

COMPARISON OF GHRELIN PLASMA LEVELS BETWEEN PRE AND POSTOPERATIVE PERIOD IN PATIENTS SUBMITTED TO GASTRIC PPLICATION ASSOCIATED WITH FUNDOPLICATION

Comparação dos níveis plasmáticos de grelina nos períodos pré e pós-operatório em pacientes submetidos à plicatura gástrica associada à funduplicatura

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ABSTRACT – Background- The recurrence of the gastroesophageal reflux disease may be related to later postoperative weight gain, therefore increasing the chances of developing columnar metaplasia and cancer. The gastric plication associated with fundoplication can be employed in order to be treating the two issues. **Aim** – To evaluate the serum ghrelin hormone in preand postoperatively as well as weight loss and control of reflux disease in patients undergoing gastroplication associated with fundoplication. **Methods** – Was performed laparoscopic gastric plication with fundoplication in eight patients; endoscopic examinations were performed pre and postoperatively as well as blood collection for ghrelin hormonal dosage. **Results** – There was control of reflux symptoms and mucosal lesions. Weight loss was significant. Since the change of the hormone ghrelin was not of great significance. **Conclusions** – Gastric plication associated with fundoplication was effective in treating reflux disease with surgical indication and for weight loss in obese patients. Appetite control occurs, but not due to ghrelin, because no significant decrease of its plasmatic levels was observed.

HEADINGS - Gastroesophageal reflux disease. Obesity. Gastric plication. Ghrelin.

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DESCRIPTORES - Doença do refluxo gastroesofágico. Obesidade. Plicatura gástrica. Grelina.

RESUMO – Racional – A doença do refluxo gastroesofágico e sua recidiva podem estar relacionadas ao ganho de peso tardio após a cirurgia bariátrica, aumentando a incidência de metaplasia colunar e neoplasia. A plicatura gástrica associada à funduplicatura pode ser empregada com o objetivo de se tratar a doença do refluxo e o sobrepeso. **Objetivos** – Avaliar o hormônio grelina no pré e pós-operatório, bem como a perda de peso e o controle da doença do refluxo em pacientes submetidos à gastroplicatura com funduplicatura. **Métodos** - Foi realizada gastroplicatura com funduplicatura videolaparoscópica em oito pacientes. Os exames endoscópicos foram realizados no pré e no pós-operatório, bem como a coleta de sangue para a dosagem do hormônio grelina. **Resultados** - Houve melhora dos sintomas do refluxo e das alterações na mucosa em todos os pacientes. A perda de peso foi significativa. Não houve significância na redução dos níveis plasmáticos de grelina. **Conclusões** - Com a plicatura gástrica e funduplicatura: 1) não houve redução significativa no hormônio grelina, apesar do relato de diminuição da fome e aumento da saciedade pelos pacientes; 2) o procedimento foi eficaz no tratamento da doença do refluxo; 3) obteve-se perda de peso significativa.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is determined as the return of gastric fluid to the esophagus, not leading to vomit. Some of the symptoms of this disease may be hoarseness, cronic cough, disphagia or heartburn¹. Its symptoms get worse when the patients gain weight, increasing the chance of intense esophagitis and esophageal adenocarcinoma. There are reports of patients who get better of GERD symptoms when they reduce weight, and there are a lot of studies that demonstrate an important improvement and the cure of

the disease². It can be treated with drugs or surgery (fundoplication associated to hiatoptasty), that improve 90% of the symptoms^{3,4}. But, in order to achieve an efficient treatment, it is necessary that the patient lose weight, as part of the therapy⁵. In 1981, Wilkison and Peloso described a surgical technique to treat obesity, when they invaginated (plicated) the stomach of obese patients. The weight loss was achieved, but due to complications and death, this technique was abandoned. Later, Fusco et al., in 2009, used this same technique on experimental models and achieved weight loss in rats that had their gastric greater curvature invaginated. Recently, Ramos et al., 2010, published that the gastric plication is a viable technique and leads to similar results when compared to "sleeve gastrectomy"⁶. As it is a reversible procedure and an alternative to patients with overweight and mild obesity, these authors propose the union of both surgical techniques: gastric plication, to decrease the intake of food, and fundoplication, to treat GERD. Hunger and satiety signs are generated in gastrointestinal tract, where there are many kinds of cells which secrete peptides that regulate food intake, providing satiety feeling when someone eats. These signs occur by peripheral nerves (afferent vagal fibers) and by receptors. One of the hormones that can lead to changes in hunger and satiety is ghrelin, a peptide with 28 aminoacids, isolated in 1999 by Kokima et al.. Serum ghrelin's level increases in fasting period and, after eating, it shows a drastic decrease. The hormone increases appetite, stimulates gastric motility, has an important function in regulating energetic balance and food intake, beyond the maintenance of body mass⁷.

A study in 2008 made by Karamanakos et al. showed an important decrease of ghrelin's levels after "sleeve" surgery for obesity, which has the same surgical principle of closing the vessels of the greater curvature and gastric fundus, dissecting and taking off the proximal stomach (gastric body and fundus), creating a tubular and narrow stomach.

