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Ghrelin and Leptin Changes Post-Sleeve Gastrectomy

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Abstract

Background: Ghrelin and leptin may regulate metabolism and appetite. Ghrelin, a newly discovered orexigenic gastric hormone, is produced when the stomach is empty. This may explain why morbidly obese people fail to diet, hence the recommendation for bariatric surgery. Leptin, a well-known adipokine, inhibits food intake and circulates at fat-mass-related levels.

Aim of the study:
To evaluate changes in the ghrelin and leptin level post-laparoscopic sleeve gastrectomy. And their relation to changes in appetite and weight loss.

Methods: This prospective study examines adult patients' clinical and lab data for pre- and post-sleeve gastrectomy at Al-Hussain Medical City and Al-Kafeel Hospital in Karbala. The study included 48 obese individuals (36 females and 12 males) with a mean age of 35.5 ± 8.9 years and a BMI of 42.4 ± 5.6 kg/m2. Clinical data comprised pre-surgery body weight, height, hunger, and ghrelin and leptin levels. Patients were seen 2–5 months following surgery for follow-up.

Results: Significant decreases in plasma ghrelin ($p<0.0001$) and leptin ($p<0.0001$) were detected. Patients reported a considerable appetite reduction post-surgery ($p <0.0001$). Serum ghrelin ($p = 0.0004$) and leptin ($p = 0.003$) decreased significantly compared to hunger fluctuations following surgery. The average patient weight loss was 20.2 kg, and excess weight loss was 36.4 ± 10.8%. All patients achieved an 8 kg/m2 weight loss and a 46 ±16.6% excess weight loss while controlling comorbidities such as diabetes, hypertension, and sleep apnea.

Conclusion: Significant reduction in ghrelin and leptin levels post-surgery. Significant correlation between decrease in ghrelin and leptin concentrations and decrease in appetite post sleeve gastrectomy.

Introduction

Over the past two decades, obesity has become a global health issue. The WHO's International Association for the Study of Obesity/International Obesity Task Force reports that 1 billion adults are overweight and 475 million are obese. Obesity treatment typically involves lifestyle changes, including proper food and exercise. Pharmaceutical therapy promotes dietary changes and avoids the decline in basal metabolism. Since the late 1990s, bariatric or metabolic surgery has been the most effective obesity treatment [1-3]. Bariatric surgery succeeds in over 80% of patients, unlike conservative care. It's the only treatment that helps morbidly obese patients lose weight permanently [5]. Laparoscopic sleeve gastrectomy (LSG) is the most common bariatric treatment worldwide. LSG involves resecting the stomach's greater curvature and fundus, while partial gastrectomy is performed vertically, parallel to the lesser curvature [6,7].

In the 1990s, LSG was called the "Magenstrasse and Mill procedure," after the physiologic "Magenstrasse" (German for "street of the stomach"), which transports food from the oesophagus to the antral "Mill" to be ground and propelled into the duodenum. We now know that LSG induces anorexia by removing most stomach fundus ghrelin-producing cells, which promotes weight loss [8]. Diet and lifestyle changes can manage obesity, but bariatric surgery is helpful for morbid obesity and its complications. Time has increased our understanding of bariatric surgery's mechanism. Procedures were typically restrictive, lowering oral intake or malabsorptive, reducing nutrient absorption time. This classification scheme did not account for gut peptides like ghrelin as a critical mechanism in clinically significant weight loss after bariatric surgery. Sleeve gastrectomy should lower plasma ghrelin levels by excising the gastric fundus, the primary source of ghrelin-producing cells [9,10].

