


# Bariatric surgery and the neurohormonal switch

## Early insulin resistance recordings after laparoscopic sleeve gastrectomy

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### Abstract

Laparoscopic sleeve gastrectomy (LSG) is a bariatric operation with a safe risk profile. It has been proven to successfully reduce weight, decrease insulin resistance (IR), and ameliorate diabetes mellitus. The aim of this study was to determine if there is an early improvement in IR after LSG and its association with weight loss.

This was a prospective observational study of 32 patients who underwent LSG at a single center over a 3-year period. Serum insulin and fasting glucose levels were recorded preoperatively, on day 1 postoperatively, and 3 weeks after LSG. IR levels were calculated using the Homeostasis Model Assessment 2 Version 2.23. IR levels were compared along with the overall weight loss, via body mass index.  $\beta$ -cell function was the secondary outcome.

IR significantly improved the day after surgery with a statistically significant mean difference of 0.89 units ( $P = .043$ ) and significantly more so 3 weeks postoperatively, with a mean difference of 4.32 units ( $P < .0005$ ).  $\beta$ -cell function reduced 3 weeks postoperatively, with a mean difference of 23.95 % $\beta$  ( $P = .025$ ), while body mass index significantly reduced, with a mean difference of 4.32 kg/m<sup>2</sup> ( $P < .0005$ ).

Early improvement of IR was observed on postoperative day 1 after LSG before any weight loss. This raises the possibility of an undetermined, underlying neurohormonal switch that improves IR. Further investigation is needed to determine this mechanism, as it may lead to an improvement in the medical management of diabetes mellitus.

**Abbreviations:** BMI = body mass index, CPAC = clinical priority assessment criteria, HOMA = homeostasis model assessment, IR = insulin resistance, LSG = laparoscopic sleeve gastrectomy, NICE = National Institute for Health and Care Excellence.

**Keywords:** bariatric surgery, diabetes mellitus, endocrine surgery, insulin resistance

### 1. Introduction

Obesity is currently a serious epidemic, with a prevalence of over 140 million people worldwide. It results in a host of medical problems for individuals and health care systems by inducing and accelerating cardiovascular disease, cancer, and type 2 diabetes mellitus, all of which subsequently increase the risk of early mortality. The association between obesity and insulin resistance (IR) is well established and arises from the fact that 70% to 80% of patients with type 2 diabetes are obese.<sup>[1]</sup> IR, which is defined as a decreased dose response to the biological effect of insulin, has been postulated to be one of the defects that contribute to the development of type 2 diabetes mellitus,<sup>[2-4]</sup> as well as the best predictor of diabetes in future.<sup>[5-7]</sup> As weight increases, IR worsens, and if the weight decreases

to normal, IR improves.<sup>[8]</sup> IR itself is poorly understood, and its etiology is believed to involve both genetic and acquired factors.<sup>[2-4,8]</sup>

There is evidence that bariatric surgery is effective in inducing weight loss, improving diabetes and its complications, and reducing the risk of cardiovascular disorders.<sup>[9-11]</sup> For example, 78% of patients who undergo bariatric surgery experience resolution of type 2 diabetes mellitus.<sup>[12]</sup> Laparoscopic sleeve gastrectomy (LSG) was initially conceived as the first stage of the biliopancreatic diversion. However, given that LSG afforded excellent weight loss on its own, it has evolved into a standalone procedure. Recently, it has gained further popularity owing to its low-risk profile and relative simplicity.<sup>[13]</sup> Advanced laparoscopic techniques have also led to further refinements in operative techniques. The effects of LSG

Informed consent was obtained from all participants included in the study.

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The data used to support the findings of this study are available from the corresponding author upon request.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This study was conducted prospectively as an observational study with data obtained for clinical purposes. Consent was obtained from all participants to use their records.

