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CLINICAL RESEARCH

Early Improvement in Glycemic Control After Bariatric Surgery and Its Relationships with Insulin, GLP-1, and Glucagon Secretion in Type 2 Diabetic Patients

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Abstract
Background The surgical treatment of obesity ameliorates metabolic abnormalities in patients with type 2 diabetes. The objective of this study was to evaluate the early effects of Roux-en-Y gastric bypass (RYGB) on metabolic and hormonal parameters in patients with type 2 diabetes (T2DM).
Methods Ten patients with T2DM (BMI, 39.7±1.9) were evaluated before and 7, 30, and 90 days after RYGB. A meal test was performed, and plasma insulin, glucose, glucagon, and glucagon-like-peptide 1 (GLP-1) levels were measured at fasting and postprandially.
Results Seven days after RYGB, a significant reduction was observed in HOMA-IR index from 7.8±5.5 to 2.6±1.7; $p<0.05$ was associated with a nonsignificant reduction in body weight. The insulin and GLP-1 curves began to show a peak at 30 min after food ingestion, while there was a progressive decrease in glucagon and blood glucose levels throughout the meal test. Thirty and 90 days after RYGB, along with progressive weight loss, blood glucose and hormonal changes remained in the same direction and became more expressive with the post-meal insulin curve suggesting recovery of the first phase of insulin secretion and with the increase in insulinogenic index, denoting improvement in β-cell function. Furthermore, a positive correlation was found between changes in GLP-1 and insulin levels measured at 30 min after meal ($r=0.6$; $p=0.000$).
Conclusion Our data suggest that the RYGB surgery, beyond weight loss, induces early beneficial hormonal changes which favor glycemic control in type 2 diabetes.

Keywords RY gastric bypass · Type 2 diabetes · GLP-1 · Insulin · Glucagon

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Introduction

Obesity is a chronic, progressive, and multifactorial disease that has reached epidemic proportions globally in adults and children. Lifestyle changes that are associated with the pharmacological treatment of obesity may not always be effective in patients with severe obesity. These changes promote weight loss between 5% and 10% of the initial weight, and approximately 100% of the patients regain in 5 years. Surgical treatment is the most effective treatment for weight loss and maintenance, and it reduces obesity-related complications, particularly type 2 diabetes [1].

Surgeries involving intestinal bypass have beneficial effects for diabetics. Approximately 84% of diabetic patients who undergo Roux-en-Y gastric bypass (RYGB) experience complete remission of the disease [2]. Important decreases in glucose levels appear earlier, and these effects seem to be independent of weight loss, which is a secondary effect. Many studies have demonstrated that RYGB surgery promotes changes in intestinal hormones, such as increasing glucagon-like peptide 1 (GLP-1) levels in response to food intake, increasing insulin secretion,

reducing glucagon secretion, improving glycemic control, and reducing appetite [3–7].

There are a few prospective studies that have evaluated the early effects of bariatric surgery by analyzing glycemic control a few days after surgery and before a massive weight loss occurs. The objective of this study was to evaluate the early hormonal influence after bariatric surgery on metabolic profile in patients with type 2 diabetes and obesity at levels II and III.

Patients and Methods

The following criteria were required for patients to be recruited in this study from Obesity and Hypertension Outpatient Clinic at the Hospital do Rim e Hipertensão, Universidade Federal de São Paulo: diagnosed with type 2 diabetes, 25 to 65 years of age, obesity at levels II and III, and the use of oral anti-diabetic medication. The diabetes diagnosis was confirmed according to American Diabetes Association criteria. Patients were excluded from the study for the following reasons: using a dipeptidyl peptidase-4 inhibitor or a GLP-1 agonist therapy; with a severe psychiatric disease; cancer, renal, cardiac or hepatic failures; alcohol or drug abuse or severe pulmonary disease. Patients taking insulin therapy and with uncontrolled blood pressure (systolic BP $\geq$160 mmHg) were also excluded.

The Ethics Committee of the Federal University of Sao Paulo approved this study, and all participants signed an informed consent form.

A multidisciplinary team of nutritionists, psychologists, and endocrinologists evaluated all patients who were selected for the study during six visits before surgery. The nutritional intervention was performed to check and encourage the patients to adhere to the proposed diet at every visit. The psychological evaluation was important to diagnose cases of depression and severe eating disorders, both of which were exclusion criteria for the study. A physical examination was performed at every visit, and waist circumference and BMI determinations were made. The waist circumference was measured at the midpoint between the last rib and the iliac crest.

