the small intestine, and the cecum, in order to have access to the inferior vena cava, from which we collected blood. We dissected and sectioned the gastro-splenic ligament, aiming to release the greater gastric curve. To calibrate the remaining gastric reservoir, we used a 10 Fr orogastric calibration probe. We applied vascular forceps, parallel to the greater curvature of the stomach adjacent to the calibration probe, we sectioned the stomach from the level of the fundus to the level of the antrum, removing most of the fundus and gastric body. We performed hemostasis of the section transection, and we sutured the section transection of the remaining gastric reservoir with a continuous 5-0 monofilament polypropylene thread (Premilene B|Braun) in a single layer, and the second sero-muscular layer.

We performed the gastric plication starting from the fundus to the antrum, in two sero-muscular layers, using continuous 5-0 monofilament polypropylene thread (Premilene B|Braun)

In the control group, after performing the laparotomy and blood collection, the stomach was mobilized towards the midline and returned to the anatomical position.

Blood glucose was determined by taking a drop of blood from the tail, using an ACCU-CHEK glucometer. The blood collected from the inferior vena cava was used to determine the serum values of ghrelin, adiponectin, leptin, using the ELISA technique.

After 36 weeks of administration of high-lipid food, the mean preoperative weight was 783.16g ± 101.38 in the sleeve gastrectomy group, 781.3g ± 103.1 in the gastric plication group, and in the control group the mean weight was 778.16g ± 90.72. No statistical differences were recorded between the 3 groups ($p>0.05$).

At 4 weeks postoperatively, the weight of rats in the sleeve gastrectomy group was 658.33g ±86.57, the gastric plication group had a mean weight of 702.33g ± 84.06, and the control group had a mean weight of 829.16g ±69.24.

Comparing the average weight one month postoperatively, rats subjected to gastric sleeve with rats that underwent gastric plication, no statistically significant differences were recorded (658.33g vs 702.33g, $p>0.05$). Comparing the mean weight of the rats in the gastric sleeve group with the control group, the gastric sleeve group had a statistically significant decrease (658.33g vs 829.16g, $p< 0.05$).

The average blood glucose in the group of animals with gastric sleeve was 152.33mg/dl ± 33.6, in the plication group 150 mg/dl ±34.74, respectively 146.5mg/dl ±39.32 in the control group.

After the metabolic surgery, four weeks postoperatively, the blood glucose in the sleeve gastrectomy group was 83.16mg/dl ± 12.7, in the gastric plication group, the rats had an average serum glucose of 86.66mg/dl ± 11.46, and in the control group the postoperative blood glucose value was 104.5mg/dl ± 9.97.

By comparing the average blood glucose values in the gastric plication group with the control group, a statistically significant decrease in blood glucose values was obtained (86.66 ± 11.46 mg/dl vs 104.5 mg/dl ±9.97, $p= 0.01$). We did not obtain statistically significant differences between the mean values of glycaemia in the gastric sleeve group and the gastric plication group.

Statistically significant decreases in postoperative ghrelin levels were recorded in the gastric sleeve group (3.23 ng/ml vs. 2.01 ng/ml p=0.0003), respectively the gastric plication group (3.08 ng/ml vs. 2.35 ng/ml p=0.006), and in the control group four weeks postoperatively there was a statistically insignificant increase (2.98 ng/ml±vs. 3.13 ng/ml p>0.05)

Comparing preoperative and postoperative adiponectin serum levels, in the gastric sleeve group, an increase in values was recorded (86.66 ng/ml vs 115.83 ng/ml, p=0.0007). Statistically significant increase was also recorded in the gastric plication group (74.5 ng/ml vs. 107 ng/ml, p<0.001). The control group recorded a statistically insignificant decrease (113.16 ng/ml vs. 101 ng/ml p>0.05.

By comparing the preoperative and postoperative results, statistically significant decreases in leptin values were obtained 563 pg/ml vs 389 pg/ml, p<0.05 in the sleeve gastrectomy group and the gastric plication group 496.33 pg/ml ± 79.8 vs. 367.5 pg/ml± 90.88, p<0.05, however in the control group the postoperative decrease was not statistically significant 503.83 pg/ml ±75.04 vs. 488.33 pg/ml p> 0.05.

2. Hormonal changes after gastric sleeve and mini-gastric bypass in a rat-based animal model with type 2 diabetes mellitus and obesity.

