The effect of fundectomy on histopathological findings and metabolic hormones in rats

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AIM: *Fundectomy, shown as an alternative to restrictive techniques, causes absorption restriction and metabolic changes. This study aimed to examine the histopathological changes caused by the fundectomy as a technique applied to rats by hormones that affect stomach and obesity metabolism and its effect on weight loss.*
MATERIAL AND METHODS: *2randomly selected Winstar-Hannover rat groups were evaluated by measuring their pre-and postoperative weights and biochemically measuring Gastrin, Ghrelin, and Leptin levels on day 30. After sacrification, the stomachs were taken for histopathological examination.*
RESULTS: *Significant weight loss was observed in the fundectomy group in the 1st month postoperatively. Biochemically, Gastrin means in the fundectomy group were statistically significantly higher than in the control group. The mean Ghrelin and Leptin levels of the Fundectomy Group were statistically significantly lower (p=0.005). Immunohistochemically, Gastrin means ™at the antrum and proximal stomach parts of the Fundectomy Group were significantly higher than in the control group. As Ghrelin, a significant decrease was observed in all 3regions of the Fundectomy Group compared to the control group. Leptin results were significantly lower at the antrum and proximal stomach parts of the Fundectomy Group. Histopathologically, in the Fundectomy Group, cystic glandular hyperplasia was moderate at the proximal stomach, foveolar hyperplasia was mild at the antrum, fibrosis was moderate at the antrum and corpus, and high at the proximal stomach.*
CONCLUSION: *Fundectomy is an effective method in terms of weight loss. This animal experiment, conducted as a pilot study, will be an essential step in elucidating metabolic and histopathological changes.*

KEY WORDS: Bariatric surgery, Fundectomy, Obesity

Introduction

Obesity, determined as one of the important causes of death by the World Health Organization (WHO), increases morbidity and mortality by causing comorbidities such as tp II diabetes and hypertension. The definition of "Morbid Obese" is used for individuals with a body mass index (BMI) of 40 and above [1]. It is necessary to provide adequate and balanced nutrition according to the patient's gender, age, physical activity status, lifestyle, and physiological condition [2]. It is essential to develop a correct and lifelong nutrition strategy by changing the bad eating habits of an obese individual. Bariatric surgery comes to the fore in patients who cannot lose weight despite lifestyle modification, diet, and exercise. Fundectomy, one of the restrictive bariatric

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surgery methods, is an easily applicable method generally used as a complication surgery in the development of fundal pockets due to inadequate sleeve gastrectomy. In this study, we aimed to evaluate the effects of the fundectomy as a bariatric technique, which we applied to rats, on the hormones that are effective on gastric metabolism and obesity and histopathological changes.

Material and Methods

Our study was carried out at the Ministry of Health Bağcilar Training and Research Hospital Experimental Surgery and Skills Development Training Center (BAD-ABEM) with the approval of the Istanbul Bağcilar Health Research and Application Center Experimental Animals Local Ethics Committee (2018/76). 16 adult Wistar Hannover rats with an average weight of approximately 500-550 grams were used. All animals were maintained in a 12-hour dark/light cycle at an average temperature of 22°C.

They were fed fresh drinking water, and 21% were supplemented with rat chow. The subjects were divided into two groups, each containing eight animals. Group 1 was determined as the control group and Group 2 as the fundectomy group. After measuring the subjects' weights under anesthesia, one cc of blood samples was taken from the preoperative jugular vein, and the operation was started. After the animals were sacrificed with high dose ketamine on the 30th postoperative day, blood samples were retaken from the animals by an intracardiac puncture.

Preoperative and postoperative changes in Gastrin, Ghrelin, and Leptin levels were evaluated biochemically. After fundectomy, the remaining part of the stomach was resected into three parts, antrum, corpus, and proximal stomach, for histopathological evaluation.

Surgical Technique

Sevoflurane value was determined as 2.6% in 100% oxygen, based on the previous study in which the minimum alveolar concentration (MAC) values of Winstar albino rats were determined [3]. The operation was started in rats that did not respond to the pedal reflex. After providing asepsis and antisepsis with 10% Povidone Iodine solution, the abdomen was entered with a 4 cm incision made in the midline of the abdomen.

Only the stomach was explored in the first group, and the abdomen was closed. In the fundectomy group, after the intra-abdominal adhesions were carefully separated, the fundus part to the left of the cardia part was determined with the help of a clamp, and the fundus was resected with the help of a scalpel (Fig. 1).