After withdrawal of anti-diabetic medication for 12 h, patients were made to fast overnight for 12 h, and blood samples were collected for glucose, insulin, and glycated hemoglobin (HbA1c) determinations. A standard liquid meal of 353 kcal (46.8% carbohydrates, 32.2% proteins, and 12.5% lipids) was then given to the patients for blood glucose, insulin, glucagon, and GLP-1 measurements at 0, 30, 60, 90, and 120 min. This procedure was performed before and at 7, 30, and 90 days after the surgery.

Bioelectrical impedance measurements were collected from all patients to evaluate body composition (body water and lean and fat masses) before and after the surgery (Quantump BIA 101Q Akern RJL Systems, Clinton Township, MI, EUA). The bioelectrical impedance analysis was performed in the morning after fasting overnight and after the first urine.

Surgical Technique

The technique used in this study was RYGB, which combines restrictive and malabsorptive mechanisms. A vertical gastric pouch (20–30 ml) was constructed with surgical staples in the lesser curvature of the stomach. Gastrojejunostomy adjustment was performed using a 32-French tube. Reconstruction was performed by RYGB with an alimentary limb measuring 100 cm and a biliopancreatic limb of 50 cm from the ligament of Treitz.

Metabolic Study

The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated from fasting glucose and insulin levels. The insulinogenic index was calculated as the ratio between the changes in insulin and glucose levels 30 min after the meal test to evaluate the first phase of insulin secretion; according to the formula (ΔI30/ΔG30).

Analytical Procedure

Plasma insulin levels were determined by an automatic immunoassay system (Auto DELFIA insulin kit, PerkinElmer Life and Analytical Sciences, Waltham, Massachusetts, USA). Glucose levels were determined by the glucose oxidase method, and HbA1c was determined by high-performance liquid chromatography.

Active GLP-1, which is an indicator of GLP potential action, was measured by enzyme-linked immunosorbent assay immunofluorescence (Linco Research, specific for humans). The assay cross-reactivity with GLP-1 7–36 and GLP-1 7–37 is 100%, but it is not with GLP-1 9–36, glucagon, and GLP-2.

Glucagon concentrations were measured by radioimmunoassay (Linco Research), and the assay cross-reactivity is 100% with glucagon, and its cross-reactivity with oxyntomodulin is less than 0.1%.

Statistical Analyses

All data were analyzed using the software Statistical Package for the Social Sciences (SPSS), version 18.0

(SPSS Inc, Chicago, IL). The Friedman test and post hoc analysis were used to compare the values of all parameters studied, which were obtained during the meal test before and at 7, 30, and 90 days after surgery. Spearman coefficient was used to determine the correlations between the different variables before and after surgery. Data are expressed as mean±standard deviation, and $p<0.05$ was considered statistically significant.

Results

Clinical and laboratory profiles of the patients before and at 7, 30, and 90 days after RYGB are shown in Table 1. High blood glucose values were observed both at fasting and after a standard meal test (Fig. 1). This was accompanied by a mild increase in postprandial insulin secretion, with values describing a flat curve. No changes in GLP-1 and glucagon levels were observed during the meal test.

No significant reductions in BMI and fat mass were observed 7 days after RYGB; however, a significant decrease in free fat mass was observed, which is presumably linked to fluid loss (Table 1). By this time, reductions in both fasting blood glucose and insulin levels lead to marked reduction in HOMA-IR index. Also, changes occurred in the shape of the blood glucose, insulin, GLP-1, and glucagon curves, delineated by the levels of these variables determined during the meal test (Fig. 1). These curves began to show peaks in GLP-1 and insulin levels at 30 min after food ingestion and a progressive decrease in glucagon and blood glucose levels throughout the meal test. A positive correlation was observed between changes in the areas under the curves of glucagon and insulin values ($r=0.8$; $p=0.015$). However, the alterations noted in the areas under the curves delineated by the postprandial hormonal and glucose values did not reach statistical significance, and no changes in the insulinogenic index were observed after 7 days of RYGB. Also, no correlations were found between these initial changes and the changes in BMI or fat mass.