The aim of the study is to analyze the changes in ghrelin, adiponectin and leptin involved in the etiopathogenesis of obesity, in an experimental model based on obese rats with type 2 diabetes mellitus, which undergo gastric sleeve and mini-gastric bypass.

We carried out an experimental study, in which we included 15 Wistar rats. After obesity was induced, at the end of 36 weeks, the rats were divided into three groups: the gastric sleeve group (5 rats), the mini-gastric bypass group (5 rats) and the control group (5 rats).

To perform the mini-gastric bypass, we performed a median laparotomy of 4 cm. We mobilized the small intestine, and the cecum, identified the inferior vena cava from which we collected blood. After sectioning the gastrosplenic ligament, we mobilized the stomach. We inserted a 10 Fr orogastric calibration probe, the gastric reservoir was created by applying vascular clamps, one perpendicular to the greater gastric curvature and one parallel to the greater gastric curvature. We sectioned the stomach, and the vertical section was sutured with 5-0 monofilament non-absorbable thread, in a full layer, while the horizontal section was anastomosed with the jejunum, end-to-side, with continuous 5-0 monofilament thread, the intestine was excluded being 20-25% of the total length of the small intestine. Sectional slices of the dissected stomach were sutured with nonabsorbable 5-0 monofilament suture.

At 36 weeks, the average weight of the rats included in the gastric sleeve group was 778 g ± 112.46, in the mini-gastric bypass group 784 g ± 84.40, and in the control group 773.6 g ± 100.64. No statistically significant differences were recorded between the 3 groups ($p>0.05$).

4 weeks after performing the surgical interventions, the average weight of the rats in the gastric sleeve group was 647.8g ± 92.39, in the mini-gastric bypass group the average weight was 631g ± 76.06, and the control group recorded an average weight of 828.8g ± 77.41.

By comparing the postoperative weights between the gastric sleeve group and the mini-gastric bypass group, no statistically significant difference was obtained (647.8g vs 631g, $p>0.05$). The statistical analysis of the gastric sleeve and mini-gastric bypass groups with the control group, identifies a statistically significant difference between the mean postoperative weights. (647.8 vs 828, $p=0.01$), (631 vs 828, $p= 0.003$)

A statistically significant decrease was recorded by comparing the preoperative and postoperative weights of the gastric sleeve group, ($p=0.0001$), a statistically significant decrease also being recorded in the mini-gastric bypass group ($p=0.0006$).

There was a statistically significant decrease in preoperative blood glucose levels compared to postoperative blood glucose levels in the sleeve group (147mg/dl vs. 85.6 mg/dl $p=0.007$), the same trend being recorded in the mini-gastric bypass group (149mg/dl vs. 84 mg/dl $p=0.001$).

By comparing the postoperative blood glucose levels between the gastric sleeve group and the control group, a statistically significant decrease was recorded (85.6 mg/dl vs 104 mg/dl $p<0.05$) The postoperative blood glucose values of the mini-gastric bypass group compared to the control group were significant statistically lower (84 mg/dl vs 104 mg/dl $p<0.05$). No statistically significant difference was detected between the postoperative blood glucose values of the gastric sleeve and mini-gastric bypass groups (85.6mg/dl vs 84mg/dl $p>0.05$)

The statistical analysis of the preoperative and postoperative results of the ghrelin levels of the gastric sleeve group indicates a statistically significant decrease (3.24 ng/ml vs 2.04 ng/ml, $p=0.002$), a statistically significant decrease also recorded in the mini-gastric bypass group (3.02 ng/ml vs. 2.74 ng/ml, p =0.0002). No statistically significant differences were detected between postoperative ghrelin levels between the gastric sleeve and mini-gastric bypass groups (2.04ng/ml vs 2.74ng/ml, p>0.05).

Statistical analysis of pre- and postoperative results of serum adiponectin levels in the gastric sleeve group indicates a statistically significant increase (93.8ng/ml vs121.4 ng/ml p=0.003). Also, a statistically significant increase was recorded in the mini-gastric bypass group (95ng/ml vs 122.8 ng/ml p= 0.0001). The control group recorded a statistically insignificant decrease in serum adiponectin values (108.4ng/ml vs 101ng/ml, p>0.05). By comparing the postoperative adiponectin serum levels of the gastric sleeve and mini-gastric bypass groups, no statistically significant difference was obtained (p>0.05).

