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Changes in ghrelin, leptin and insulin levels after laparoscopic sleeve gastrectomy

Laparoskopik sleeve gastrektomi sonrası grelin, leptin ve insülin düzeylerindeki değişiklikler

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Abstract

Aim: The objective of this study was to evaluate the effects of laparoscopic sleeve gastrectomy (LSG), performed upon patients with morbid obesity, on weight loss and recovery of comorbid diseases as well as on metabolic and hormonal mechanisms by comparing pre and postoperative hormone levels.

Materials and Methods: 38 patients having undergone LSG between May 2013 and May 2014 were included in the study. In this prospective study, patients' demographic data and associated diseases; weight loss; pre and post-operative insulin levels in addition to pre and post-operative leptin and ghrelin levels in the eighth weeks were compared.

Results: Of 38 patients included in the study there were 32 (84.2%) females and 6 (15.8%) males. Median leptin level was 11.16 ng/mL in the preoperative blood sample, whereas postoperative hormone level in the eighth week was 4.39 ng/mL. When ghrelin levels were examined; preoperative median was 25.72 pg/mL, whereas postoperative hormone level was 14.16 pg/mL in the eighth week. Preoperative median body mass index was determined to be 44.27 and post-operative median was observed to be 36.6 in the eighth week. No mortality was observed.

Conclusion: Today LSG has become a unique surgical technique in the treatment of morbid obesity due to its efficiency in obtaining weight loss and its feasible complication rates. After reviewing the results of our study; we believe this surgical technique does not only provide continuity in weight loss by restrictive changes but at the same time by metabolic ones, too.

Keywords: Morbid obesity, sleeve gastrectomy, hormonal changes.

Öz

Amaç: *Bu çalışmada, morbid obezite tanılı hastalarda tedavi amacıyla uygulanan LSG'nin kilo kaybı ve yandaş hastalıkların tedavisinin yanı sıra metabolik ve hormonal mekanizmalar üzerindeki etkinliğinin, operasyon öncesi ve operasyon sonrası dönemdeki hormon düzeyleri karşılaştırılarak irdelenmesi amaçlandı.*

Gereç ve Yöntemler: *Mayıs 2013-Mayıs 2014 tarihleri arasında, LSG uygulanan 38 hasta çalışmaya dahil edildi. Prospektif olan bu çalışmada hastaların demografik verileri, yandaş hastalıkları, takipte kilo kaybı, morbidite ve mortalite oranları, operasyon öncesi ve sonrası insülin düzeyleri ile operasyon öncesi ve operasyon sonrası sekizinci haftadaki leptin ve grelin hormonlarının düzeyleri irdelenerek karşılaştırıldı.*

Bulgular: *Çalışmaya dahil edilen 38 hastadan 32'si (%84,2) kadın, altısı (%15,8) ise erkekti. Operasyon öncesi alınan kandaki leptin düzeylerinin ortalaması 11,16 ng/mL iken, operasyon sonrası sekizinci haftadaki hormon seviyesi 4,39 ng/mL olarak belirlendi. Grelin düzeylerine bakıldığında ise; operasyon öncesi ortalama 25,72 pg/mL iken, operasyon sonrası sekizinci haftadaki hormon seviyesi 14,16 pg/mL olarak belirlendi. Operasyon öncesi ortalama vücut kitle indeksi (VKİ) 44,3, operasyon sonrası sekizinci haftada ise 36,6 olarak belirlendi. Hiçbir hastada mortalite gözlenmedi.*

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Sonuç: *LSG, günümüzde mükemmel kilo kaybı sağlaması ve kabul edilebilir oranlarda düşük komplikasyon riskleri nedeniyle morbid obezite tedavisinde tek başına uygulanan bir cerrahi teknik haline gelmiştir. Çalışmamızın sonuçlarına baktığımız zaman; bu ameliyat tekniğinin sadece restriktif değil, aynı zamanda metabolik değişikliklere neden olarak da kilo kaybındaki devamlılığı sağladığı kanaatindeyiz.*

