

## Original Article

# Role of Hunger Hormone “Ghrelin” in Long-Term Weight Loss Following Laparoscopic Sleeve Gastrectomy

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ABSTRACT

**Introduction:** Laparoscopic sleeve gastrectomy (LSG) has become a popular weight loss technique in morbidly obese patients. The aim of our study was to evaluate the changes in plasma ghrelin levels in relation to weight loss following LSG and to study the efficacy of LSG in terms of long-term glycemic control and resolution of diabetes. **Methodology:** The study was conducted on 70 morbidly obese patients (body mass index [BMI] >40 kg/m<sup>2</sup>) or severely obese patients (BMI >35 kg/m<sup>2</sup>) with comorbidities who underwent LSG in Dayanand Medical College and Hospital, Ludhiana, India. Ghrelin levels were measured preoperatively and postoperatively at 1 week, 3 months, and 6 months along with measurements of various weight loss parameters and glycosylated hemoglobin. **Results:** A significant decrease in plasma ghrelin levels was observed in relation to the mean weight and percentage excess weight loss at 3 months postoperatively. However, at 6 months, fall in ghrelin reached a plateau phase while weight loss was still sustained and significant. There was a significant fall in glycosylated hemoglobin levels with patients achieving good control/resolution of diabetes Type II. **Conclusion:** LSG is an effective weight loss surgery and brings about excellent weight loss in morbidly obese individuals in addition to achievement of good glycemic control in diabetic individuals. Serum levels of ghrelin fall significantly after sleeve gastrectomy. However, long term implications of ghrelin induced weight loss cannot be elucidated.

**KEYWORDS:** Ghrelin, laparoscopic sleeve gastrectomy, morbid obesity surgery

## INTRODUCTION

Laparoscopic sleeve gastrectomy (LSG) has become a favored surgical option in most of the countries owing to its cost, safety, and effectiveness in weight reduction.

Three mechanisms have been proposed for weight loss after LSG mainly decreased capacity (restriction), decreased receptive relaxation (no fundus), and hormonal (decreased ghrelin, increased GLP, and PPY-Incretin effect).<sup>[1-3]</sup> Of late, the hormonal effect of LSG came into light when despite the procedure, the weight loss was not adequate, occurrence of weight regain after LSG in a few participants and the very question that why did bariatric surgery lead to suppression of hunger and diet-induced weight loss did not.<sup>[4]</sup>

Ghrelin is a 28-amino acid peptide produced from the fundus and body of the stomach. It was discovered in 1999 by Kojima *et al*,<sup>[5]</sup> named after its role as a growth hormone-releasing peptide (GHRhlin). It is the only known orexigenic gut hormone (Anti-orexigenic-GLP1 and PPY). Additional evidence suggests that ghrelin may also participate in long-term body weight regulation, and blockade of ghrelin signaling is actively being explored as a potential antiobesity modality.<sup>[5,6]</sup> The following observations are consistent with the hypothesis that ghrelin contributes to prandial hunger and meal

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initiation.<sup>[4,6]</sup> The greatest amount of ghrelin is produced by the stomach and duodenum, organs that are well positioned to sense the presence or absence of recently ingested food.<sup>[7-11]</sup>

As predicted for a meal initiator, ghrelin levels increase with fasting and are suppressed within minutes by refeeding or enteral infusions of nutrients but not water. Exogenous ghrelin stimulates eating when administered at times of minimal spontaneous food intake. Ghrelin's orexigenic actions are extremely rapid and short-lived, as required for a signal influencing individual meal-related behavior.<sup>[12-14]</sup> A detailed analysis of meal patterns after ghrelin injections reveals that the primary orexigenic effect of ghrelin is to decrease the latency to feed, leading to one extra episode of eating that occurs directly after ghrelin administration.<sup>[15]</sup> Ghrelin stimulates gastric motility and acid secretion, both of which increase in anticipation of meals.<sup>[16]</sup>

According to the existing literature, the effects of bariatric procedures on plasma ghrelin levels are diverse. LSG has been found to cause reduction in ghrelin levels in many studies in over a past decade. It is probably the result of resecting the gastric fundus where the majority of ghrelin production takes place.

The landmark study of Cummings and Schwartz in 2003 showed that plasma ghrelin increases following diet-induced weight loss, thereby potentially contributing to weight regain. In the same study, a profound suppression of ghrelin levels following Roux-en-Y gastric bypass (RYGB) was found, which bought the interaction of weight loss operations and the gut-brain axis into focus.<sup>[5,6]</sup>

### Aim

The aim of this study was to compare the changes in fasting plasma ghrelin levels pre- and post-operatively at 1 week, 3 months, and 6 months following LSG obese patients.