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on weight loss have been attributed to a number of mechanisms, including mechanical processes such as its restrictive effect on the stomach volume,<sup>[14]</sup> gastrointestinal motility modifications,<sup>[15]</sup> hormonal changes (glucagon-like peptide 1, PYY),<sup>[16,17]</sup> neural signaling pathway modifications,<sup>[18]</sup> and changes in intestinal microbiota.<sup>[19]</sup>

Patients with diabetes who undergo LSG experience diabetes resolution, and this effect has been found to be sustained over time.<sup>[12]</sup> It is theorized that this effect is due to a loss of fat cell mass and consequent decrease in triglyceride deposition in the liver and muscles. This, in turn, leads to an improved effect of insulin on the peripheral muscles and liver through the glucose transporter receptors, thereby improving glycemic control. Over a sustained period, LSG is an effective long-term metabolic surgery, as one meta-analysis suggested that diabetes prevalence decreased postoperatively to 20.5% at 5 years, with complete resolution observed in 60.8% of patients.<sup>[20]</sup> However, the immediate metabolic response after sleeve gastrectomy (SG) is less well known, although the improvement is more dramatic and occurs as early as 1 week after LSG.<sup>[21]</sup> The literature on immediate postoperative outcomes after LSG is scant, and the relationship between insulin sensitivity and weight loss is unknown. We sought to clarify the timeline of early improvement in IR in patients who have undergone LSG and assess its relationship with weight loss.

## 2. Materials and Methods

This was a prospective observational study of all patients who underwent LSG at a hospital in the Wellington region of New Zealand over a 3-year period from November 2012 to March 2015. For all patients, this was the first bariatric procedure.

### 2.1. Patient selection

Standardized criteria as per the National Institute for Health and Care Excellence (NICE) guidelines from the United Kingdom were utilized to select patients for bariatric surgery. All patients referred for bariatric surgery initially were invited to participate. After acceptance for bariatric surgery, the patients were subsequently stratified using the New Zealand Clinical Priority Assessment Criteria (CPAC) scoring tool which is used to prioritize patients for surgery. Patients complete a questionnaire to assess the impact their condition has on their day to day living and overall function. Once a score is allocated, out of 100, patients are then prioritized to determine the order of treatment. The aim of the NZ CPAC score is to deliver equitable treatment which provides fairness in the decision making. This scoring tool was developed to prioritize those who urgently need the procedure because of limited funding for all surgical procedures. Finally, each individual was evaluated using a rigorous multidisciplinary process, involving a specialist bariatric nurse, psychologist, dietician, and surgeon.

For the purposes of this study and to avoid confounding factors, the following patient groups were excluded: patients who had significant weight loss prior to surgery, patients lost to follow-up, or those who did not have their insulin and blood glucose levels recorded postoperatively. Patients lost to follow-up could not be addressed.

### 2.2. Perioperative preparation and surgical technique

All patients underwent LSG as a standardized procedure. A 34-Fr bougie was introduced, and a mechanical stapling device was used to fashion a smaller stomach. The patients were usually discharged on postoperative day 2 after the commencement of a pureed diet and once they were deemed safe to be discharged.

### 2.3. Data collection and statistical analysis

Relevant blood test results and preoperative weights were recorded and cross-referenced with patient notes and a medical electronic record database. Patients were scheduled for follow-up at 1 month, 3 months, 8 months, and 12 months, with both a surgeon and dietician. Prior to these appointments, serum insulin levels and blood panels were obtained. We only focused on early insulin measurements, which included measurements taken the day after and 3 weeks after surgery. The Homeostasis Model Assessment 2 (HOMA2) Version 2.23 calculator<sup>[22]</sup> was used to calculate the IR and  $\beta$ -cell function in each individual for the entire cohort of patients, given its simplicity and pragmatic use compared to other measures.<sup>[23]</sup> Statistical analysis was performed using IBM SPSSv20 (IBM SPSS Statistics for Windows, version 20.0., Armonk, NY; IBM Corp., 2011). Paired t-tests were used to compare the means between time points for each patient. Wilcoxon signed-rank tests were used to confirm these test results to guard against nonnormally distributed data. Data were presented as the mean  $\pm$  standard deviation or median. Statistical significance was set at a *P* value of  $<.05$ .