Anahtar Sözcükler: *Morbid obezite, sleeve gastrektomi, hormonal değişiklikler.*

Introduction

Obesity is a public health issue that lowers the quality of life as well as affecting both adults and children and is associated with many comorbid diseases. The prevalence of obesity is increasing across the world. Obesity induces comorbidities such as diabetes, hypertension, hyperlipidemia, sleep apnea and degenerative joint diseases (1). Bariatric surgery is the most effective treatment method that provides intensive weight loss and lowers comorbidities associated with over-weight (2). Though laparoscopic sleeve gastrectomy (LSG) is relatively new in the treatment of morbid obesity, it is a standard technique used in patients with different rates of obesity. Actually, LSG is not a new method. LSG is a method used as a restrictive component of the biliopancreatic diversion with duodenal switch (BPD-DS), a procedure of a more complicated bariatric surgery. After Regan et al. (3) first applied BPD-DS method laparoscopically, LSG was started to be performed as the first stage of a gradual surgical approach in patients with morbid obesity. In this procedure a large proportion of the stomach is resected throughout the greater curvature between the gastroesophageal junction and pylorus, turning the remaining stomach into a narrow tube (4). Originally performed as the first stage of a 2-stage bariatric procedure for high-risk patients with morbid obesity, today LSG itself is a bariatric procedure thanks to its success in obtaining adequate weight loss. LSG is a technique with clinical advantages such as; obtaining adequate weight loss, not causing obstruction (due to internal herniation) thanks to not requiring intestinal rotation, not requiring a foreign body like a gastric band and thus eliminating the risk of gliding and erosion in association with foreign bodies (5). LSG is not only a method providing weight loss restrictively, but also by its metabolic effects, especially inducing changes in hormone levels related to nutrition such as leptin and ghrelin. Ghrelin levels show changes throughout the day. Especially the increase in levels before food intake and during the night and the postprandial decrease underlay the suggestion that this hormone plays a signal role triggering food-seeking (6). In some studies, fasting plasma ghrelin levels were detected to increase proportionate to body mass index lowered after weight losses obtained by diets (7,8). Morbid obesity is characterized by an increased insulin resistance with hyperglycemia and hyperinsulinemia and T2 diabetes developing over time as a result of insufficient compensatory mechanisms. Ghrelin decreases insulin secretion, and ghrelin secretion is controlled by glucagon, insulin and leptin (9). Leptin joins circulation in concentrations correlated with fat mass and is a hormone reducing food intake. Leptin levels drop during fasting. Leptin reduces food intake by inhibiting orexigenic neuropeptides in hypothalamus arcuate nucleus and stimulating anorexigenic neuropeptides (10,11). The objective of this study was to evaluate the effects of LSG in collaboration with literature on weight loss rates of patients with morbid obesity, changes in leptin, ghrelin and insulin levels, comorbid diseases and quality of life.

Materials and Methods

During the period from May 2013 to September 2014, a total of 38 patients underwent surgical treatment (LSG) for morbid obesity in Başkent University Hospital Clinic of General Surgery and of these total of patients 32 (84.2%) women and 6 (15.8%) men with a mean age of 33 years) were enrolled in the study. In this prospective study, patients' demographic data and associated diseases; weight loss, morbidity and mortality rates during follow-up; pre and post-operational insulin levels and pre and postoperative leptin and ghrelin hormone levels in the eight weeks were compared. Blood samples were taken for hormone levels in addition to blood samples routinely taken from patients in preparation stage, and insulin, leptin and ghrelin levels were compared in the blood samples taken during routine controls in the eighth week of post-operation. Written informed consent was obtained from patients who participated in this study. Ethics committee approval was received for this study from the Ethics Committee of Başkent University Hospital.

Operation technique

In all patients a total of 5 trocars (one 15 mm, two 12 mm and two 10 mm in diameter) were used. Greater curvature of the stomach was liberated with the help of laparoscopic vessel sealing device from 2-4 cm proximal of pylorus to the angle of HIS. 32 F thick dilatation tube was placed in the lesser curvature of stomach. The stomach was resected using two 4.5 mm staples in antrum and 3.8 mm in more proximal parts (Staples; Medtronic, Minnesota, USA). Posterior dissection was performed meticulously in the proximal stomach during resection to avoid a wide fundic pouch. Using the stapler after observing 1 cm of stomach tissue at the side of remaining stomach before the last staple would reduce

the risk of leakage. Hemorrhages from the staple line were kept under control using laparoscopic clips. The stomach was tested for leakage by filling the operation area with physiological saline and then was inflated with air for air-water test.