Gastric voiding alterations and lowered obesity hormones like ghrelin boost post-operative weight loss. Lack of food causes the stomach to produce ghrelin, a 28-amino-acid orexigenic gastric peptide hormone identified in 1999. Lean persons have higher ghrelin levels than morbidly obese folks. The failure of dieting in morbidly obese people may be due to plasma ghrelin levels rising, which sends an orexigenic signal [11]. Ghrelin levels rise before and during the night and fall after food intake, suggesting that it stimulates appetite, increases gastric motility and secretion, elevates growth hormone secretion, and reduces fat utilization as a hunger signal. Ghrelin is produced by gastric fundus cells, which are mostly destroyed after sleeve gastrectomy [12].

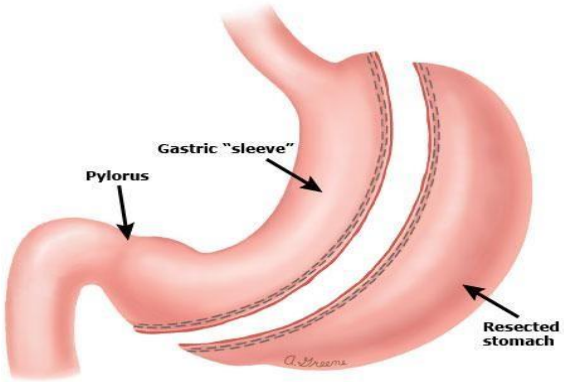

Figure 1: In a sleeve gastrectomy, the majority of the greater curvature of the stomach is excised, and a tubular stomach is formed. The tubular stomach has a small capacity, is resistant to stretching due to the absence of the fundus, and has few ghrelin [a gut hormone involved in regulating food intake) --producing cells.

The OB gene produces leptin, which adipocytes express. LEPRs, extensively distributed, are responsible for leptin's impacts on energy homeostasis and neuroendocrine, reproductive, and immunological function. [13] Leptin is present in fat cells and the placenta. Leptin, a well-known adipokine, inhibits food intake and circulates at fat mass-related concentrations [14]. Starvation lowers circulating leptin, which is diurnal. It reduces food intake by inhibiting orexigenic and motivating anorexigenic neuropeptides in the hypothalamus arcuate nucleus via its receptor across the blood-brain barrier. BMI and body fat correlate with leptin synthesis and circulating concentrations [15, 16]. The brain (and other organs) receives leptin concentrations to indicate adipose tissue and energy reserves under average food intake. [18] Overeating raises blood leptin levels by 40% in 12 hours before fat stores change. In contrast, fasting lowers serum leptin concentrations by 60 to 70% in 48 hours and 80% in three days in normal-weight and obese subjects, indicating that leptin measures long-term energy stores and acute energy intake [19,20]. The discovery of leptin fifteen years ago brought considerable enthusiasm that obesity could be treated. Hence, this prototype adipocyte-secreted protein/cytokine was named after the Greek word "leptos," meaning thin. It invented the idea that adipose tissue is an active endocrine organ rather than an energy store. Leptin failed to treat obesity in subsequent clinical trials[21].

Research on leptin's role in human physiology has led to a renewed understanding of its regulation of energy homeostasis, neuroendocrine function, and metabolism, mostly in states of energy deficiency. This review discusses leptin's biology and physiology, its role in numerous illnesses' pathogenesis, and its emerging therapeutic uses. [22] All investigations show that dietary-induced weight loss increases fasting plasma ghrelin concentration proportionally to BMI decrease. [23] The effects of bariatric surgeries on ghrelin concentration are unclear, and published data are inconsistent. The adiposity product leptin is commonly lowered after weight loss. [24] This study tracks ghrelin and leptin levels after sleeve gastrectomy.

Definitions:

Obesity was characterized as a BMI ≥ 30 kg/m2. The definition of morbid obesity is a BMI above 40 kg/m2. [25] Hypertension was 130/90 mmHg or greater or antihypertensive treatment.