## 3. Results

Sixty-seven patients underwent LSG between November 2012 and March 2015; of which 35 patients were excluded due to the exclusion criteria. Of the remaining 32 patients, 37.5% (12/32) were male and 62.5% (20/32) were female (3:5). The median age of the patients was 52 years (range, 31–66 years). The commonest ethnicity was New Zealand European (46.9%, 15/32), followed by Māori (37.5%, 12/32); 71.9% (23/32) patients had a formal preoperative diagnosis of diabetes, and 9.4% (3/32) had impaired glucose tolerance; 21.9% (7/32) were receiving insulin, and 46.9% (15/32) were receiving oral antihyperglycemic medication. The preoperative body mass index (BMI) varied between 40 and 44 kg/m<sup>2</sup> in 46.9% (15/32) of the patients, and the mean BMI was 44.2 kg/m<sup>2</sup> (range, 34.5–51.8 kg/m<sup>2</sup>). The preoperative HbA1c level was 40 to 49 mmol/L in 43.8% (14/32) of the patients, while it was over 50 mmol/L in 50% (16/32), and the mean was 55.3 mmol/L (range, 34–115). Finally, the commonest comorbidities were hypertension in 62.5% (20/32), asthma in 40.6% (13/32), and obstructive sleep apnea in 37.5% (12/32) of patients. Table 1 summarizes the baseline characteristics.

For technical operative outcomes, blood loss was negligible. The mean hospital admission stay after the operation was 2.4 days. The commonest length of stay was 2 days with 25 patients. The longest length of stay was 6 days and that was due to a grade IIIb Clavien–Dindo complication. This patient required a reexploration for postoperative intra-abdominal bleeding for an iatrogenic injury to the stomach, away from the staple line. Only 3 other patients had a complication, 2 patients had a grade II and 1 patient had a grade I Clavien Dindo complication.

The mean preoperative BMI was 44.2 kg/m<sup>2</sup> (range, 34.5–51.8 kg/m<sup>2</sup>) and postoperative BMI (at 3 weeks) was 39.88 kg/m<sup>2</sup> (range, 36.4–43.4 kg/m<sup>2</sup>), with a mean difference of 4.32 kg/m<sup>2</sup>, which was statistically significant (*P*  $<.0005$ ). There was no difference between the preoperative BMI and BMI on postoperative day 1.

The calculated mean IR was 3.76 units  $\pm$  2.07 preoperatively and 2.87 units  $\pm$  1.77 on postoperative day 1, showing a statistically significant difference of 0.89 units (*P* = .043). The calculated mean IR further decreased at 3 weeks postoperatively to 2.19 units  $\pm$  1.61, with a statistically significant difference of 1.57 units (*P*  $<.0005$ ). All patients stopped their antidiabetic medication postoperatively and were discharged.

The calculated mean  $\beta$ -cell function was 131.0  $\pm$  81.66 % $\beta$  preoperatively and 107.05  $\pm$  45.28 % $\beta$  on postoperative week 3, with a statistically significant difference of 23.95 % $\beta$  (*P* = .025). There was no significant difference on postoperative day 1, with a mean of 124.153 % $\beta$   $\pm$  51.55, as compared to the preoperative

**Table 1**  
**Summary of patient baseline characteristics prior to laparoscopic sleeve gastrectomy at Wellington Regional Hospital, New Zealand, between 2012 and 2015.**

Baseline characteristics	All patients (N = 32), % (n)
Male	37.5% (12)
Female	62.5% (20)
Age, yr	
<40	9.4% (3)
40–49	37.5% (12)
50–59	37.5% (12)
≥60	15.6% (5)
Ethnicity	
New Zealand European	46.9% (15)
Māori	37.5% (12)
Fijian-Indian	6.3% (2)
African	3.1% (1)
Other European	3.1% (1)
Samoan	3.1% (1)
Diabetes status	
Nil	18.8% (6)
Impaired glucose tolerance	9.4% (3)
Type 2 diabetes mellitus	71.9% (23)
Diabetes management control	
Nil	31.3% (10)
Oral	46.9% (15)
Insulin	21.9% (7)
Preoperative body mass index (kg/m <sup>2</sup> )	
<35	3.1% (1)
35–39	12.5% (4)
40–44	46.9% (15)
45–49	31.3% (10)
≥50	6.3% (2)
Preoperative hemoglobin A1c (mmol/L)	
<40	6.3% (2)
40–49	43.8% (14)
50–59	15.6% (5)
60–69	12.5% (4)
70–79	12.5% (4)
≥80	9.4% (3)
Smoking history	
Current smoker	0% (0)
Exsmoker	31.3% (10)
Nonsmoker	68.8% (22)
Alcohol consumption	
Yes	28.1% (9)
No	71.9% (23)
Comorbidities	
Hypertension	62.5% (20)
Asthma	40.6% (13)
Obstructive sleep apnea	37.5% (12)
Dyslipidemia	31.3% (10)
Gout	25% (8)
Ischemic heart disease	9.4% (3)
Polycystic ovary syndrome	6.3% (2)
Gastroesophageal reflux disease	6.3% (2)
Others*	15.6% (5)