### METHODOLOGY

The study was conducted on 70 morbidly obese patients (body mass index [BMI] >40 kg/m<sup>2</sup>) or severely obese patients (BMI >35 kg/m<sup>2</sup>) with comorbidities who underwent LSG in Dayanand Medical College and Hospital, Ludhiana, India, from 2013 to 2016. LSG was standardized to bougie size of 36 Fr for all patients over which gastric sleeve was created and the procedure by performed by the same surgeon in all patients. Serum ghrelin levels were measured preoperatively and postoperatively at 1 week, 3 months, and 6 months using human ghrelin ELISA kit along with measurements of glycosylated hemoglobin (HbA1c) and weight loss parameters. Inclusion criteria were

morbid obesity (BMI >40 kg/m<sup>2</sup>), severe obesity as BMI >35 kg/m<sup>2</sup> with comorbid conditions such as obstructive sleep apnea, Pickwickian syndrome, diabetes mellitus or degenerative joint disease, and metabolic syndrome/syndrome X/Insulin resistance syndrome. Exclusion criteria were history of any bariatric surgical intervention and patients with contraindications to bariatric surgery including advanced stage cancer and end-stage renal, hepatic, and cardiopulmonary disease. Ethical committee clearance was obtained from the Institutional ethics board before the start of the study.

### RESULTS

There were 43 males and 27 females in our study population. Mean age of our patients was 42.57 years. A total of 48 of our patients were morbidly obese, and 22 patients were severely obese. Majority of the patients were male with mean BMI of 51.27 [Table 1].

Weight loss was found to be significant and sustained over a period of 6 months postoperatively [Table 2].

There was a significant decrease in plasma ghrelin levels at day 1 compared with preoperative levels (35.8 ± 12.3 fmol/ml vs. 109.6 ± 32.6 fmol/ml). During follow-up, plasma ghrelin remained stable at a low level at 1 month (43.7 ± 11.3 fmol/ml) and 6 months (44.8 ± 13.2 fmol/ml) postoperatively. However, plasma ghrelin levels were found to reach a plateau phase after postoperative 3 months leading to a mild rise, though insignificant, in mean ghrelin levels at postoperative 6 months [Table 3].

Nine out of 70 patients had weight regain, i.e., a significant rise in weight at 6 months as compared to postoperative 3 months. On the other hand, ghrelin levels in these participants still showed a decreasing trend, though statistically insignificant, at postoperative 6 months. There were 22 diabetic individuals in our study population. HbA1c levels showed a significant fall at 3 months and 6 months post-LSG in these patients [Table 4].

**Table 1: Demographics**

Parameters	Values
n	70
Male (%)	43 (62.32)
Female (%)	26 (37.68)
Morbid obesity (%)	48 (68.57)
Severe obesity (%)	22 (31.42)
Mean age (years)	42.57
Mean height (m)	1.614
Mean weight (kg)	133.37
Mean BMI (kg/m <sup>2</sup> )	51.27

BMI: Body mass index

**Table 2: Mean weight of study population preoperative, at postoperative 1 week, 3 months, and 6 months**

Time	Preoperative	1 week, <i>P</i>	3 months, <i>P</i>	6 months, <i>P</i>
Weight (kg)	133.37±16.10	129.47±15.73, 0.71	113.03±13.44, <0.05	90.00±11.61, <0.05
Weight loss (kg)		3.90±1.44, 0.21	20.33±4.95, <0.05	43.37±10.30, <0.05
Mean percentage excess weight loss		5.82±2.29, 0.52	29.7±4.58, <0.05	63.25±8.10, <0.05

**Table 3: Ghrelin levels preoperative, at postoperative 1 month, 3 months, and 6 months**

Time	Preoperative	1 week, <i>P</i>	3 months, <i>P</i>	6 months, <i>P</i>
Fasting plasma ghrelin levels (pg/ml)	42.48±18.13	22.47±10.67, <0.05	18.54±9.17, <0.05	19.57±8.93, <0.05

**Table 4: Mean glycosylated hemoglobin levels preoperative and postoperative 1 month, 3 months, and 6 months in diabetic population**