Diabetes mellitus is diagnosed when fasting plasma glucose levels exceed 126 mg/dL, HBA1C is ≥6.5%, or random plasma glucose is ≥200 mg/dL with symptoms. [26]. Ghrelin, a 28-amino-acid peptide hormone produced by enteroendocrine cells of the gastrointestinal tract, especially the stomach, is sometimes called a "hunger hormone" because it increases food intake, weight gain, and growth hormone secretion. Fasting and starvation/anorexia increase it. Ghrelin levels drop after eating or with hyperglycemia. Ghrelin appears to be crucial to food intake and energy homeostasis neurohormonal structure [27,28]. The central brain system and peripheral organs get dietary signals from leptin, an adipocyte hormone. Leptin is generated in the placenta and gastrointestinal system, but its role is unknown. Leptin levels fluctuate and follow the circadian rhythm. Leptin regulates body weight by varying body mass index and body fat percentage. Leptin plasma concentrations are also altered by sex, metabolic hormones, and energy needs [29].

Aim of study:

To assess changes in the ghrelin and leptin level post-laparoscopic sleeve gastrectomy and their association with appetite and weight loss changes.

Materials and Methods:

This prospective study examines clinical and lab data from adult patients before and after sleeve gastrectomy at Al-Hussain Medical City and Al-Kafeel Hospital in Karbala. Clinical and biochemical data are collected before and 2–5 months after surgery. March 2020 marked the commencement of patient data gathering.

Before collecting data, formal approvals were obtained, including:

-The Iraqi Board approved this study of Health Specializations.

-Hospital approval for data collection.

-Formal patient consent was obtained.

Complete histories and physical exams were taken.

Data included age, gender, weight, height, BMI, hunger, blood pressure, random blood glucose and HBA1c, and sleep apnea. Before and after surgery, ghrelin and leptin levels Laparoscopic sleeve gastrectomy were performed on 48 patients, 36 women and 12 males aged 16–51. Al-Hussain Medical City and AlKafeel Hospital in Karbala, Iraq, treated them surgically. International Federation for the Surgery of Obesity and Metabolic Disorders standards were used to choose obesity surgery patients. Patients had a BMI ≥ 40 kg/m2, ≥ 35 kg/m2 with co-morbidities, or < 35 kg/m2 with a weight reduction history from rigorous therapy and weight rebound. [30] Blood was sampled for ghrelin and leptin testing before surgery after telling the patient of the study's goal and signing consent.

Blood samples were taken during anaesthesia induction following an overnight fast of roughly 8 hours to avoid ghrelin concentration fluctuations. The blood sample was venipuncture and allowed to clot for 30–60 minutes at room temperature before centrifugation to separate serum. Split plasma was frozen and stored in the lab for analysis.

Patients and Methods.

The operation was done head-up with the legs separated and strapped on the operating table. All pressure points were cushioned. The surgeon positioned himself between the patient's legs, with the cameraman on the right and the first assistant on the left.

All operations were laparoscopic; therefore, open surgery was unnecessary. Four 12, 10, 5, and 5 mm trocars were used. Dissection of the stomach's more significant curvature and separation of the greater omentum with a harmonic (vessel sealing device) began from the pylorus to the fundus to the left crus of the diaphragm, cutting all short gastric vessels. After mobilizing the greater curvature, the anesthesiologist inserted a bougie catheter size 40 Fr. trans-orally, advanced under direct pylorus visualization, and put it against the lesser curvature. The gastric transection is then conducted using linear staplers from 4 cm proximal to the pylorus to the gastroesophageal junction, where 1 cm of the gastric wall is left from the fundal fat pad's lateral border.

We strengthened the staple line with a second layer of suturing and injected blue dye into the bogie to check for leaks. With no severe surgical problems, these patients were released home with food recommendations in the following days after overnight hospitalization and closed supervision. A second blood sample was taken 2-5 months post-op to evaluate ghrelin and leptin levels during the patient's follow-up visit.

After collecting all the samples, commercial enzyme immunoassay kits in a fully automated ELISA analyzer (Elisys Uno-human) analyzed and documented ghrelin and leptin in one lab.