\*Other includes instances where there was only 1 patient with any of the following comorbidities: atrial fibrillation, previous venous thromboembolic event, hepatitis b, hypothyroidism, or epilepsy.

function of 6.847 %β (P = .631). Table 2 summarizes the calculated average across all datasets at preoperative, postoperative day 1 and 3 weeks postoperative time points.

#### 4. Discussion and Conclusions

In our study, after LSG, we found a statistically significant reduction in IR in our patients immediately on postoperative day 1 prior to any weight loss (BMI unchanged), which was further

**Table 2**  
**The 3 datasets, body mass index, β-cell function, and insulin resistance, and the changes with time postoperatively.**

	Preoperative	Postoperative day 1	Postoperative week 3
Body mass index (kg/m <sup>2</sup> )	44.20	44.00	39.88
Insulin resistance (units)	3.76	2.87	2.19
β-cell function (%B)	131.00	124.15	107.05

enhanced at 3 weeks when the BMI had also statistically reduced. Interestingly, β-cell function reduced significantly at 3 weeks.

There is a well-established link between obesity, diabetes, and IR, such that IR worsens with increase in weight, eventually resulting in the onset of type 2 diabetes. Therefore, it is theorized that diabetes can be resolved after bariatric surgery and its intended weight loss.<sup>[12]</sup> As expected, there was an improvement in BMI at 3 weeks postoperatively, but intuitively, there was no change in BMI on postoperative day 1. Interestingly, the day after surgery, we observed a significant improvement in IR from 3.76 units to 2.87 units, and this change occurred prior to any weight loss. This improvement in IR was further enhanced at 3 weeks postoperatively with an improvement from 3.76 units to 2.19 units. This indicates that although weight loss may play a role in the amelioration of IR at 3 weeks, there is likely to be another mechanism by which IR improves immediately after surgery. As a result, instead of IR being a direct consequence of the effects of an increase in adipose tissue and serum free fatty acids, there may be other mechanisms that modulate the decline in insulin sensitivity.

From our data, the role of pancreatic function can also be theorized. Immediately postoperatively, there was no statistically significant change in β-cell function, which is a direct marker of pancreatic function. However, our results suggest a statistically significant reduction at 3 weeks postoperatively from 131.0 %β to 107.05 %β, which is statistically significant. This may highlight the change of the end organ sensitivity to insulin, or reduced IR. The significance of this is unclear and requires longer follow-up in association with IR for a reliable longitudinal analysis. Furthermore, all patients ceased their use of diabetic medications postoperatively and on discharge from the hospital, including the patients previously receiving insulin. This clinical observation was supported by a recent randomized control trial by Schauer et al. in which there was a reduction in the use of diabetic medications well before the achievement of maximal weight loss; therefore, other mechanisms may be at play immediately after LSG.<sup>[24]</sup>

Evidence of early or rapid improvement in IR after various bariatric procedures is well described. For example, for Roux-en-Y gastric bypass, Wickremesekera et al. observed an improvement within 6 days postoperatively.<sup>[25]</sup> Similar results have also been reported for gastric banding. However, the literature on early postoperative IR changes in patients undergoing LSG is scant. Rizzello et al.<sup>[26]</sup> demonstrated a sharp decline at 5 days postoperatively in serum glucose and HOMA-IR levels. Our study suggests that the magnitude of HOMA-IR improvement is significant in the immediate postoperative period. The clinical advantage of this study is the beneficial impact of bariatric surgery on the amelioration of IR and diabetes mellitus. This poses beneficial and reversible complications of early metabolic syndrome. The improvement in IR is a rapid process that occurs suddenly and might be mediated by surgery, possibly an instantaneous physiological switch that reverses the pathophysiology of diabetes. Currently, it is well documented that the gastrointestinal tract is one of the largest neuroendocrine organs in the body, producing >40 neurohormonal mediators. It is possible that LSG results in an immediate modification of the neurohormonal axis, thus resulting in an improvement in