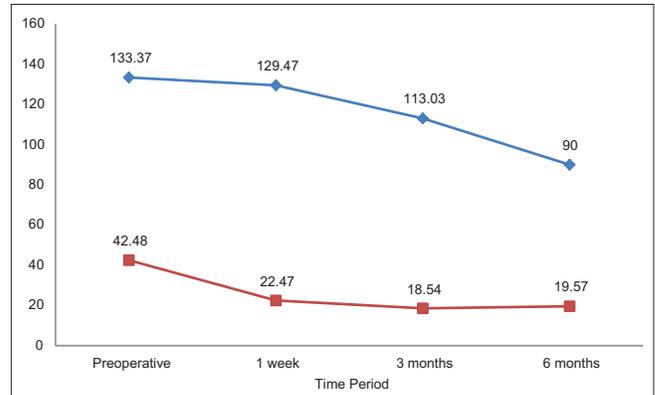
Time	Preoperative	1 week, <i>P</i>	3 months, <i>P</i>	6 months, <i>P</i>
HbA1c				
Diabetic (n=19, 27.53%)	7.98±1.06	7.63±1.15, 0.81	6.53±1.03, <0.05	5.51±0.76, <0.05

HbA1c: Glycosylated hemoglobin

## DISCUSSION

LSG leads to excellent immediate and delayed weight loss. The weight loss could be partly due to restriction caused as a result of reduced volume, peristalsis, and receptive relaxation of stomach and partly due to plasma ghrelin levels which fell significantly post-LSG, thus causing the reduction of appetite leading to, effective weight loss after surgery. Similar findings were noted by Langer *et al.*,<sup>[17]</sup> who compared changes in plasma ghrelin levels and weight loss following LSG in 20 morbidly obese patients. There was a significant decrease in plasma ghrelin levels at day 1 compared with preoperative levels, and during follow-up, plasma ghrelin remained stable at a low level at 1 month (43.7 ± 11.3 fmol/ml) and 6 months (44.8 ± 13.2 fmol/ml) postoperatively. Karamanakos *et al.* studied plasma ghrelin levels in 16 obese patients undergoing LSG and gave results similar to our study. Because sleeve gastrectomy involves the removal of gastric fundus which is the main location of ghrelin-producing cells, one would expect the observed decreased plasma ghrelin levels after LSG.

However, the prolonged and sustained weight loss after LSG may not be related to hormonal factors alone. Other vital factors, such as decrease capacity of stomach, improved dietary habits, increased awareness toward exercise, and the feeling of well-being or fear of being obese again also contribute to patient's own gravitational efforts for weight maintenance.



**Figure 1: Trend of mean ghrelin levels comparative to mean body weight**

In our study, the reduction in plasma ghrelin levels had a positive correlation with weight loss during the early postoperative period up to 3 months after surgery. At postoperative 6 months, ghrelin levels were seen to increase as compared to the levels at 3 months. This increase was, however, not statistically significant. On the other hand, weight loss was sustained in patients even at postoperative 6 months, and this difference was statistically significant when compared to weight loss parameters at 3 months. A significant decrease in plasma ghrelin levels after LSG was also shown in a study by Hady *et al.* in 100 obese patients; however, in this study, a slight insignificant rise in ghrelin level was observed at 6 months post-LSG.<sup>[18]</sup>

In another study conducted by Adami *et al.*, only temporary effects on postoperative plasma ghrelin levels were found in 23 patients who underwent sleeve gastrectomy. After an initial decrease, plasma ghrelin levels returned to preoperative levels at only 2 months following the operation. The authors suggested that compensatory ghrelin secretion from the remnant gastric fundus and the extragastric ghrelin producing structures would compensate for the initial decrease in plasma ghrelin levels and subsequent rise in ghrelin levels.<sup>[19]</sup>

This paradoxical rise in ghrelin in our study could be explained by the above hypothesis. However, it did not lead to any concomitant weight gain in these patients. [Figure 1].

As per the current literature, there are evidence of long-term weight regain after LSG and it cannot be denied. In our study, we observed nine patients who regained weight significantly at postoperative 6 months

as compared to 3 months. However, in these patients, ghrelin levels did not show a rising trend which could explain a rebounding orexigenic behavior in these participants. This could be related to improper dietary counseling and the relapse of feeding habits due to loss of psychological control, leading to intake in copious amounts which is accompanied by vomiting later, but increases the gastric capacity in long term. This further emphasizes the importance of dietary counseling in these patients to avoid weight regain, irrespective of surgery-induced weight loss.

Majority of the diabetic patients achieved good glycemic control at 3 months and 6 months after surgery, as indicated by a significant fall in HbA1c levels. Majority of the patients discontinued their oral hypoglycemic drugs, and a few patients came down to a daily insulin requirement of less than one-third of their preoperative dosages.

## CONCLUSION

LSG is an effective weight loss surgery and brings about excellent weight loss in morbidly obese individuals in addition to achievement of good glycemic control in diabetic individuals. Serum levels of ghrelin fall significantly after sleeve gastrectomy. LSG can thus have a metabolic component along with a restrictive component in causing weight loss in such patients.

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## Conflicts of interest

There are no conflicts of interest.

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