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Original article

Q3 Q1 Resolution of type 2 diabetes after sleeve gastrectomy: a 2-step hypothesis

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Abstract

Background: Weight loss (WL) and altered gut hormonal levels are involved in glucose homeostasis after laparoscopic sleeve gastrectomy (LSG).

Objectives: The aim of this study was to evaluate the time-related effects of WL, ghrelin, and glucacon-like peptide-1 (GLP-1) plasma concentrations on type 2 diabetes resolution after LSG.

Setting: University hospital, Italy.

Methods: Ninety-one patients who underwent LSG were investigated. Insulin secretion (insulinogenic index [IGI]), insulin resistance, plasma glucose level and percentage glycated hemoglobin using the oral glucose tolerance test were assessed before surgery, on postoperative day 3, and then at 6, 12, 24, and 36 months after LSG. At the same time points, WL, ghrelin, and GLP-1 levels were determined.

Results: During follow-up, the resolution rate of type 2 diabetes was 9.4%, 42.3%, 71.8%, 81.2%, and 91.8%, respectively. Ghrelin plasma concentrations decreased significantly after LSG (271.5 ± 24.5 pg/mL versus 122.4 ± 23.4 pg/mL, $P = .04$). GLP-1 plasma concentrations increased significantly after LSG (1.7 ± 2.6 pg/mL versus 2.5 ± 3.4 pg/mL, $P = .04$). The percentage of excess weight loss and IGI presented a positive linear correlation (r) at all follow-up time points with a strong positive correlation at 12 and 24 months. A strong negative correlation between ghrelin and IGI was recorded during the first 3 days after LSG ($r = -.9$). GLP-1 and IGI presented a strong positive correlation at day 3 and 6 months (i.e., .8 and .8, respectively).

Conclusion: LSG may affect glucose homeostasis by 2 different time-related modes: a first step in which the hormonal changes play a predominant role in glucose homeostasis and a second step in which the percentage excess weight loss determines the metabolic results. (Surg Obes Relat Dis 2018;▮:00–00.)

Keywords: Laparoscopic sleeve gastrectomy; Type 2 diabetes; Ghrelin; GLP-1; Insulin secretion; Insulin resistance

In developed countries, obesity is currently a widespread health problem associated with considerable morbidity and mortality [1]. The association with diabetes is well established; 90% of patients with type 2 diabetes (T2D) have excess weight [1,2]. Bariatric surgery has emerged as a highly effective treatment for obesity-associated T2D, especially compared with medical therapy alone [2,3]. Several observational studies have suggested that metabolic

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surgery can rapidly improve glycemic control and cardiovascular risk factors in severely obese patients with T2D [2,4].

Laparoscopic sleeve gastrectomy (LSG) is an effective surgical procedure to treat obesity and T2D with results similar to Roux-en-Y gastric bypass [3,5,6]. The mechanisms of T2D resolution after LSG continue to be an active area of research. The literature has focused on 2 mechanisms involved in T2D improvement after LSG: weight loss and alterations in gut hormonal levels [3–9]. The removal of the gastric fundus and rapid gastric emptying have been proposed to explain hormonal changes, highlighting the role of the stomach in the regulation of glucose metabolism [7,10,11]. Furthermore, some authors suggest that changes in ghrelin and glucacon-like peptide-1 (GLP-1) after LSG may play a pivotal role in glycemic control and insulin resistance [7–9]. Currently, the long-term effects of hormonal changes and weight loss on glycemic homeostasis after LSG are not yet clearly defined.

The aim of the present study was to evaluate long-term changes in percentage excess weight loss (%EWL), ghrelin, and GLP-1 plasma concentrations after LSG and their effects on insulin secretion, insulin resistance, and T2D resolution in patients with obesity and diabetes.

Methods

Study design

This was a prospective observational study that included morbidly obese patients who underwent LSG between August 2011 and October 2012 at San Salvatore University Hospital. According to the National Institutes of Health, all patients with a body mass index (BMI) ≥40 kg/m^2 or patients with a BMI ≥35 kg/m^2 and at least 1 obesity-related co-morbidity were eligible for the study. The other inclusion criteria were as follows: diabetes duration <10 years (the literature suggests 10 yr as a cut-off prognostic factor for the effect of LSG on diabetes) [12,13]; diagnosis of poorly controlled T2D after the administration of hypoglycemic drugs for 6 months; glycated hemoglobin (HbA1C) level ≥6.5%; age between 20 and 60 years; no corticoid therapy.

Before surgery, each patient was evaluated and followed for at least 6 months by a multidisciplinary team including a psychologist, an endocrinologist, a gastroenterologist, and a nutritionist. Weight loss was expressed as %EWL, with the calculation of ideal weight as that equivalent to a BMI of 25 kg/m^2.

Only 96 of 128 patients enrolled for LSG met the inclusion criteria (2 patients with a diabetes duration >10 yr and 30 patients without diabetes were excluded). Five of the remaining patients were lost during follow-up. Finally, 91 patients completed the 3-year follow-up and were assessed.

The Ethical Committee of the Surgical Department of the University of L'Aquila approved the study protocol. All patients signed an informed consent form.

Surgical procedure and postoperative management

All procedures were performed laparoscopically, using a 4-port technique. The greater curvature of the stomach was dissected by dividing the short gastric vessels with an ultrasonic scalpel (Ace; Ethicon Endo-Surgery). Dissection started opposite to the crow's foot (~6 cm proximal to the pylorus) and reached the angle of His. Sleeve calibration was obtained by a 36-Fr gastric bougie pushed along the lesser curvature, and the stomach was transected with sequential firings of linear green and blue GIA reloads (Echelon 60 mm; Ethicon Endo-Surgery). A silicon drain was placed along the suture line. The resected stomach was extracted intact from the abdomen in a plastic bag by enlarging the right subcostal incision.

All patients were double-checked with a methylene blue test and upper gastrointestinal transit on postoperative day (POD) 2; if no leakage was detected, a liquid diet was started on POD 3 and the patient was discharged.

Investigations

An oral glucose tolerance test (OGTT) with 75 g of glucose (in a total volume of 400 mL) was administered in the morning after a 12-hour overnight fast. During the night, only 1.5 L of intravenous noncaloric liquids was administered without antidiabetic drugs. Patients with a basal plasma glucose level (PGL) over 200 mg/dL were excluded from the study. The OGTT was performed in all patients 48 hours before surgery, 3 days after surgery, and then at 6, 12, 24, and 36 months after LSG. After the test PGL, %HbA1C, insulin secretion, insulin resistance, ghrelin, and GLP-1 were measured. Samples of blood for insulin dosage, calculated by the total area under the curve (AUC), were collected 1, 30, 60, 90, and 120 minutes after the oral glucose load. The early insulin secretory response to the specific glycemic response was measured by the insulinogenic index (IGI): (insulin radio-immune (IRI)$_{30\ min}$ − IRI$_{fasting}$/PGL$_{30\ min}$ − PGL$_{fasting}$) [14]. Insulin resistance was assessed using the homeostasis model assessment (HOMA$_{IR}$): (IRI$_{fasting}$ [mU/mL] × PGL$_{fasting}$ [mM]/22.5) [15]. Ghrelin and GLP-1 levels were evaluated pre- and postoperatively before and 15 minutes after the OGTT. The postoperative follow-up was conducted by a bariatric surgeon on our team 1, 3, 6, 12, 18, and 24 months after the operation and yearly thereafter. The diabetologists on our team monitored the patients every 3 weeks. A PGL <100 mg/dL and HbA1C level <6.5% without hypoglycemic drugs were considered to indicate the resolution of diabetes [8].