Statistical analysis

The Shapiro-Wilk test was performed for the numerical data whether the normal distribution. In repeated measures, for 2 measurements paired T-test analysis was performed. In more than two measurements, variance analysis was performed for repeated measurements. A value of $p<0.05$ was considered significant statistically.

Results

LSG as a bariatric surgical procedure was performed upon all the patients included in the study. Concurrent cholecystectomy was performed upon 4 patients due to symptomatic cholelithiasis using LSG trocars. Of 38 patients included in the study there were 32 (84.2%) females and 6 (15.8%) males. Median age was 33 (19-54) (Table-1). Median hospital stay was 8.5 days (3-110). Of 38 patients, 2 (5.26%) had diabetes type 2, 3 (7.9%) had hypertension and 16 (42.1%) were complained of arthralgia (in knee and hips). Patients' average weight loss was 10.1 kg in the second week, 14.6 kg in the fourth week and 20.6 kg in the eighth week. Preoperative median body mass index (BMI) was 44.27, and postoperative median BMI was 40.63 in the second week, 38.87 in the fourth week and 36.6 in the eighth week. Compared to preoperative values, postoperative second, fourth week and second month BMI values were lower and statistically significant ($p<0.01$) (Figure-1).

Table-1. General Characteristics of Patients Before Operation.

	n=38
Age	33 (19-54)
Gender	
Female	32 (84.2%)
Male	6 (15.8%)
Weight (kg)	120.6 (91-147)
Length (cm)	164.7 (150-185)
BMI (kg/m^2)	44.27

Table-2. Preoperative and Postoperative Leptin, Ghrelin and Insulin Levels.

	Preoperative	**Postoperative (8th week)**
Leptin	11.16 ng/mL	4.39 ng/mL
Ghrelin	25.72 pg/mL	14.16 pg/mL
Insulin	40.31 µU/L	11.3 µU/L

When the postoperative weight loss rates were examined; average weight loss was 10.13 kg in the second week, 14.65 kg in the fourth week and 20.63 kg in the second month. Weight losses in second and fourth week and second month were statistically significant compared to preoperative period ($p<0.01$) (Figure-1). Of 38 patients 26 (68.4%) had insulin resistance (n=20) (76.9%), five had noninsulin-dependent diabetes type 2 (19.2%) and one patient (3.9%) was taking insulin due to diabetes type 2. In the post-LSG second month check, one patient was observed to show partial recovery in insulin levels, but the highness of insulin levels continued and the insulin levels of other 25 patient decreased to normal values. The patient who took insulin during preoperative period with the diagnosis of diabetes type 2 ceased taking insulin. The three patients diagnosed with hypertension, no longer needed medicine and complaints of 16 patients with arthralgia were reduced two months after the procedure. Leptin levels were 11.16 ng/mL (median) in preoperative blood samples, whereas eighth week postoperative hormone levels were 4.39 ng/mL (Figure-2). When ghrelin levels were examined; preoperative levels were 25.72 pg/mL (median), whereas eighth week postoperative hormone levels were 14.16 pg/mL (Figure-2). Compared to preoperative levels postoperative leptin and ghrelin levels decreased and were statistically significant ($p<0.01$). Insulin levels measured in the preoperative blood sample were 40.31 µU/L (median), 1st month postoperative insulin levels were 18.53 µU/L (median) and insulin levels in the second month were 11.3 µU/L (Figure-3)[OB1]. Compared to preoperative period, 1st and second month postoperative insulin levels were lower and statistically significant ($p<0.01$) (Table-2). No mortality observed in patients. Two (5.26%) patients were treated with gastroesophageal stent due to proximal stomach staple line leakage, one (%2.6) patient underwent splenectomy + hemostasis due to post-operative hemorrhage.