Statistical analyses:

Using the chi-square test, data analysis was performed using SPSS (statistical package for social sciences) version 26 for the Windows operating system (SPSS, Chicago, IL). P values <0.05 were considered statistically significant. [31]

Result.

The distribution of gender within the study sample is depicted in Figure 2. The ratio of females to males was 3:1. The average age was 35.5 ± 8.9 years, and the body mass index (BMI) was 42.4 ± 5.6 kg/m2. (Refer to Tables 1 and 2). The subsequent data were documented throughout the postoperative follow-up period, which occurred once, spanning from 2 to 5 months, as reported by the patient. The study saw a significant mean reduction in body weight of 20.2 kg, as well as a reduction in BMI of 8 kg/m2, with all p-values being less than 0.001. The results indicate that the percentage of excess BMI loss was 46 ± 16.6%, whereas the percentage of excess weight loss (EWL) was 36.4 ± 10.8% (Table 2).

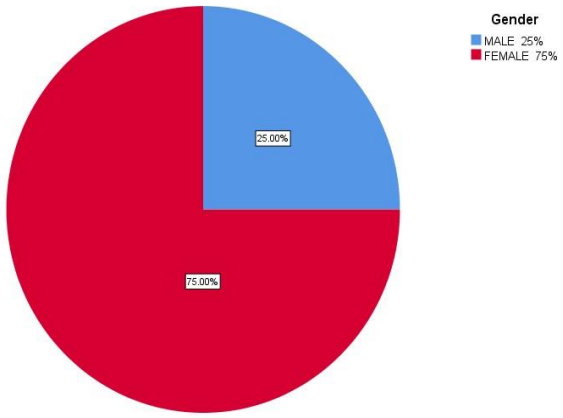

Figure 2: Gender Distribution

Number	(N=48)	
Age (years)	Mean ±SD	35.5 ± 8.9
	Range	16-51
Gender f:m=3:1	Male	12 (25%)
	Female	36 (75%)
Patients of Co-morbidities		16 (33.3%)
History of hypertension		4 (8.3%)
History of DM		10 (20.8%)
Sleep apnea		2 (4.2%)

Table 1: Demographic data of the study population.

The surgical procedure resulted in a decrease of ghrelin (ng/ml) ($p < 0.0001$) and leptin (ng/ml) ($p < 0.00001$) concentrations in blood serum (Table 2).

Table 2. parameter changes after surgery (n = 48; 36 females and 12 males).

Variable	Pre-operative Mean ± SD	Post-operative Mean ± SD	p value
Weight [kg]	**113.4 ± 21.9**	**92.9 ± 18.6**	**<0.001**
BMI [kg/m2]	**42.4 ± 5.6**	**34.7 ± 5.1**	**<0.001**
mean body weight reduction	**–**	**20.2 ± 6.55**	
Mean BMI reduction	**–**	**8 ± 2.5**	
Excess weight loss (EWL) %	**–**	**36.4 ± 10.8%**	
Excess BMI loss (EBL) %	**–**	**46 ±16.6%**	
Ghrelin (ng/ml)	**1.65 ± 1.54**	**0.68 ± 0.88***	**< 0.0001**
Leptin (ng/ml)	**183.3 ± 146.6**	**84.2 ± 48.6****	**< 0.00001**

The study revealed a statistically significant reduction in appetite following the surgical procedure. Forty-four patients, accounting for 91.6% of the sample, reported a notable decrease in appetite after the surgical procedure (p <0.0001). After the surgical procedure, it was observed that four individuals, accounting for 11.4% of the total sample, did not experience any alterations in their appetite. Following the surgical procedure, a notable reduction in blood ghrelin levels to modifications in the patient's hunger was observed, with statistical significance (p <0.0004). Additionally, a statistically significant decrease in serum leptin levels relative to changes in the patient's appetite was also observed (p <0.003) (refer to Table 3).

