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Leptin/Melanocortin pathway hormones in obese patients after laparoscopic sleeve gastrectomy

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Abstract. – OBJECTIVE: The melanocortin system is an important neural system underlying the control of body weight and food intake. This system has recently received great attention as a potential target for obesity treatment. Therefore, the objective of this study was to find out the leptin-melanocortin pathway before and after Laparoscopic Sleeve Gastrectomy (LSG) in obese patients.

PATIENTS AND METHODS: The study was carried out with a total of 144 individuals in 3 groups [control, obese group before LSG and obese group after LSG (who underwent LSG one year ago)]. The amount of leptin (LEP), leptin receptor (LEPR), tropomyosin receptor kinase receptor B (TrkB), brain-derived neurotrophic factor (BDNF), pro-opiomelanocortin (POMC) and melanocortin-4 receptors (MC4R) molecules were measured by using Enzyme-Linked Immunosorbent Assays.

RESULTS: A statistically significant difference was found between the groups in terms of body mass index (BMI) values ($p = 0.001$). There was also statistically significant difference present between obese before LSG group and obese after LSG group regarding the levels of LEP, TrkB, BDNF and proteins ($p < 0.05$). A decline was determined in the LEP and BDNF levels one year follow-up after LSG.

CONCLUSIONS: The evidence suggests that the leptin melanocortin pathway strictly regulates food intake and BMI before and after LSG surgery. This pathway should be kept under control for effectively reducing food intake and body weight in the treatment of obesity.

Key Words:
Obesity, Leptin-melanocortin pathway, Leptin, LEPR, TrkB, BDNF, POMC, MC4R, Laparoscopic sleeve gastrectomy.

Introduction

Obesity is one of the serious global health problems that is increasing in prevalence across all sectors of society and is also associated with higher all-cause mortality[1,2]. This disease is a very complicated and versatile disease as one of the strongest risk factors for development of insulin resistance. It is estimated that more than 300 million people will have insulin resistance as a complication of obesity until 2025[3]. Insulin resistance due to obesity leads to a broad spectrum of metabolic anomalies, such as dyslipidemia, non-alcoholic fatty liver disease, hypertension, coronary heart disease and stroke[4].

Bariatric surgery is an effective treatment method for obesity that contributes to the recovery from much comorbidity associated with obesity and elevation in life quality. Bariatric surgery is a component of some treatment algorithms used in the medical management of patients with Type

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2 diabetes mellitus (T2DM) and serious obesity. Laparoscopic Sleeve Gastrectomy (LSG) effectively induces long-term weight loss in patients with morbid obesity and it relieves metabolic disorders and diabetes mellitus[5-8] is among bariatric surgeries. Most of these procedures are performed using laparoscopic technique that provides rapid recovery and reduction of postoperative pain and scar-associated complications[5-8].

Over the past two decades, research in human and mouse genetics has highlighted the central role of the brain leptin-melanocortin pathway in controlling genetic degradation and mammalian food intake that results in extreme obesity. U.S. Food and Drug Administration (FDA) approved setmelanotide (a melanocortin 4 receptor agonist) for use in individuals with severe obesity due to either pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency[9,10].

Leptin (LEP) is a hormone related to weight gain and obesity due to its capacity to control energy balance and metabolism[11]. LEP binds to leptin receptors and activates those[12]. LEP reduces desire to eat in the hypothalamus and thermogenesis[13]. Leptin-melanocortin pathway is a well-documented pathway of food intake for energy balance[14]. LEP plays an important role in energy homeostasis by presenting a defensive function against increased body weight via partially coordinating POMC neurons and suppressing agouti-related peptide (AgRP) neurons[15-17]. After binding to POMC neurons, leptin activates a series of intracellular signaling network including Jak-Stat3 and phosphoinositide 3-kinase (PI3K) pathways that eventually leads to elevation in neuronal activity and production of melanocortin[16,18]. POMC is processed to produce melanocortins and α-melanocyte stimulating hormone (α-MSH) that shows catabolic activity mediated by melanocortin-4 receptors (MC4R) to create feeling of satiety for suppression of appetite[19]. MC4R is a G-protein coupled receptor that is widely expressed in hypothalamus and central nervous system and plays a role in energy homeostasis as well as glucose and lipid metabolism[20]. At the same time, MC4R is an important factor in regulation of body foot distribution[21]. In addition, MC4R is a receptor of brain-derived neurotrophic factor (BDNF). These cause reduction in food intake and energy expenditure[22]. BDNF is accepted as an important effector of leptin/melanocortin pathway on energy balance[23].