The open line was closed continuously with a 5/0 prolene suture. Abdominal incisions were closed primarily with double-layered 3/0 silk sutures. After the operation, the rats were allowed to regain consciousness by breathing 100% oxygen and were followed up in the intensive care unit for one month. The same surgeon operated on the rats. On the 30th day after the operation, all animals were sacrificed after their weight was measured under ketamine and xylazine anesthesia.

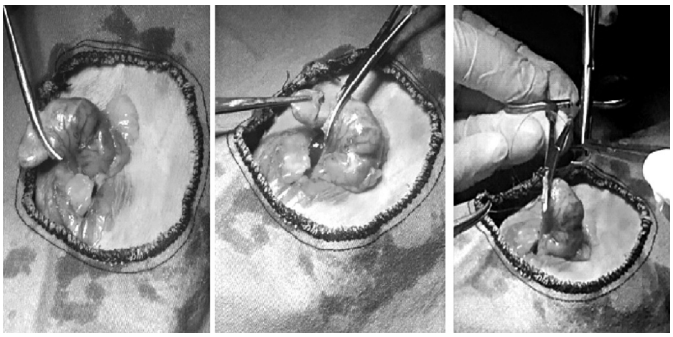
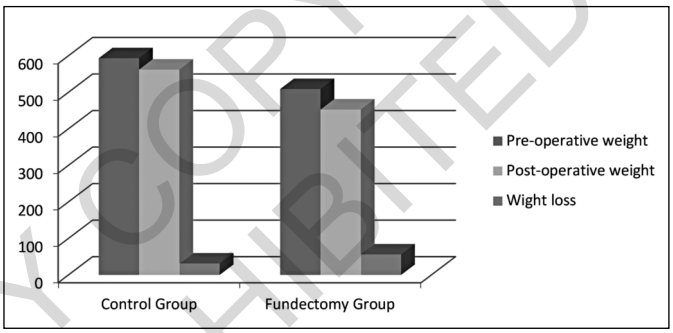


Fig. 1: Fundectomy application.



Graphic 1: Weights of study groups before and after surgery.

Biochemical Analysis

Gastrin, Leptin, and Ghrelin levels were measured before and after the operation. First, eight standard kits obtained 24 ng/ml stock with standard batch solutions. Antibody-coated microplate walls were added as standard 50 µl, 50 µl of Streptavidin HRP was placed on the standards. Serum samples were pipetted onto microplates as 40 µl per microwell. Gastrin, Ghrelin, and Leptin antibodies were added onto 10 µl and 50 µl streptavidin HDR serum samples.

The microplate was then covered and incubated at 37°C for 60 minutes. After x30 washing solution was prepared, Elisa plates were washed five times in the washer at 350 µl. Chromogenic solutions A and B were pipetted in 50 microliters per microwell. Incubation was done in the dark at 37° for 10 minutes. Fifty microliters of the stop solution were added to each microwell. Microplate absorbance was measured at 450 nm in 10 minutes.

Histopathological Analysis

The resected rat specimens were sent for pathological examination in 10% formaldehyde solution, and the tissues were fixed in the solution for 24 hours. The antrum, corpus, and remaining proximal stomach sections of the pieces were sampled and embedded in paraffin blocks after routine tissue follow-up. H&E and Masson Trichrome stains were applied for histopathological analyzes by taking 5 µm thick sections. The preparations were evaluated under a light microscope. Tissue samples taken from rats were made blindly by the same pathologist who did not know which group the samples belonged to in the Pathology Laboratory of Bagcilar Training and Research Hospital. In the histopathological examination, foveolar hyperplasia, cystic enlargement of the glands, and degrees of fibrosis were investigated in the antrum, corpus, and proximal stomach sections. Scoring was done semi-quantitatively by giving relative percentage values.

Immunohistochemical Analysis

Gastrin, Ghrelin, and Leptin antibodies were applied to the tissues taken on lysine-coated slides for immunohistochemical examination. All tissues were studied with positive control. Cells showing immunoreactivity were counted in 3 different areas: antrum, corpus, and proximal stomach. At a magnification of 10, 5 different areas with the most intense staining were counted and divided into 5. In this way, the average value was obtained. Tables of immunohistochemistry analysis were made based on the total cell count showing immunoreactivity in all rats.

Statistical Analysis

In this study, statistical analyzes were performed with NCSS(Number Cruncher System) 2007 Statistical System) 2007 Statistical Software(Utah, USA) package program. In the evaluation of the data and descriptive statistical methods, one-way variant analysis was used to compare groups with normal distribution, Tukey multiple comparison test for subgroup comparisons, independent T-test for comparison of paired groups, and Chi-Square Test for comparison of qualitative data. A p-value of <0.05 was accepted as significant in the evaluation.