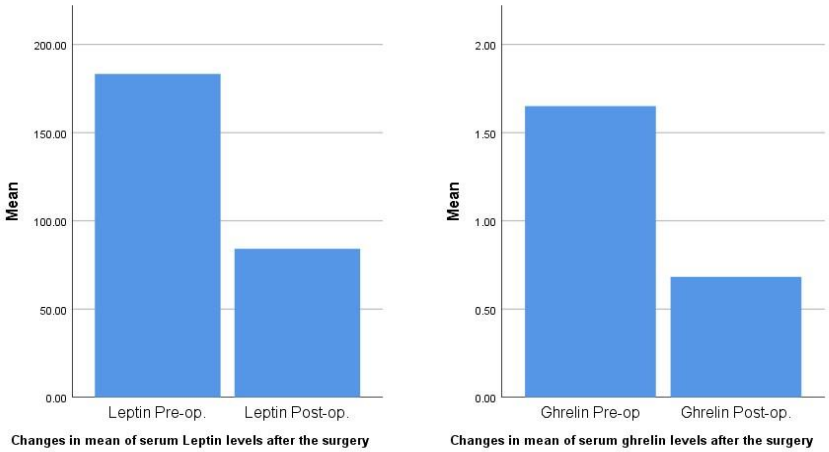

Figure 3. changes in the mean level of ghrelin and leptin (ng/ml) after surgery.

Table 3. Changes in serum levels of ghrelin and leptin (ng/ml) relative to changes in patient's appetite after the surgery.

	Pre-operative mean ± SD	Post-operative mean ± SD
Ghrelin p = 0.0004		
Patients with decrease of appetite (n = 44)	**1.5 ± 1.5**	**0.69 ± 0.92**
Patients without change of appetite (n = 4)	**3 ± 1.07**	**1.60 ± 0.15**
Leptin p=0.003		
Patients with decrease of appetite (n = 44)	**175.3 ± 143.8**	**85.75 ± 49**
Patients without change of appetite (n = 4)	**271.35 ± 171.3**	**67 ± 45.8**

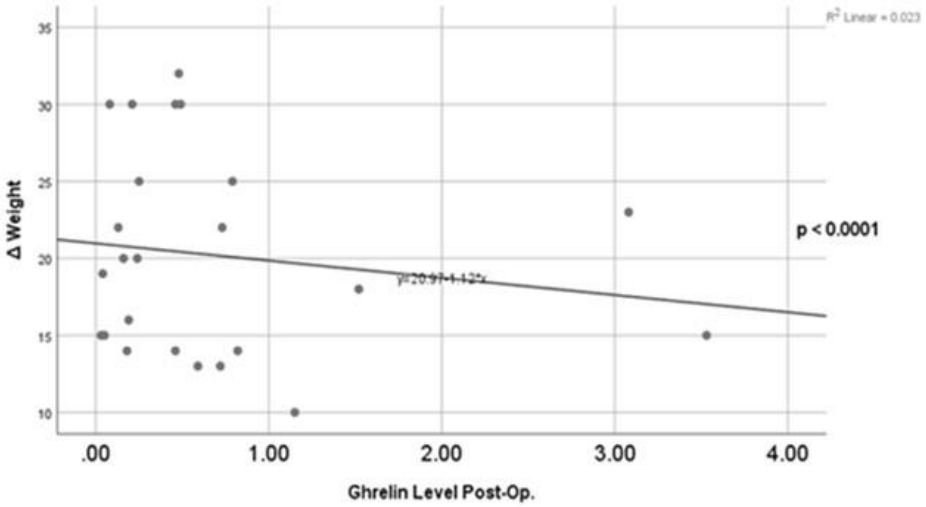

Figure 4: Chart depicting the relationship between the degree of weight loss (kg) and the level of ghrelin (ng/ml) post-operatively.