The mechanism that leads to satiety and hunger control is still controversive, but it's known that, as it is a restrictive technique, some hormones don't have their metabolic effects anymore.

Even being a very popular surgery, there are late complications on patients submitted to "sleeve", such as GERD, a symptom that could be common after the surgery⁸.

The aim of this study was to find the difference on serum ghrelin levels (the hormone related to the control of hunger) after the invagination of gastric body with previous ligation of the vessels of gastric greater curvature and fundus. Was chosen ghrelin because it is a hormone related to the control of hunger and satiety, and it is secreted by gastric

mucosal cells⁹, where the vessels are closed by ultrasonic scalpel and it is made an antireflux wrap (Nissen 360°) to cure GERD. A second aim was to evaluate the regression of GERD on patients submitted to gastric plication and fundoplication, evaluating the weight loss after the surgery.

METHODS

Were selected eight patients with body mass index (BMI) from 29 to 35 kg/m² and presented gastroesophageal reflux symptoms, erosive esophagitis and/or other symptoms of GERD (the changes were observed at high digestive endoscopy). As a routine before the surgery, the patients were submitted to superior abdomine ultrasound and blood exams: hemogram, glicemia, coagulogram, creatinine, iron, lipidogram, hepatic function, total and fractionated proteins, zinc, thireoid function, insulin, glycated hemoglobin, cortisol and PTH. The patients agreed with the rules of the study and signed a free consentiment term. The exams and surgery procedures were made at the service of bariatric surgery at Sugisawa Hospital, Curitiba, PR, Brazil. The patients were submitted to surgical procedures of gastric plication and fundoplication by laparoscopy. The procedures were made from November 2011 to February 2012.

To the surgical procedures, was chosen "long" Nissen for fundoplication⁴ and, to the gastric plication, the technique described by Almino Ramos et al. in 2010. The patients were submitted to general anesthesia, in dorsal decubit, with inferior members opened and in proclive. By laparoscopy, the vessels of the gastric greater curvature were ligated with ultrasonic scalpel Sonosurg Olympus®, from 2 cm above pylorus until the right pillar of the diaphragm. Dissection of abdominal esophagus was done, maintaining an extension of 5 cm, and correction of hiatal hernia. Was also done aproximation of diaphragmatic pillars using "X" suture with poliester 2-0 (Ehthibond®), calibrated with n° 20 nasogastric tube in the esophagus and leaving a place of an opened pinch of dissection (2 cm). Confection of fundoplication in 360° Nissen type, placing the gastric fundus behind the dissected abdominal esophagus and sutured with poliester 2.0 (Ehthibond®) with four single sutures, the first and the second being fixed on abdominal esophagus. Then, it was made the first plan of the longitudinal plication of the gastric body with continuous suture, with poliester 2.0 (Ehthibond®), starting under the fundoplication and finishing next to the pylorus. The gastroplication plan was made with single sutures, calibrated with 32 F Fouchet tube in the interior of the stomach, until it

was observed a tubular aspect, similar to the final aspect of sleeve gastrectomy.

After three months of surgery, the patients were submitted to a new endoscopy. They were prepared with an eight-hour fasting before the exam. They were in a left lateral decubit position, drank 100 drops of dimeticone and a sedation with propofol 1% (1,5–2,5 mg/kg of weight intravenous) and the procedure was made with Olympus® model CV 165. Videoendoscope was introduced through the mouth until the stomach, observing distensibility, mucosal aspect, presence of lesions and their regressions (compared with the lesions observed before the surgery) and the resolution of hiatal hernia. Was complemented observing the endoscopic aspect of the longitudinal plication of gastric body and if the valve of the fundoplication was continent, its extension and simetry. Blood was collected before surgery (during anesthesia induction) and after three months (before the endoscopy). During both blood exams, the patients had an eight-hour fasting. Blood was collected by a venous puncture. Ten milliliters of blood were taken and conditioned in tubes with anticoagulant EDTA. The tubes were submitted to immediate centrifugation 3000 rpm during 15 min at macro centrifuge EV:025 (Evlab®). Plasma was put in microtubes of 1,5 ml and freezer (-20°C) until analyze. Plasmatic levels of ghrelin were measured on the samples collected before and three months after gastroplication. Ghrelin measures were obtained in plasma through an ELISA kit for human ghrelin (total) by Millipore®. The results were obtained at ELISA ELx800 of Biotek. All the samples were analyzed together, but duplicated. The results analyzed showed the difference between ghrelin levels and weight before and after surgery. To evaluate if there was significant difference ($p < 0,05$) between the groups, Wilcoxon test was used with SPSS 20 software.

RESULTS

All of the eight patients presented BMI $\pm 31,27$ kg/m² (from 29 to 35 kg/m²). Two of them were male and six female, varying from 22 to 53 years old. Four presented heartburn and nauseas, while four did not know what symptoms they were feeling.