Results

According to the study results, no significant change was observed between the pre-and postoperative weights of the control group (p=0.064), while a significant decrease was found in the pre-and postoperative weights of the fundectomy group (p=0.002). The pre-and postoperative weights of the fundectomy group were also found to be significantly lower than the control group (p=0.0001). According to the results of our study, the subjects in the fundectomy group lost 11.4% of their initial mean weight values within one month after the operation (Graph. 1).

Biochemical Analysis

When the fundectomy group's preoperative and postoperative Gastrin levels were evaluated, a significant increase was observed in the fundectomy group (p= 0.0487). A significant change was observed in the plasma Ghrelin values measured in the control and fundectomy groups after surgery (p=0.005). Ghrelin was significantly decreased in the fundectomy group. There was a significant change in plasma Leptin levels between the control and fundectomy groups considering the postoperative periods (p=0.001). Plasma Leptin levels were significantly decreased after fundectomy. When the pre-and postoperative Leptin levels of the fundectomy group were examined, a significant change was observed (p=0.004).

Histopathological Analysis

In the pre-and postoperative studies of the control and fundectomy groups, no significant changes were found in the antrum and corpus sections. Statistically, significant moderate cystic glandular hyperplasia was found in the proximal part of the postoperative fundectomy group, where the resection was performed (p=0.0001).
In the control group, fibrosis did not change significantly in all three stomach parts. In the fundectomy group, it was found to be moderate (p=0.0001) in the antrum and corpus after surgery and statistically significantly higher in the proximal stomach section where resection occurred (p=0.001).
There was no significant change in foveolar hyperplasia in the control and fundectomy groups' corpus and proximal stomach sections. However, in the antrum studies of the fundectomy group, mild foveolar hyperplasia was observed, which was statistically significant.

Immunohistochemical Analysis

Gastrin values ™were statistically significantly higher in the antrum and proximal stomach sections of the fundectomy group compared to the control group, respectively (p=0.001, p=0.017). No statistically significant difference was found in the samples taken from the corpus in either group.
The fundectomy group's mean Ghrelin at the proximal stomach, corpus, and antrum regions was significantly

Table I - *Statistical analysis of Gastrin, Ghrelin, and Leptin hormones in study groups.*

Biochemical Analysis		Control Group	MGB Group	P**
Gastrin(pg/ml)	Pre-operative	382,77±134,26	643,24±140,42	0,141
	Post-operative	374,56±136,30	1098±404,40	0,001
	p*	0,841	0,0478	
Ghrelin(ng/ml)	Pre-operative	2,614±0,810	2,646±0,799	0,791
	Post-operative	2,632±0,810	0,683±0,362	0,001
	p*	0,228	0,004	
Leptin(ng/ml)	Pre-operative	14,669±3,811	14,98±3,97	0,781
	Post-operative	14,977±3,971	0,89±0,86	0,001
	p*	0,228	0,004	

*: Comparison of Pre-operative/Post-operative; **: comparison of Control group/MGB group

Table II - *Histopathological statistical analysis of study groups in terms of FH, CGD, and F*

Histopathological Analysis	Location	Presence	Control group	%	Studygroup	%	p
FH	Antrum	None	8	%100	4	%50	0,021
		Mild	0	%0	4	%50	
	Corpus	None	8	%100	8	%100	
	Proximal	None	8	%100	6	%75	0,131
		Mild	0	%0	2	%25	
CGD	Antrum	None	8	%100	8	%100	
	Corpus	None	8	%100	8	%100	-
	Proximal	None	8	%100	8	%100	0,0001
		Mild	0	%100	4	%50	
		Moderate	0	%0	4	%50	
F	Antrum	None	8	%100	0	%0	0,0001
		Moderate	0	%0	8	%100	
	Corpus	None	8	%100	0	%0	0,0001
		Moderate	0	%0	8	%100	
	Proximal	None	8	%100	0	%0	0,001
		Mild	0	%0	1	%12,5	
		Moderate	0	%0	6	%75	
		Intense	0	%0	1	%12,5	

FH: Foveolar Hyperplasia; CGD: Cystic Glandular Dilatation; F: Fibrosis

lower than the control group (p=0.001). When the fundectomy group was examined within itself, the ghrelin level at the proximal stomach was significantly lower than the corpus and antrum (p=0.001).
Leptin was significantly lower in the fundectomy group's antrum and proximal stomach regions than in the control group. (p=0.001) No significant change was found in studies from the corpus. In the internal evaluation of the fundectomy group, Leptin levels in the antrum region were found to be significantly lower than in the other two regions (p=0.0001).