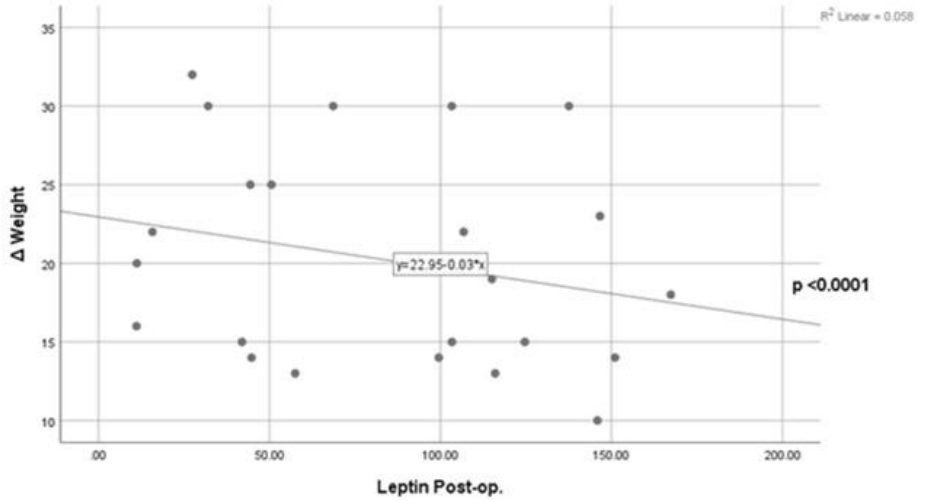

Figure 5: Chart depicting the relationship between the degree of weight loss (kg) and the level of leptin (ng/ml) post-operatively.

Discussion.

This study adds to the knowledge of how sleeve gastrectomy affects hormone levels (ghrelin and leptin) and hunger and weight reduction in this region. This study sheds light on the clinical and biochemical consequences and results of weight loss surgery in our community.

This study's average age was 35.5 ± 8.9 years, and BMI was 42.4 ± 5.6 kg/m2. The 3:1 female/male ratio supports the assumption that cosmetic bariatric surgery is more popular among women. Despite gender equality in obesity statistics, Sherif Aly et al. in the US showed that 80% of bariatric surgery patients were women in 2020. Women seek weight loss surgery for appearance and psychological reasons, while males do it for medical reasons (hypertension or diabetes). [32] Another study by Jeanne Kochkodan et al. found 20% of male patients. The procedure successfully controlled all patients' DM, HTN, and sleep apnea [33] (see Table 2).

This is consistent with other studies on weight loss surgery with hypertension and diabetes. David Sjöström et al. found in 2012 that purposeful weight loss in obese people reduces the two-year risk of diabetes, hypertension, and several lipid disorders. Results suggest treating severe obesity is possible. A 2014 study by Cristian Ricci et al. found a significant decrease in cardiovascular risk following surgery [34]. After surgery, a BMI decrease of 5 reduced hypertension by 27% and type-2 diabetes by 33%. [35] Sheila M. Wilhelm et al. (2014) concluded that bariatric surgery improves and resolves hypertension in a meta-analysis [36].

In 2017, Pratyusha Priyadarshini et al. in India reported that a considerable number of bariatric surgery patients have obstructive sleep apnea (OSA), with OSA improvement in both objective and subjective measures. The average CPAP requirement dropped from 11.3 cm of H2O to 6 cm, while some patients went from 15 to 3. [37].

The study found a mean weight loss of 20.2 ± 6.55 kg after 2-5 months after sleeve gastrectomy. After the operation, the EWL was 36.4 ± 10.8% (see table 2). A bariatric surgery is successful if EWL is 40% or more of preoperative body weight. Based on the 6-month follow-up time [38, 39], reaching a 36.4 ± 10.8% EWL percentage is considered adequate, considering our 2- to 5-month follow-up term. A study by Hady RH et al. (2012) found a considerable weight decrease of 22.34±±3.85% one-month post-laparoscopic sleeve gastrectomy, supporting our findings. According to all studies, weight loss and BMI reductions were more significant within the first six months after surgery [40]. According to research by Marek Bužga et al., patients lost an average of 31.7 kg 12 months following surgery. EWL was 55.2 ± 20.6%. [41] Rafał Paluszkiewicz et al. observed similar results in 2012. In 2008, Karamanakos et al. found a similar EWL 6 months following LSG (55.5% ± 7.6% vs. 50.2% ± 6.5%, P = 0.04). The second six months saw lower reduction rates. A more extended follow-up period is needed to confirm the rapid reduction in appetite and food intake in the first six months after sleeve gastrectomy. This may be due to decreased gastric size, causing early satiety.