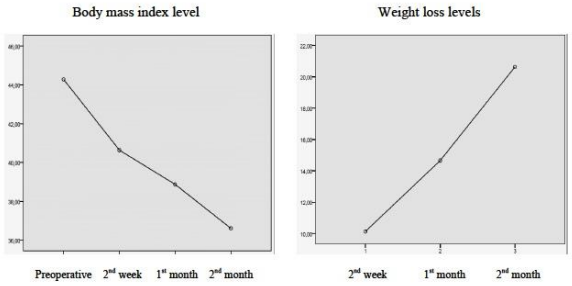

Figure-1. Preoperative and postoperative BMI levels and postoperative weight loss levels.

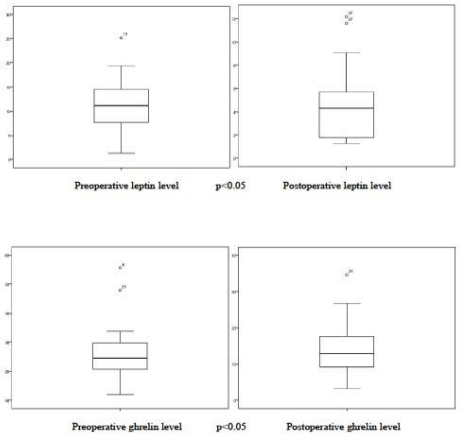

Figure-2. Preoperative and postoperative leptin and ghrelin levels.

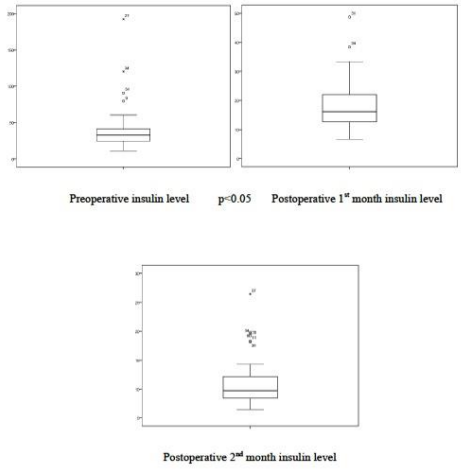

Figure-3. Preoperative and postoperative insulin levels.[OB2]

Discussion

LSG is a basic bariatric surgery procedure whose popularity is increasing, and it provides satisfactory and permanent weight loss. This increasingly popular procedure not only induces weight loss by restricting food intake, but also triggers metabolic changes. Even though there are certain criteria in determining the operation technique, the patient's preference is one of the most common indications (12).

Average weight loss of the follow-up patients was 20.6 kg in these series. When we examined the changes in BMI; postoperative value which was 44.27 regressed to 40.63 in second week, 38.87 in the fourth week and 36.6 in the eighth week. Compared to preoperative period, second month postoperative BMI value was lower and statistically significant (p=0.011). In a study conducted by Hady et al. (13), in 100 patients underwent LSG and preoperative BMI was 52.15 (median), postoperative values were found respectively 42.72 in the third month and 37.98 in the sixth month and the decrease in the BMI was reported to be statistically significant. One (3.9%) patient who had type 2 diabetes during follow-up and who was using insulin no longer needed insulin take, three (7.9%) patients taking antihypertensive exhibited a full recovery and the complaints of 16 patients with arthralgia regressed. Two (5.26%) patients were treated with gastroesophageal stent due to proximal stomach staple line leakage and their post-treatment weight loss rates were similar to those of other patients. One (2.6%) patient underwent splenectomy + hemostasis due to postoperative hemorrhage and was discharged without further complications. Hospitalization duration of one patient that developed leakage was 110 days and the others was 60 days. Mean duration of hospitalization of other 36 (94.74%) patients were 4.27 days. No mortality was observed. The questionnaire made in the second month check showed that postoperative patient satisfaction was full, and quality of life had progressed.