Discussion

The management of overweight and obesity is initially achieved by combining diet, exercise, and behavioral conditions. If 5% of body weight can be lost in the first six months with this modality, this treatment is considered successful and can be continued [4]. Unfortunately, these treatments generally did not give very successful results in the long term. For this reason, bariatric surgery has started to heal obese patients who cannot benefit from medical treatment in recent years and who are accompanied by comorbidities. The most critical factors in planning bariatric surgery are working with a multidisciplinary team and the best follow-up of patients in the postoperative period.
Bariatric surgery has become increasingly popular due to the increasing incidence of obesity globally and obesity-related comorbidities.
This increasing popularity has brought with it new bariatric surgery techniques. While sleeve gastrectomy, which is currently the two most popular techniques globally, stands out in terms of convenience, R&Y gastric bypass is preferred because of its permanent and best postoperative results. The search for "near-perfect" techniques with excellent postoperative results, easy surgical

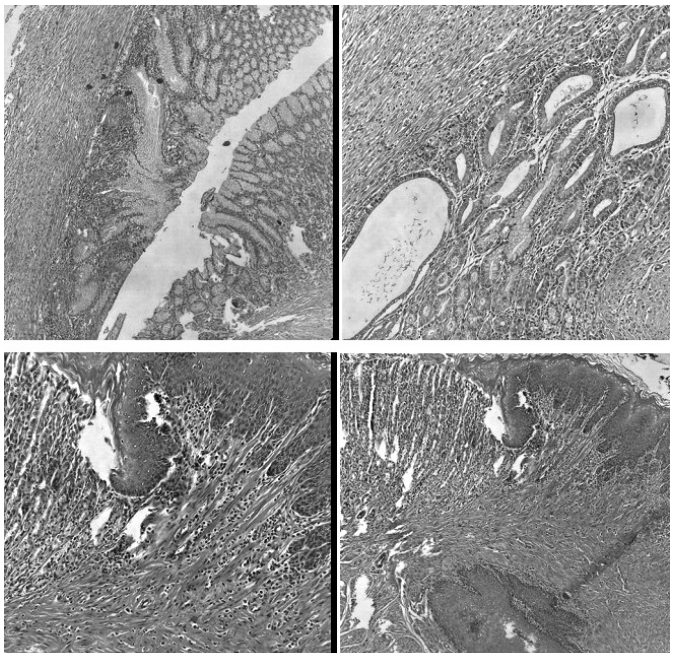


Fig. 2: Histopathological views of Fundectomy group: A) Mild FH at the antrum (H&E, x10), B) Moderate CGD at the proximal. (H&E, x20), C) and D) Intensive Fat the proximal(H&E, x10, and x20).

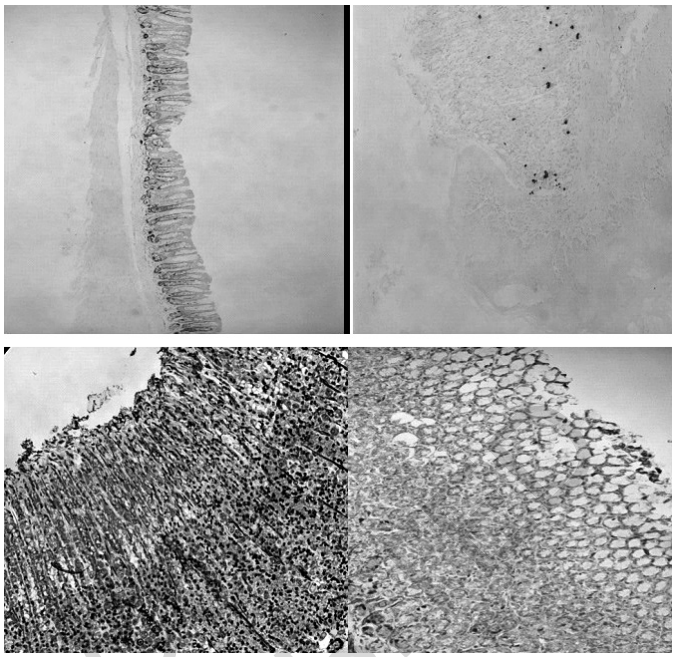


Fig. 3: Immunohistochemical views of Fundectomy group: A) Intense immunohistochemical Gastrin staining at the antrum. (x10). B) Mild immunohistochemical Ghrelin staining at the anastomosis (x10). C) Intense immunohistochemical Leptin staining at the corpus (x10). D) Low immunohistochemical Leptin staining at the antrum (x10).

techniques, and fewer postoperative complications continues.