Also tropomyosin receptor kinase receptor B (TrkB) is a BDNF receptor and plays an important role in the initiation of intracellular signaling cascade; it accelerates activation of intracellular signaling pathways and circulates intracellular BDNF concentration. Both BDNF and LEP interact with melanocortin signal to reduce food intake[24]. It has been detected that hypothalamic reduction of BDNF modulates energy homeostasis that affects food intake and promotes an anorectic signal[25]. It has been determined that insufficiency of TrkB[23,26] or its false mutations are associated with hyperphagia, weight gain and obesity in both human and mice models[27].

To the best of our knowledge, no prior studies have examined the relationship between LEP, LEPR, TrkB, BDNF, POMC and MC4R molecules together in obese patients who underwent LSG. Therefore, the present study was to evaluate the changes in LEP, LEPR, TrkB, BDNF, POMC and MC4R protein levels in the leptin-melanocortin pathway before and after in obese patients who underwent LSG.

Patients and Methods

Study Design and Patient Selection

This study was approved by the Local Research and Ethics Committee (Sivas Cumhuriyet Ethics Committee, Approval Date: 06.02.2018; Numbered: 2018-02/02). The study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent has been obtained from all participants.

Control Group

After formation of the study patient group, control group was constituted by 54 healthy volunteer individuals with similar age and gender range who applied to the Department of Gastroenterology of Sivas Cumhuriyet University Medical Faculty for routine yearly checkup and were diagnosed with no insulin resistance or obesity. The inclusion criterium for the control individuals was to have BMI<25 kg/m^2. The exclusion criteria for the control group were absence of any bariatric surgery in the medical history, current compliance to calorie-restricted diet or use of therapeutic drug for weight loss and absence of any malignancy in the medical history. The control participants were selected to have similar age with the patient group and similar questions were asked to fill in the questionnaire form.

Obese Group Before LSG

The study included 60 obese patients (OP) diagnosed with Body Mass Index (BMI)>40 kg/m^2

and BMI>35 kg/m^2 and chronic diseases such hypertension, sleep apnea and venous insufficiency who have applied to Bariatric and Metabolic Surgery Polyclinic of Department of General Surgery, Sivas Cumhuriyet University Medical Faculty. The study included the patients who failed to lose weight by diet prior to LSG surgery. In addition, obese patients with ongoing medication for a psychiatric disorder, chronic alcohol use and diagnosis of T2DM were excluded from the study. The anthropometric data of the patients including height, weight, BMI and excess body weight (EBW) were measured. BMI value was calculated by the formula weight (kg)/ height x height (m^2).

Obese Group After LSG (Who Underwent LSG One Year Ago)

Obese group after LSG was constituted by 30 patients that applied for control examination 1 year after LSG surgery out of the 60 patients with obesity that applied to Bariatric and Metabolic Surgery Polyclinic of Department of General Surgery. The other 30 patients who underwent LSG surgery could not be reached for control examination due to their residence in different cities.

All the patients were examined 1 year after LSG. Percent excessive weight loss (%EWL) and percentage excess body weight loss (%EBMIL) percentages were calculated according to the following formulas; %EWL= (preoperative weight-follow up weight)/ (Preoperative weight-ideal weight) x100. Robinson (1983) formulas were used for ideal weight calculations. %EBMIL= (preoperative BMI-follow up BMI)/ (preoperative BMI-25) x100.

Collection of Blood Samples

Each individual's blood samples were taken 5 mL into vacuum tubes containing citrate an empty stomach in the morning. This blood centrifuged at 3000 rpm (1400×g) for 10 min at room temperature to obtain plasma. The obtained plasma samples were put into sterile, dry Eppendorf tubes and stored at − 80°C until the evaluation day.

Laparoscopic Sleeve Gastrectomy Procedure

In this study, LSG was performed in all the patients by a consultant surgeon. All operations were performed following the same procedural guidelines. Temporarily, the gastrocolic omentum was divided above great curvature and starting approximately 4 cm proximal to the pylorus. The dissection was performed up to the left crus of the hiatus and all extensions were released to mobilize the fundus completely. The gastric sleeve was performed using a 60-mm linear stapling device. The staplers were applied alongside a 39-Fr calibrating bougie positioned in the stomach against the lesser curve. The resected specimen was eventually retrieved using a 15-mm surgical port.