Ghrelin hormone discovered by Japanese scientists in 1999 is a 28-amino acid hormone that has a role in regulating energy and restoring food intake (14). Blood levels increase during fasting and decrease with food intake. Ghrelin is a profound orexigenic (appetizer) hormone and central and peripheral stimulation of ghrelin causes an increase in food intake. Ghrelin is originally secreted by endocrine cells (X/A-like cells) in oxyntic glands in stomach's fundus (15). As well as the stomach, the hormone synthesized in small quantities in small intestine, hypothalamus, pituitary gland, kidney, and pancreas. Ghrelin has a wide distribution in body tissues. So, this hormone plays an important role in regulating the biological activity (16). In a study conducted by Shijiya et al. (17), blood levels of this hormone were stated to be high in patients with obesity. Postoperative ghrelin blood levels decrease after the removal of almost all the stomach fundus with LSG. All the patients included in the study showed diminishing appetite during follow-up. In another study conducted by Vigneshwaran et al. (18) LSG method is applied to 20 patients, with type 2 diabetes mellitus, having BMI

ranging from 30-35 kg/m2. After LSG, ghrelin levels decrease considerably, at sixth month after surgery, if compared measurements before the surgery. As it is stated in other studies, we think that the decrease in plasma ghrelin levels induce a loss of appetite (19,20). In our study, pre-operative ghrelin levels were 25.72 pg/mL (median), whereas eighth week postoperative results were determined to decrease up to 14.16 pg/mL and this decrease was found to be statistically significant ($p<0.05$). In a study conducted by Langer et al. (19), first and sixth month postoperative serum ghrelin levels of 10 patients having undergone LSG were reported to decrease significantly, which was similar to our study.

Leptin is a hormone found in concentrations correlated with fatty tissue in body and its levels are related to BMI. Leptin is an Ob gene product and an adipocytokine (21). Decrease observed in leptin levels in the circulation is related to increase of hunger (22). Leptin was proposed to act as a signal indicating abundant adipose stores to the hypothalamus to limit energy intake and increase energy expenditure (23). There is some evidence that leptin have a direct activity on adipose tissue metabolism through inhibition of lipogenesis and stimulation of lipolysis (23). Leptin levels in circulation increase with presence of obesity and decrease with weight loss (25). Plasma levels of leptin increase during and after eating (26). In a study conducted by Kalinowski et al. (9), leptin levels decreased significantly 1 month after surgery and continued to decrease at 6 and 12 months after LSG. In our study leptin levels were 11.16 ng/mL (median) in preoperative blood samples, whereas eighth week postoperative hormone level was determined to be 4.39 ng/mL in association with weight loss ($p<0.05$).

Comorbidities of obesity resolved in association with the weight loss obtained by LSG. Amongst these comorbidities recovery in diabetes type 2 and insulin resistance together with recovery of glucose metabolism constituted the most striking example of beneficial effects of LSG. In a study conducted by Behrens et al. (27) 74% of the patients with diabetes type 2 displayed post-LSG improvement in less than six months. Again, in a study conducted by Silecchia et al. (28) , 69.2% and 76.9% of the patients with noninsulin-dependent diabetes type 2 showed post-LSG improvement respectively in 12th and 18th months and 15.4% showed recovery. In our study, 26 (68.4%) had insulin resistance (n=20) (76.9%), five had noninsulin-dependent diabetes type 2 (n=5) (19.2%) and one (3.9%) patient had insulin-dependent diabetes type 2. In the second month post-LSG follow-up 1 (3.9%) patient showed partial recovery in insulin levels, though the highness continued and the insulin levels of the other 25 patients decreased to normal levels. One patient that took insulin before operation no longer needed insulin medication.

Conclusion

LSG is a technique that has feasible complication rates and effective in obtaining satisfactory weight loss together with the recovery of comorbid diseases related to obesity. Though this technique is known for its restrictive effects due to partial removal of stomach, we believe it is efficient in obtaining weight loss by inducing changes and recovery in leptin, ghrelin and insulin levels. Despite the relatively low number of patients included in the study, the relation between weight loss and hormonal changes were determined to be statistically significant. Therefore, we are of the opinion that LSG is efficient in the treatment of morbid obesity as a basic bariatric procedure if performed in an experienced clinic with standardized operation techniques.

Conflict of interest: The authors declare they have no conflict of interest. The authors received no funding for this study.

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