The hormones thought to have an important place in the pathophysiology of obesity are Gastrin, Ghrelin, and Leptin, respectively. The main task of Gastrin is to provide mucosal growth in the stomach, to provide gastric motility, and to help the secretion of hydrochloric acid to the gastric mucosa. It is secreted from G cells in the antrum and duodenum. Gastrin is secreted primarily by postprandial vagal stimulation and by peptides, amino acids, gastric distension, and high stomach pH [5]. There is a significant relationship between gastric acidity and Gastrin levels. With the increase in gastric pH after eating, the release of Gastrin increases in the stomach, and the same direct proportion occurs when the gastric pH decreases.

Therefore, serum gastrin rates are high in acid suppression treatment applied for various reasons [6]. High Gastrin rates have also been determined due to tension in outlet stenosis causing gastric expansion. Malignancies such as atrophic gastritis, antrectomy, and gastrinoma occurring after parietal cell atrophy also increased gastrin levels [6]. In our study, gastrin levels were significantly higher in the fundectomy group. After resection, plasma gastrin levels increased secondary to loss of parietal cells and decreased acid secretion in the stomach. As a result of the immunohistochemical data, gastrin levels were high in the antrum and proximal stomach area where fundectomy was performed, in parallel with the studies in the literature.

Ghrelin is a 28 amino acid polypeptide found in human and rat stomachs in 1999. Ghrelin has been found to have many effects, such as the release of growth hormone, increasing appetite, regulating glucose metabolism, memory, and antidepressant. Ghrelin has also been proven to increase gastric acid secretion and gastrointestinal motility [5]. In a study, plasma ghrelin levels decreased by 65% ™in humans and 80% in rats after gastrectomy. This shows that the primary source of Ghrelin circulating in the plasma is the stomach [7]. Studies in rats showed that ghrelin levels decreased after oral and intravenous glucose intake [8,9]. The effect of glucose level on the plasma concentration of Ghrelin has also been determined in the same direction in studies on humans. [8,9]. In another study, injection of 30 pmol ghrelin to the intracerebrovascular region of the brain caused an increase in food intake, which was reduced by ghrelin antibody treatment [10]. In our study results, plasma ghrelin levels in the fundectomy group were significantly decreased. The main reason for this is the surgical removal of the fundus part, which accounts for a high percentage of body ghrelin production. As a result of immunohistochemical studies, ghrelin levels were significantly lower in the antrum, corpus, and proximal stomach sections. These results were attributed to the decrease in Ghrelin secreting cells after fundectomy and