glucose homeostasis.<sup>[27]</sup> A number of peptides or incretins have been identified as putative factors that may mediate this effect, including GLP-1, ghrelin, and gastric inhibitory peptide (GIP).<sup>[28]</sup> Such factors may contribute to the anorexigenic pathway after LSG and may explain the switch-like IR reversal mediated by surgery.

Studies in animal literature suggest that sustained improvement of glucose metabolism and insulin sensitivity after SG may be the result of variations in hormone levels caused by SG.<sup>[29]</sup> GLP-1 is secreted mainly by L-cells, predominantly located in the terminal ileum. The role of GLP-1 in diabetes remission after bariatric surgery has been studied. In studies on rats, GLP-1 increases in rats that underwent SG.<sup>[30–33]</sup> It has been postulated that the improvement in glucose homeostasis is mediated by this effect. Interestingly, GLP-1-based treatment has been associated with weight loss and reduced risk of hypoglycemia in patients with type 2 diabetes.<sup>[34]</sup> In contrast, some studies on rats demonstrated either a deficiency or no change in GLP-1 after SG but an improvement in glucose metabolism nevertheless.<sup>[35–37]</sup> Therefore, the role of GLP-1 in improving IR is not well known. The literature on changes in GIP and ghrelin plasma concentration after SG is scant, but some animal studies suggest that there may be a decrease in both.<sup>[38]</sup> No other animal or human studies have exhibited a clear understanding of the biochemical changes and their correlation with weight loss after bariatric surgery. To postulate a hypothesis for the cause of improvement in IR in our study would be presumptive and unreliable as the mechanism was not investigated. Future studies would need to investigate the role of GLP-1, GIP, ghrelin, and other potential factors, and such studies would need large prospective observational studies on humans.

One of the limitations of this study is that it was a single-center study. Although the surgical technique involved in LSG is standardized between the 3 surgeons at this center, subtle differences may exist between centers; for example, the bougie size inserted into the stomach prior to stapling can lead to a small or large residual stomach. However, our sample size of 32 patients improved the reliability of this study. Gold-standard tests such as the hyperinsulinemic–euglycemic clamp and hyperglycemic clamp could be used; however, they are dynamic tests and provide varying information on IR and  $\beta$ -cell function.<sup>[23]</sup> The HOMA2 model was used in this study as it yields a steady-state basal value, but it also has limitations, especially related to differences caused by ethnicity, and the measurement of HOMA-%B may be incorrect for those taking exogenous insulin.<sup>[23]</sup> Future prospective studies could examine other neuroendocrine profiles. A scope for future studies is to further capture the timeline of IR and  $\beta$ -cell fluctuations to accurately characterize the onset of the improvement of IR before and after LSG and whether there are changes in other hormones or peptides shortly after the surgery. Further, a long study period of up to 1 year postoperatively could help determine whether patients have had partial or complete remission from diabetes according to the Buse criteria.<sup>[39]</sup>

Early biochemical postoperative changes after LSG are unknown; however, this study aims to shed light on the early responsiveness of the human body after LSG. This study adds evidence on the beneficial effects of LSG in patients with obesity, namely weight loss at early follow-up and remission of IR. The exact mechanism by which IR improves almost immediately on the following postoperative day remains unknown. Through medical management, an accurate understanding of the mechanism underlying this surgically induced sudden improvement may assist in preventing the initial development of IR. Future research should be directed at characterizing the timeline of the improvement in IR and whether there are responsible neurohormonal systems other than those involved in the enteric system.

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## Author contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Cheyaanathan Haran, Yukai Lim, and Susrutha Wickremesekera. The first draft of the manuscript was written by Cheyaanathan Haran and Yukai Lim, and all authors commented on the previous versions of the manuscript. All authors read and approved the final manuscript.

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