Thirty and 90 days after RYGB, blood glucose and hormonal parameters changes continued in the same direction, becoming more expressive and statistically significant. Particularly, an expressive peak of GLP-1 and insulin was observed at 30 min after the meal test Considering all the observations made during the post-surgical 3-month period, a positive correlation was found between changes in GLP-1 and insulin levels measured at 30 min after meal ingestion ($r=0.6$, $p=0.000$; Fig. 2). As a consequence, the insulinogenic index showed values higher than those observed before surgery, which reflects a recovery in the first phase of insulin, contrasting with a pronounced suppression of the glucagon levels and reductions in blood glucose values observed (Fig. 1). This improvement in glycemic control resulted in progressive reductions in HbA1c while HOMA-IR remained low (Table 1).

Table 1 Subject characteristics before and after RYGB

	Surgery			
	Before	7 days after	30 days after	90 days after
Weight (kg)	103.3±16.4	96.5±16.1	92.0±14.3*	86.0±12.0*
BMI (kg/m^2)	39.7±1.9	37.0±2.1	35.3±1.5*	33.1±1.6*
Waist (cm)	116.1±8.6	113.9±9.7	107.4±9.3*	102.3±8.0*
Fat mass (kg)	42.7±5.1	39.4±4.6	34.3±4.5*	29.0±4.7*
Free fat mass (kg)	60.6±13.0	57±14.5*	57.7±12.39	57.0±11.0*
H2O (kg)	44.5±9,5	42.0±10.4	42.4±9.2	41.8±8.2*
Fasting glucose (mg/dl)	239.5±101.9	158.4±59.4	123.5±33.1*	119.1±45.2*
AUC glucose (mg/dl)	1,106.4±434.1	883.3±404.0	608.6±179.1	511.6±229.9*
Fasting insulin (mcU/ml)	16.5±16.8	6.6±3.4*	8.3±3.0	7.1±2.7
AUC insulin (mcU/ml)	114.5±61.4	86.6±41.2	159.7±76.9	158.0±85.0
Insulin peak (mcU/ml)	17.7±9.9	34.8±17.8	78.8±40.8*	95.4±67.2*
Fasting GLP-I (pmol/L)	8.8±10.1	6.6±4.0	5.0±4.3*	5.6±2.4
AUC GLP-1 (pmol/L)	37.3±40.5	49.6±21.0	49.4±20.8	62.8±19.9*
GLP-1 peak (pmol/L)	0.6±1.4	12.0±12.0	21.4±15.0*	26.7±14.8*
Fasting glucagon (pg/ml)	78.0±20.5	97.1±39.7	86.8±30.0	86.7±20.4
AUC glucagon (pg/ml)	296.0±75.1	267.6±80.7	247.9±39.4	249.0±64.1
HbA1c%	9.1±2.3	8.1±1.1	7.0±1.0*	6.2±1.3*
HOMA-IR	7.8±5.5	2.6±1.7*	2.6±1.2*	2.1±1.0*
Insulinogenic index	0.5±0.2	0.5±0.3	1.7±1.7*	12.2±23.5*

AUC=area under the curve 0–120 min, *insulinogenic index* =30 min insulin−fasting insulin/ 30 min glucose−fasting glucose