the decrease in ghrelin production after weight loss.
The importance of the leptin molecule was first revealed in an animal experiment conducted in the 1950s. It was determined that the Leptin molecule was not secreted in one group of the subjects and that the leptin receptor did not function in the brain in the other group. These two groups of animals are obese and have diabetes paved the way for further studies on Leptin [11]. Leptin, a protein with 167 amino acids, is mainly produced in adipose tissue and participates in circulation, but it is not the only place where it is produced. The leptin gene has also been detected in salivary glands, placental trophoblasts, endocrine glands such as the pituitary and pancreas, and cardiac and skeletal muscle cells. Moreover, Leptin is secreted from the gastric mucosa at very high levels, especially after food intake [12]. In the study of by suture materials after gastric surgery cause compression of the gastric glands in the submucosa after muscularis mucosal injury [16]. In our study, while the presence of cystic glandular dilatation was not observed in the antrum and corpus, it was slightly and moderately significantly higher in the proximal stomach section where we resected.
Fibrosis, which is seen physiologically in the stages of wound healing, can also be seen pathologically as a response to injury. In a study comparing sleeve gastrectomy and gastric plication techniques, Considine et al., it was observed that plasma level of Leptin decreased by 53% after 10% weight loss, and leptin level increased to 70% again after four weeks of continued weight loss [13]. In our study, a significant decrease in plasma leptin levels were measured after fundectomy compared to the control group. In immunohistochemical studies, leptin levels were decreased in the fundectomy group's antrum and proximal gastric mucosa analyses. This decrease has been attributed to both weight loss and a decrease in the area of ™ the leptin-secreting gastric mucosa.
Cystic glandular dilatation due to hyperplasia of glands extending to the submucosa and cystic dilatation is seen in the remaining gastric tissue after resection for any reason [14]. Although cystic glandular dilation is accepted as a benign lesion, the presence of this lesion in studies performed on pre-malignant gastric polyps carries the risk that it may have malignant potential [15]. It is thought that long-term chronic inflammation, ischemia, or secondary changes created postoperative fibrosis rates were significantly increased compared to the control group immunohistochemically. This rate was higher in the sleeve gastrectomy group than in the plication group [17]. In our study, fibrosis degrees were significantly higher in all three areas in the stomach that underwent fundectomy compared to the control group. The degree of fibrosis is more intense, especially in the resection of the proximal antrum, compared to the other two regions.
Foveolar hyperplasia is a lesion where elongated and enlarged fovea are seen in mucosal structures. While it is seen in the antrum and corpus due to alkaline bile reflux and non-steroidal anti-inflammatory drugs, it can also be seen in the normal mucosa of the cardia region [18]. Whether foveolar hyperplasia has malignant potential or not is still controversial today. Onzi Tr et al., in their study, examined the pre-and postoperative weights and histological changes in the stomach of patients who had undergone sleeve gastrectomy. While 58.3% of foveolar hyperplasia was detected preoperatively, this rate decreased to 33.3% after the operation [19]. In our study, while significant foveolar hyperplasia was not observed in the control group, mild, statistically significant foveolar hyperplasia was observed in the resected proximal part of the fundectomy group.
In this study, in which we examined fundectomy operation, which is not a currently accepted bariatric technique, as an alternative to restrictive methods, we think that we reached target weight and metabolic changes with low complication rates and low cost. However, this is the result of an animal experiment and supported by clinical studies; we can see whether fundectomy as a technique will be included in bariatric surgery procedures in the future.

Conclusion

After the fundectomy procedure on experimental animals, we achieved our targeted weight, biochemical and histopathological results in obese rats. In the world of bariatric surgery, which is changing and developing day by day, the search for the standard gold technique continues. This study, which can help with metabolic and histopathological results, is inspiring for future similar studies.

Riassunto

La resezione del fondo gastrico, indicata come alternativa alle tecniche restrittive, provoca restrizione dell'assorbimento e alterazioni metaboliche. Questo studio mirava a esaminare i cambiamenti istopatologici causati da questo intervento eseguito su ratti ad opera di ormoni che influenzano il metabolismo dello stomaco e dell'obesità e il suo effetto sulla perdita di peso. Sono stati utilizzati 2 Gruppi di ratti Winstar-Hannover, selezionati casualmente, valutando il loro peso pre e postoperatorio e misurando biochimicamente i livelli di gastrina, grelina e leptina al giorno 30. Dopo il sacrificio, gli stomaci sono stati sottoposti ad esame istopatologico.
Risultati: È stata osservata nel 1° mese dopo l'intervento una significativa perdita di peso nel gruppo dei resecati del fondo gastrico. Dal punto di vista biochimico, i livelli medi della Gastrina è risultato statisticamente e significativamente più elevato nel gruppo dei gastroresecati rispetto al gruppo di controllo. I livelli medi di grelina e leptina sono risultati statisticamente e signi-

ficativamente più bassi (p=0,005) nel gruppo dei gastro-resecati. Dal punto di vista immuno-istochimico i livelli medi della Gastrina sono risultati significativamente più elevati nelle parti dell'antro e dello stomaco prossimale nel gruppo dei gastro-resecati rispetto al gruppo di controllo.
Per quanto riguarda la Grelina, è stata osservata una diminuzione significativa in tutte e 3 le regioni del gruppo della fundectomia rispetto al gruppo di controllo. I risultati della leptina sono risultati significativamente più bassi nelle parti dell'antro e dello stomaco prossimale del gruppo dei fundectomizzati. Dal punto di vista istologico nel gruppo della fundectomia, l'iperplasia ghiandolare cistica era moderata nello stomaco prossimale, l'iperplasia foveolare era lieve all'antro, la fibrosi era moderata all'antro e al corpo ed elevata nello stomaco prossimale. Conclusione: la fundectomia si è dimostrata un metodo efficace ai fini della riduzione del peso. Questo studio sperimentale sugli animali, condotto come studio pilota, potrà rappresentare un passaggio essenziale per chiarire i cambiamenti metabolici e istopatologici della resezione del fondo gastrico.

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