Leptin/Melanocortin Pathway Proteins Assay

The levels of LEP (Catalog no: 201-12-1560 Sunred Biological Technology Co., Ltd., Shanghai, CHINA), LEPR (Catalog no: YLA0298HU Biont Co., Ltd., Shanghai, CHINA), TrkB (Catalog no: 201-12-7579 Sunred Biological Technology Co., Ltd., Shanghai, CHINA), BDNF (Catalog no: 201-12-1303 Sunred Biological Technology Co., Ltd., Shanghai, CHINA), POMC (Catalog no: 201-12-1692 Sunred Biological Technology Co., Ltd., Shanghai, CHINA) and MC4R (Catalog no: 201-12-4225 Sunred Biological Technology Co., Ltd., Shanghai, CHINA) in the plasma samples were measured using ELISA kits according to the protocol as instructed by the manufacturer company. The detectable maximum and minimum value ranges of LEP, LEPR, TrkB, BDNF, POMC and MC4R ELISA kits were 0.2-60 ng/mL, 2-600 ng/mL, 10-3000 pg/mL, 0.1-10 ng/mL, 0.1-15 ng/mL and 8-2000 ng/mL, respectively. Plates were washed using automated washer Bio-Tek ELX50 (BioTek Instruments, USA) and absorbance readings were carried out by using Microplate Reader device (BioTek, Epoch, USA).

Statistical Analysis

In our study, the data were analyzed using the SPSS Software (Version 22.0) program. Arithmetic mean, standard deviation, median and Min-Max values of descriptive statistics are given. Kolmogorov-Smirnov and Shapiro-Wilk tests were used for the assumption of normality. Peer-to-peer Independent Samples Test was used for the variables providing the assumption of normality. Mann Whitney-U and Wilcoxon tests were used for the variables that did not show normal distribution. A $p<0.05$ value was considered as statistically significant. Data were expressed as mean standard deviation (SD).

Results

Patients were asked to come to hospital one year after LSG, but only 30 patients came. There-

Table I. Demographic characteristics of the study groups (n=144).

Variable	Control	Obese before LSG	Obese after LSG
Sample size (n)	54	60	30
Age (year)	41.24 ± 9.85	40.72 ± 9.27	39.47 ± 8.94
BMI (kg/m²)	24.44 ± 2.48	45.09 ± 2.97[a]	25.09 ± 2.27[b]

BMI: body mass index, LSG: Laparoscopic sleeve gastrectomy.
a: Control group versus obese before LSG group ($p = 0.001$).
b: Obese before LSG group versus obese after LSG group ($p = 0.001$).

fore only 30 patients were evaluated one year follow-up after LSG in this study. The demographic characteristics of the participants were presented in Table I. There was significant difference between the BMI values of the participants (control and obese groups) (p=0.001). There was also significant difference between the BMI values of obese participants before LSG and after LSG group (p=0.001), (Table I).

When the LEP, TrkB, BDNF, and MC4R of the control and the obese groups were compared, there was a significant change in the LEP (p=0.001), TrkB (p=0.007), BDNF (p=0.001), and MC4R (p=0.014) (Table II).

When the LEP, TrkB and BDNF level before LSG and after LSG were compared, there was a significant change in the LEP (p=0.000), TrkB (p=0.000), and BDNF (p=0.000) levels (Figure 1 and Table II). There was also significant difference between the BMI (EBMIL% and EWL %) values of obese participants before LSG and one year follow-up after LSG (p=0.001, X^2=60.00) (Table III).

Discussion

LSG was commonly performed to reduce stomach volume, leading to feeling full earlier or a reduced ability to absorb nutrients from food. However, to date, there are no clear studies showing the alteration of leptin-melanocortin pathway[28] and BMI before and after in obese patients who underwent LSG. When the value of BMI of participations was compared before (BMI= 45.09 ± 2.97), and one year follow-up after LSG (BMI=25.09 ± 2.27) it was recorded that there was a significant decrease of BMI of participations, which were similar to those of control's BMI. These results were consistent with previous studies showing an association between low body fat levels and decreased BMI[29,30]. Body weight and BMI are easily measured and are simple and effective tools for screening the risk of obesity, providing a better insight into the relationship between BMI and anthropometric uses in general public health strategies after LSG[31].

In this current study it was also found that LSG caused significant decreases in the LEP and BDNF levels while it caused increases of MC4R and POMC levels, but not significant at year follow-up after LSG. It was interpreted that, after LSG, obese patients reach the same blood levels as normal healthy individuals within 1 year, and the changes may partially mediate weight loss and related metabolic improvements[29]. Because significant reductions in body weight, fasting glucose, LEP and ghrelin plasma levels and contrarily a significant increase in adiponectin levels have been also reported[30].