*$p<0.05$×before surgery

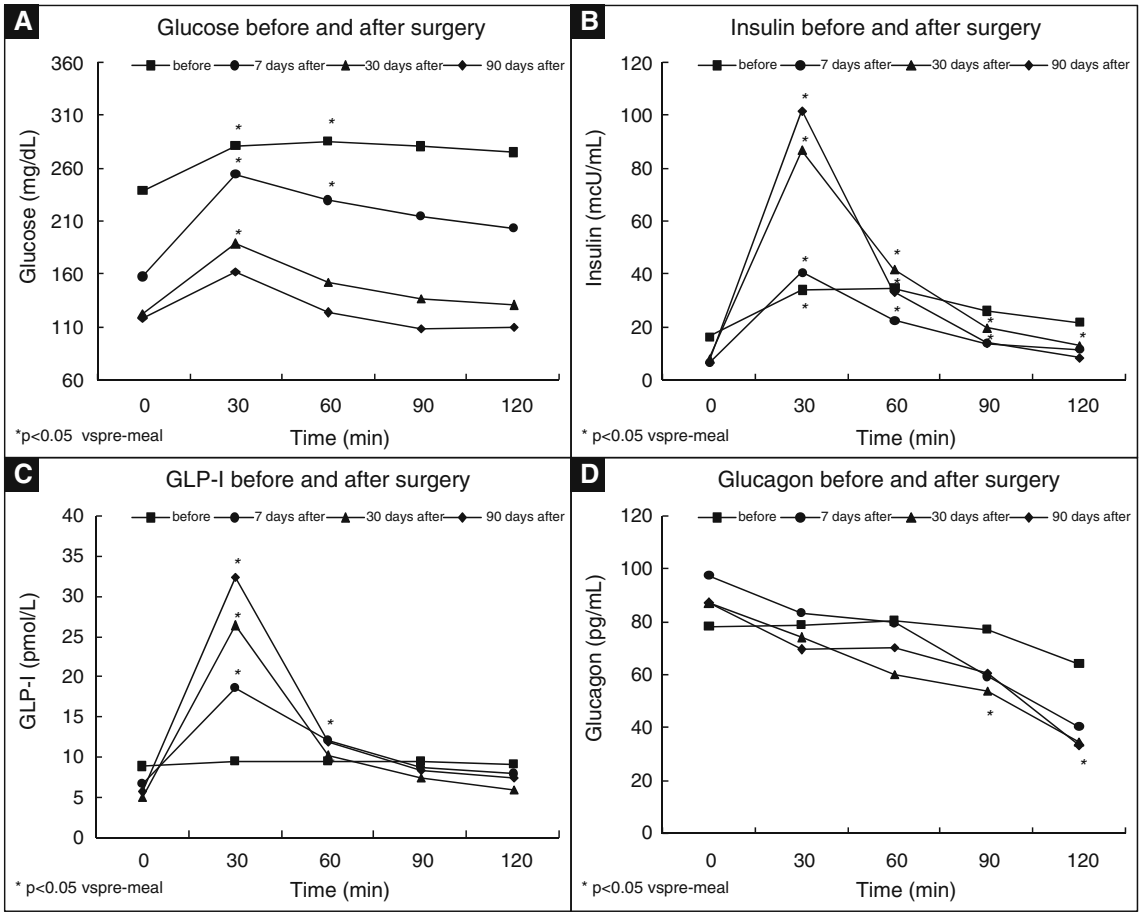

Fig. 1 **a**, **b**, **c**, and **d** Plasma glucose, insulin, GLP-1, and glucagon levels during meal test, respectively, evaluating fasting levels 30, 60, 90, and 120 min postprandial, before and after RYGB

Discussion

The present study demonstrated a progressive improvement in glycemic control, along with gastrointestinal hormonal changes and improvement in both insulin sensitivity and production after bariatric surgery, in obese patients with diabetes.

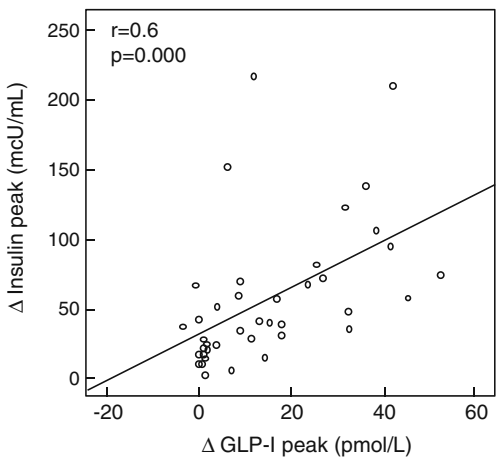

Fig. 2 Spearman's correlation between ΔGLP-I peak and ΔInsulin peak

Initially, 7 days after surgery, we noticed a decrease in both fasting plasma insulin and glucose with a consequent reduction in HOMA-IR index, which characterizes an improvement in insulin sensitivity. Although only marginally significant by this time, the reductions in the areas under the curves of insulin and blood glucose levels after meal also indicate a decrease in insulin resistance.

The marked reduction in HOMA-IR of 67% was associated with 7.7% reduction in fat mass, suggesting that other factors than body weight reduction could be influencing the early changes in glucose homeostasis. One mechanism to be considered could be dependent on caloric restriction [8, 9]. Isbell et al. [10] investigated the influence of caloric restriction on insulin resistance and production, comparing a group of obese individuals undergoing RYGB surgery to a control group of obese patients, 4 days after an equivalent post-bariatric surgery diet. They observed similar decreases in insulin production and improved

insulin sensitivity in both groups, while there were increases in GLP-1 secretion, which took place only in the group submitted to bariatric surgery. The authors, thus, concluded that the changes observed in insulin production and sensitivity were independent both on the surgical procedure and GLP-1 production and proposed the caloric restriction as the mechanism responsible for the changes observed. In fact, after RYGB, starvation can activate enzymes involved in gluconeogenesis. The mechanisms that involve the portal vein sensors promote a decrease in hepatic glucose production and decrease insulin resistance. These effects are independent of GLP-1 [11–14].