On preoperative endoscopies, one patient presented biliar reflux, seven erosive esophagitis, two hiatal hernia and two both the last symptoms.

All were successfully submitted to fundoplication and gastric plication by videolaparoscopy. The time of the surgery varied from 180 to 240 min, without mortality. The hospital stay was one or two days. The postoperative

complications were: difficulty to transpose distal esophagus (one case) being submitted to two dilatations by endoscopy with Cook® 18x8 baloon.

All patients presented improvement on DRGE symptoms after surgery, fact that was confirmed by endoscopic evaluation, where all of them had regression of the esophagitis (Tables 1, 2 e 3). There were no patients with recidive of hiatal hernia. These results were similar to the ones related by Cardoso et al.

TABLE 1 - Frequency and percentage of preoperative esophagitis grades through endoscopic findings

ESOPHAGITIS GRADE	FREQUENCY	PERCENTAGE
Without esophagitis	1	12,5%
Grade I or A	3	38%
Grade II or B	2	25,0%
Grade III or C	0	0,0%
Grade IV or D	2	25,0%

TABLE 2 - Frequency and percentage of preoperative hiatal hernia through endoscopic findings

HIATAL HERNIA	FREQUENCY	PERCENTAGE
Present	5	62,5%
Absent	3	37,5%

TABLE 3 - Frequency and percentage of postoperative esophagitis grades through endoscopic findings

ESOPHAGITIS GRADE	FREQUENCY	PERCENTAGE
Without esophagitis	5	62,5%
Grade I or A	1	12,5%
Grade II or B	0	0,0%
Grade III or C	0	0,0%
Grade IV or D	0	0,0%
Other findings (Metaplasia)	2	25%

All patients submitted to surgery presented significant weight loss after three months. The average weight on preoperative period was 85,0 kg, while on postoperative period was 73,6 kg, showing significant statistic difference ($p = 0,012$). The average weight loss was 11,4 kg, that means a loss of 13,4% of initial body weight (Table 4).

TABLE 4 – Difference between weight pre and postoperative per patient (average, standard deviation and significance)

PATIENT	PREOPERATIVE WEIGHT (kg)	POSTOPERATIVE WEIGHT (kg)	LOSS OF WEIGHT (kg)	% OF LOSS OF WEIGH	p
A	87	81	6	6.9	
B	79	69	10	12.7	
C	81	67	14	17.3	
D	110	95	15	13.6	
E	85	69,5	15.5	18.2	
F	85,5	72,5	13	15.2	
G	70,6	62,8	7.8	11	
H	82	72	10	12.2	
Average of groups ± S.D.	85,0125 ± 11,3239	73,6 ± 10,1042	11,4 ± 3,4873	13,4 ± 3,6148	0,012*

* =significant difference

Despite the fact that the appetite of the patients after the surgery decreased and an early satiety, serum ghrelin levels did not change on postoperative period. The average concentration and standard deviation after surgery was 257,0601 pg/ml±72,7289, while after surgery was found 272,5707 pg/ml±59,01297 (p=0,674), without significance (Table 5).

TABLE 5 - Concentrations pre and postoperative of total plasmatic ghrelin per patient and average of groups with standard deviation and statistic significance

PATIENT	[] PREOPERATIVE (pg/ml)	[] POSTOPERATIVE (pg/ml)	p
A	285.393	222.616	
B	317.888	285.393	
C	216.552	307.14	
D	296.33	389.903	
E	228.473	222.616	
F	317.888	257.339	
G	103.16	210.368	
H	290.797	285.191	
Average of groups ± S.D.	257,0601 ± 72,72894	272,5707 ± 59,01297	0,674

DISCUSSION

It's known that ghrelin during fasting stimulates food intake because it leads to hunger, being an important hormone on body weight control¹⁰. But there are other hormones that regulate food intake and satiety as YY peptide (YYP), glucagon like peptide (GLP-1) and leptin^{8,11}. Leptin produced on white adipose tissue acts on hypothalamus, leading

to satiety and regulating energetic balance. GLP-1 acts decreasing gastric emptying, leading to a long satiety¹². PYY, another inhibitor of food intake, is expressed by intestinal mucosa cells during postprandial period¹³.

All of them acts on hypothalamus and are responsible by alimentary behaviour. On the gastrointestinal tract, there are quimiorceptors and mecanoreceptors that control the physiologic activity sent to the brain, leading to the "satiety signs"¹⁴. So, it is possible an alteration on these other hormones after the surgery used on this study. Further researches are necessary in order to evaluate other orexigen and anorexigen hormones, to show the mechanisms that make the surgeries (gastropllication and fundoplication) to decrease the appetite giving early satiety. Is needed to have more information about this new surgical procedure to understand it better, for example, which neurohormones are affected by the modification of gastric morphology and which mechanisms are involved on satiety and control of hunger after the surgery.

CONCLUSION

Gastric plication associated with fundoplication was effective in treating reflux disease with surgical indication and for weight loss in obese patients. Appetite control occurs, but not due to ghrelin, because no significant decrease of its plasmatic levels was observed.

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