In the early months after surgery, gastrointestinal discomfort is more common, which helps lose weight. Due to weight loss and mobility, patients report more physical activity. The observed participants' appetites fell dramatically within 2–5 months of surgery. Forty-four patients (91.6%) reported a decrease in appetite post-surgery ($p < 0.0001$). Four patients (11.4%) had no appetite changes following surgery. Restrictive bariatric surgeries reduce stomach volume, causing faster meal satiety, reduced food intake, and weight loss. [30] According to a 2014 study by Marek Bužga

et al., patients reported decreased appetite ($p < 0.001$) even 12 months following surgery [41]. Karamanakos et al. (2008) found similar results. [11] Studies demonstrate lower appetites Even two years after sleeve gastrectomy. [43,44] Neurohumoral alterations such as lower ghrelin levels affect weight reduction after sleeve gastrectomy.

This study found a significant decrease in ghrelin concentration ($p < 0.0001$) in blood serum (Table 2, Figure 3). Additionally, weight loss is closely related to ghrelin reduction (Figure 4).

Sleeve gastrectomy removes the gastric fundus cells, which produce ghrelin, causing a permanent decrease in ghrelin levels and preventing a compensatory increase in hunger; this matches earlier post-bariatric surgery ghrelin investigations [23, 45]. Langer et al. found that the fundus resection and permanent drop in ghrelin decreased hunger; this may explain why the sleeve treatment caused more significant weight loss than other bariatric surgeries. [12] In 2008, Karamanakos et al. found that LSG suppressed after meals and lowered fasting ghrelin (P 0.0001). [11] 2014 Bužga et al. discovered a substantial decrease in ghrelin and leptin levels ($p = 0.0.043$; $p = 0.006$) after sleeve gastrectomy. [41] Studies indicate that diet-induced weight loss may lead to weight return due to increased plasma ghrelin levels, unlike stringent bariatric operations. [46] Ghrelin levels decreased significantly ($p = 0.0004$) compared to appetite changes following the operation (table 3). Similar findings were made by Tymitz et al. (2011). Table 2 shows a significant post-operative decrease in leptin concentrations ($p < 0.00001$), which was precisely linked to weight loss (Figure 5). Leptin levels closely match body fat. They are higher in obese persons and lower in skinny people [48]. A significant connection ($p = 0.003$) was found between lower leptin concentrations and appetite post-op (table 3). Reducing hunger increases fat loss and leptin lowering. Major P et al. found that leptin levels dropped significantly after laparoscopic sleeve gastrectomy in 2015. P=.0005 indicated statistical significance. The authors believe weight loss rather than hormonal changes cause this impact. Buchwald observed decreased leptin levels following bariatric surgery [49, 50]. In her investigation of the delayed effects of laparoscopic gastric bypass and LSG, Terra found a significant decrease in leptin levels [51]

Conclusion:

- Significant reduction in ghrelin and leptin levels after laparoscopic sleeve gastrectomy.
- Significant correlation between the decrease in ghrelin and leptin concentrations and the decrease in appetite after sleeve gastrectomy.

Recommendations:

- A Longer follow-up period is required to study long-term changes in the level of ghrelin and leptin in laparoscopic sleeve gastrectomy and to study the effects of other bariatric procedures on ghrelin and other hormones.
- Obtaining data from other centres to achieve larger multicenter studies.

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