Seven days after RYGB surgery, a peak in GLP-1 serum levels occurred 30 min after the test meal diverging from what was observed before surgery. This was also associated with alterations in the shape of the postprandial glucagon and insulin curves. Despite the decrease in the area under the curve of insulin secretion after meal, a peak in insulin levels was observed 30 min after food ingestion, similar to that observed in the GLP-1 curve. In addition, a positive correlation was observed between the decrease in the areas under curves of glucagon and insulin after meal, suggesting the occurrence of two related phenomena or the presence of a third factor interfering with the secretion of these two hormones. The early improvement in GLP-1 secretion after RYGB could be explained by these early hormonal changes. Some authors have suggested that RYGB surgery might affect the enteroinsular axis by delivering incomplete digested food to the ileum, leading to increases in GLP-1 secretion [2, 15–18]. The higher levels of GLP-1 could contribute indirectly to reductions in blood glucose and insulin levels after meal and the suppression of glucagon levels. Comparing the acute effects of RYGB versus gastric restrictive surgery in obese patients with T2DM, Kashyap et al. [19] observed, after 7 days of surgery, similar changes in BMI in both groups. Insulin sensitivity increased only after RYGB, suggesting that some other factors than caloric restriction could be involved in the amelioration of glucose homeostasis. These observations contrast with those reported by Isbell et al. and us, which indicate that during the first days following RYGB surgery, an early increase in insulin sensitivity, but not in insulin production, contributes for the early improvement in blood glucose control. Although an increase in GLP-1 has been observed after a meal, no changes in the insulinogenic index were observed after 7 days of RYGB, suggesting that the response of insulin secretion to blood glucose levels was not altered during this short period.

Thirty days after RYGB surgery, we observed a substantial reduction in body weight and fat mass and a further decrease in both fasting and postprandial blood glucose levels. These changes were associated with remarkable increases in GLP-1 levels and with additional decreases in serum glucagon after meal. A marked increase in insulonogenic index was noted, suggesting increased β cell sensitivity to glucose with recovery in the first phase of insulin secretion with maintenance of insulin sensitivity. Our results are in accordance to those reported by Kashyap et al. [19] who also observed robust increases in GLP-1 secretion after meal and improvement in β cell function only 4 weeks after RYGB, which did not occur after restrictive surgery. The significant positive correlation observed between changes in GLP-1 and insulin, from the basal levels to those observed at 30 min after meal, before and all time after surgery, strongly suggests an important role of GLP-1 in the improvement of insulin secretion. The mechanisms by which the GLP-1 response to food ingestion is blunted and improves after RYGB are not fully understood. It has been accepted that, after RYGB, the early exposition of the lower gut to the ingested nutrients would anticipate the physiological release of gut incretins [20–23]. However, other mechanisms could contribute to increases in GLP-1 levels or action. It has been shown recently that there was a decrease in dipeptidyl peptidase-4 activity [24] and an improvement in incretin effect on insulin secretion [25] after RYGB in type 2 diabetic patients by mechanisms independent of weight loss. Other determinants of impaired insulin secretion in type 2 diabetes, such as glucose toxicity and lipotoxicity [26–28], which probably are reduced after surgery, may contribute to improve β cell function. Thus, changes in the incretin levels are probably not the only factor responsible for the improvement in insulin secretion early after RYGB [29–33].

In summary, our data showed that RYGB induces significant hormonal changes that influence glucose metabolism and begins soon after the RYGB postoperative period. As early as 7 days after surgery, we observed reductions in glucose, insulin, and HOMA-IR associated with increases in GLP-1 and decreases in glucagon levels. Improvement in beta cell function and a more expressive decrease in glucagon secretion can be observed only later on, and they are associated with further increases in GLP-1 levels and greater weight loss. Our data suggest that the RYGB surgery induces early beneficial hormonal changes and is a very efficient surgical therapy for rapid glycemic control in obese patients with type 2 diabetes.

Conflict of Interest The authors declare that they have no conflict of interest.

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