By comparing the postoperative leptin serum levels in the gastric sleeve group, a statistically significant decrease was recorded (546.8 pg/ml vs 368.6 pg/ml p=0.0006). The serum leptin levels in the postoperative mini-gastric bypass group were statistically significantly lower compared to the preoperative levels (355.2 pg/ml vs 565.4 mg/dl p<0.0001). No statistically significant difference was detected between the postoperative leptin values of the gastric sleeve and mini-gastric bypass groups (368.6 pg/ml vs 355.2 pg/ml p>0.05).

3. Ghrelin levels after short term follow-up of obese patients who underwent sleeve gastrectomy compared to greater curvature plication

The aim of the study is to compare serum levels of acylated ghrelin (the active form of ghrelin) preoperatively and postoperatively in patients who underwent laparoscopic gastric sleeve and gastric plication and to correlate it with weight loss and hunger after short term follow-up.

A non-randomized prospective study was carried out in the Department of General Surgery II of the "Pius Brînzeu" County Emergency Clinical Hospital Timișoara and Ponderas Academic Hospital Bucharest between March and September 2015. The laparoscopic procedures performed were longitudinal gastrectomy - LSG and plication of the greater gastric curve - LGCP. Patients completed a questionnaire assessing subjective hunger both preoperatively and postoperatively. Evaluation was performed using a scale from 1 to 10 for quantifying the feeling of hunger. Results are expressed as mean values ± standard deviation (SD).

18 patients were enrolled in the study, out of which 10 patients were operated using the longitudinal gastrectomy procedure and 10 patients were operated using the greater gastric curvature plication. All procedures were performed by laparoscopic approach. Out of the total of 18 patients, 17 patients were female and one patient was male. The mean age in the LSG group was 34.9 ± 9.7, while in the LGCP group the mean age was 35.8 ± 8.91. Regarding the BMI value, in the LSG group the average was 37.33 ± 2.08 kg/m2, and in the LGCP group the average was 36.92 ± 1.43 kg/m2.

The preoperative mean levels of ghrelin in the gastric plication group was 318.08 pg/dl ± 161.70 SD, at one month postoperatively it was 190.58 ± 116.75 SD (p= 0.01), and at 3 months postoperatively 91.57 ± 56.70 SD (p= 0.004) . Comparing the values of the 2 groups, no notable differences are observed between the two groups, 212.21 pg/dl ± 140.57SD in the longitudinal gastrectomy group compared to 318.08 pg/dl ± 161.70SD (p =0.16) in the gastric plication group. One month postoperatively, the ghrelin levels were lower in the LSG group compared to the LGCP group (74.47 ±29.55 pg/dl vs 190.58 ± 116.75SD, p=0.02). At 3 months, the differences between the two groups were statistically significant (41.47 ± 15.19 SD vs 91.57 ± 56.70 SD, p=0.04).

The preoperative mean BMI value in the LSG group was 37.33 kg/m2 ± 2.08 SD, at one month 33.62 kg/m2 ± 2.13 SD, and at 3 months it was 30.25 ± 1.89 SD. The mean preoperative BMI value in the LGCP group was 36.92 kg/m2 ± 1.43 SD, decreasing to 33.61 kg/m2 ± 1.14 SD one month postoperatively and 30.85 kg/m2 ± 2.34 SD three months postoperatively.

Regarding the correlation between the feeling of hunger and the preoperative level of ghrelin in the sleeve gastrectomy group, a positive linear correlation was revealed with a Pearson coefficient of r = 0.59. And within the LGCP group, a similar correlation was highlighted, with a value of r = 0.58. Within the same group, 3 months postoperatively, the r value was 0.59. Comparing the postoperative values at 3 months, the feeling of hunger was more diminished in the LSG group than in the LGCP group (p=0.03).

In addition to caloric restriction, longitudinal gastrectomy can also regulate the plasma levels of the hormone called ghrelin, which stimulates food intake, and of leptin, which inhibits the feeling of hunger, maintaining a unique hormonal balance through which weight loss is achieved. Thus, longitudinal gastrectomy not only contributes to significant weight loss, but also improves the metabolic profile and the resulting complications.

The first study performed analyzed the levels of ghrelin, adiponectin and leptin in obese rats with type 2 diabetes after gastric sleeve and gastric plication. Comparing the average weight one month postoperatively, rats subjected to gastric sleeve with rats that underwent gastric plication, no statistically significant differences were recorded (658.33g vs 702.33g, $p>0.05$). However, comparing the average weight of the rats in the gastric sleeve group with the control group, the gastric sleve group had a statistically significant decrease (658.33g vs 829.16g, $p< 0.05$).