Also, Mazahreh et al[32] have identified LEP and LEPR levels prior to and 1 year after LSG

Table II. Comparison of LEP, LEPR, TrkB, BDNF, POMC and MC4R levels among the study groups.

Group	LEP	LEPR	TrkB (pg/mL)	BDNF (ng/mL)	POMC (ng/mL)	MC4R (ng/mL)
Controls(n=54)	15.09 ± 2.41	177.64 ± 31.37	311.25 ± 34.23	1.87 ± 0.64	4.12 ± 0.70	610.50 ± 73.44
Obese individuals before LSG (n=60)	**25.34**[a] ± 4.07	187.94 ± 26.30	**531.25**[a] ± 122.17	**2.82**[a] ± 0.51	4.13 ± 0.46	**621.00**[b] **± 82.94**
Obese individuals After LSG (n=30)	**13.54**[c] ± 2.38	180.29 ± 39.57	**564.37**[c] ± 50.79	**2.15**[c] ± 0.28	4.92 ± 0.89	647.50 ± 142.45

BDNF: Brain derived neurotrophic factor, LEP: Leptin, LEPR: Leptin receptor, LSG: Laparoscopic sleeve gastrectomy, MC4R: Melanocortin-4 receptor, POMC: Pro-opiomelanocortin, TrkB: Tropomyosin receptor kinase B.
a = Control group versus Obese before LSG group ($p < 0.01$).
b = Control group versus Obese before LSG group ($p < 0.05$).
c = Obese before LSG group versus Obese after LSG group ($p < 0.01$).

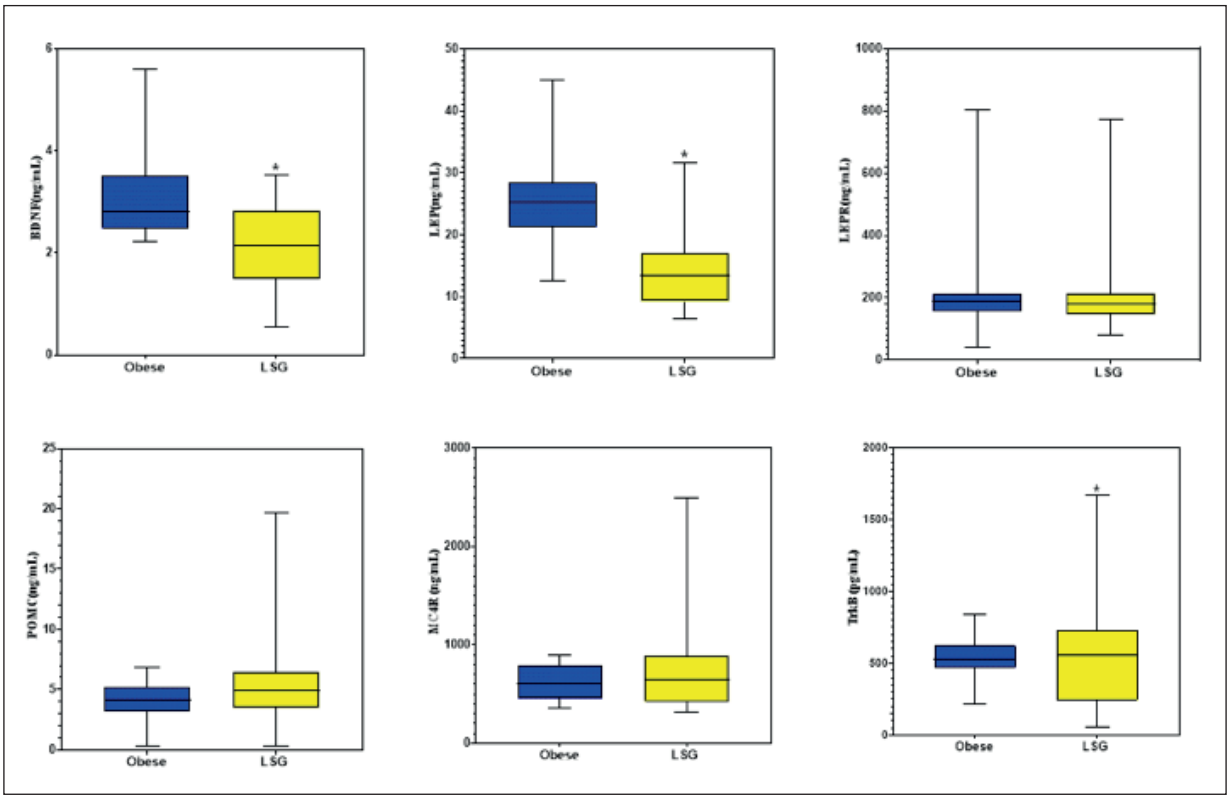

Figure 1. LEP, LEPR, TrkB, BDNF, POMC and MC4R protein levels of participants. LEP (p=0.000), BDNF (p=0.000) and TrkB (p=0.000) levels were found statistically significant (*$p < 0.001$).