Ghrelin is mainly produced by the stomach, therefore it is believed that after longitudinal gastrectomy the ability of endocrine cells to produce ghrelin decreases, but the exact mechanism by which the acylated ghrelin/total ghrelin ratio regulates glycemic changes is not fully known.

Adiponectin is a key adipokine that is mainly expressed by adipose tissue. Two endogenous receptors, ADIPOR1 and ADIPOR2, are expressed in the hypothalamus and the pituitary gland. Obesity is associated with a low level of adiponectin, as well as with a decrease in insulin sensitivity.

Gastric leptin, which is secreted in the intestinal lumen from the stomach, plays an important role in blood sugar regulation.

In the second study, there were significant differences in the mean weight variation of sleeve gastrectomy/mini-gastric bypass rats compared to the control group, although the preoperative weight was similar to that of the control group. However, between the two interventions the differences are almost negligible, with a small advantage in terms of weight loss in the group of rats operated through mini-gastric bypass. Data from literature confirms the data obtained in this study, showing not only that excess weight is greatly reduced, but also the fact that the group of "mini-gastric bypass" subjects have a greater and faster reduction compared to that of subjects undergoing gastric sleeve. This could be attributed to the fact that there is additional nutritional malabsorption following the mini-gastric bypass procedure.

Adiponectin is an adipokine that has multiple roles in the body. It is involved in lipid and carbohydrate metabolism (being involved in the regulation of energy consumption), but also has an anti-atherogenic, antioxidant and anti-inflammatory effect.

Mechanisms of leptin-lowering include caloric restriction (eg, carbohydrate-restricted diets) or starvation. Patients who undergo mini-gastric bypass surgery experience iatrogenic restriction of caloric intake and, consequently, a decrease in long-term adipose tissue. The intervention also involves a certain degree of intestinal malabsorption that additionally decreases the amount of absorbed nutrients.

In the third part of our study we compared two laparoscopic procedures, unlike the first two parts where the study was based on an experimental animal model.

Regarding BMI assessed preoperatively, no notable differences are observed between the values of the two studied groups. The postoperative evaluation at one month shows very close values in the two groups (33.62 vs 33.61 kg/m2). However, the decrease was more pronounced in the LSG group at 3 months, as evidenced by a lower BMI in this group, although at the first 2 assessments the gastric plication group showed lower mean values.

The preoperative ghrelin value in the LSG group was statistically significantly higher compared to the value revealed one month postoperatively, respectively 3 months postoperatively, where the lowest level was otherwise observed.

In the LGCP group, the preoperative ghrelin value was significantly higher compared to the evaluations performed at one month and 3 months postoperatively. And within this group, the lowest value was highlighted at 3 months postoperatively. However, unlike the LSG group, at 3 months postoperatively the patients presented a greater variation of values within the same group.

An attempt was made to identify a correlation between the level of ghrelin and the feeling of hunger, starting from the fact that this hormone stimulates the appetite and induces the feeling of hunger. Thus, at serial assessments performed preoperatively, at 1 month, and at 3 months, a significant decrease in hunger was observed as ghrelin levels progressively decreased in both groups.

4. Final conclusions

1. In the experimental animal study, we obtained a decrease in weight after gastric sleeve and gastric plication, demonstrating the beneficial effect of bariatric surgery on obesity.

2. Serum glucose levels decreased significantly following gastric sleeve and gastric plication.

3. Plasma levels of the active form of ghrelin decreased significantly both after gastric sleeve and after gastric plication

4. Plasma levels of adiponectin increased significantly after gastric sleeve and gastric plication, thus demonstrating the beneficial effect of bariatric surgery.

5. Although the hypoglycemic role of adiponectin is known, by increasing insulin sensitivity, in the experimental study it is difficult to specify whether the improvement in blood sugar is due to adiponectin or the effect of bariatric surgery.

6. Plasma levels of leptin, an anorexigenic hormone, secreted mainly by adipose tissue, by decreasing the mass of adipose cells, decreased following gastric sleeve and gastric plication.

7. Both gastric sleeve and mini gastric bypass are two effective interventions for treating morbid obesity and type 2 diabetes mellitus.

8. Excess weight loss is greater following mini-gastric bypass, being a bariatric procedure that is both restrictive and malabsorptive.

9. Laparoscopic gastric sleeve and laparoscopic gastric plication of the greater curve result in a decrease in the level of ghrelin, but also in the feeling of hunger.

10. Future studies are needed to unravel the complex mechanisms of obesity, hormonal changes, and weight loss.