in 38 obesity patients. They have found a significantly higher LEP/BMI ratio in the obese patients compared with control individuals whereas serum LEPR was encountered to be significantly lower. They have determined a significant reduction in LEP resistance in the obese patients 1 year after LSG[32]. Hence, LEP levels that chronically elevate in obesity might cause a decline in response capability of pancreatic β-cell receptors and consequently elevation of insulin secretion. As a consequence, emerging hyperinsulinemia may exacerbate obesity and might increase LEP levels furthermore and that may lead to a diabetic positive feedback cycle[33,34].

In the current study, the mean blood BDNF levels were significantly decreased when compared with before and after LSG. Increased blood BDNF levels before LSG might represent an adaptable mechanism that functions to balance positive energy imbalance by stimulating energy expenditure and reducing food intake, similarly, reduction of BDNF levels after surgical weight loss may promote food intake to balance negative energy[35-37].

MC4R and TrkB receptors levels were lower in obese patients before LSG while MC4R and TrkB receptors were increased after LSG. This condition could be explained by low levels of MC4R

Table III. Comparison of anthropometric changes in obese patients after LSG.

	n	Mean ± SD	Min-Max	Median	
BMI (kg/m²)	30	20.18 ± 2.79	15.87 - 27.92	19.7250	X^2=60.00
EBMIL (%)	30	100.17 ± 11.42	79.27 - 124.80	99.0875	***p*=0.001**
EWL (%)	30	88.57 ± 10.40	72.28 - 108.30	87.2952	***p*=0.001**

BMI: body mass index, EBMIL (%): The Percentage of Excess BMI Loss, EWL (%): The Percentage of Excess Weight Loss, SD: Standard deviation.

and TrkB receptors despite high BDNF levels and consequent inability to suppress appetite and energy expenditure in the obese patients. Similarly, low TrkB levels were monitored in a study that was carried out on stimulation of obesity with a high-fat diet in adult male wild mice and application of psychosocial stress[38,39]. Also some other studies demonstrated that blood BDNF levels were higher in the obese individuals than controls and that no significant difference was found between two groups[40-42].

In this current study, POMC levels were higher before LSG when compared with after LSG. Thus, reported lower POMC protein levels after LSG could be due to leptin resistance in the obese patients or a mutation might be present in the genes encoding proteins involved in the leptin-melanocortin pathway such as POMC gene. POMC neurons plays a crucial role in the central regulation of food intake and energy homeostasis at multiple levels[43-45], and also nucleus-deficient mice[46] causes hyperphagia and besity.

In this study mean percent of EBMIL and mean percent EWL values were 100.17±11.42 and 88.57±10.40 in the obese after LSG, respectively. Obese patients had reductions of 59.61% and 72.99% of preoperative body weight and BMI value at the end of postoperative 6th month[47]. Therefore, these results indicated that implementation of LSG provided sufficient weight loss in the obese patients.

This current study had also some limitations. First, the study was carried out by a sampling size of 60 patients and that number may potentially affect the accuracy of analysis results. Second, 30 patients did not come for follow-up examinations 1 year after LSG.

Conclusions

This novel study investigated the changes in LEP, LEPR, TrkB, BDNF, POMC and MC4R protein levels before and after LSG. Here we first time reported that LEP, TrkB and BDNF were significantly high in obese patients before LSG when compared with control values. Decreased LEP and BDNF after LSG might have some potential use in the diagnosis of the obesity disease and also follow-up the fate of LSG surgery outcomes. The leptin/melanocortin pathway should be strictly kept under control for effectively reducing food intake and body weight in the treatment of obesity.

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Ethical Approval Statement

This study was approved by the Local Research and Ethics Committee (Sivas Cumhuriyet University Ethics Committee; Date: 06.02.2018; Issue: 2018-02/02).

Conflicts of Interest

The Authors declare that they have no conflict of interests.

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