

Comparative Effects of Roux-en-Y Gastric Bypass and Sleeve Gastrectomy on Glucose Homeostasis and Incretin Hormones in Obese Type 2 Diabetic Patients: A One-Year Prospective Study

Authors

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Key words

- bariatric surgery
- diabetes
- GI hormones
- insulin sensitivity
- insulin secretion

Abstract

▼ The aim of the work was to compare the hormonal and the metabolic mechanisms involved in weight loss and remission of T2DM one year after Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG) in morbidly obese type 2 diabetic (T2DM) patients. Insulin sensitivity, insulin secretion, and the gastrointestinal (GI) hormone response to a mixed meal test (MMT) were evaluated before and one year after BS (14 RYGB and 19 VSG). RYGB and VSG groups had similar characteristics at baseline. Weight loss at one year was similar in the 2 groups (Δ BMI%: -32 ± 10 and $-30 \pm 7\%$, $p=0.546$). Insulin sensitivity and insulin secretion improved similarly after either procedures with a similar rate in T2DM remission (86% in RYGB and 76% in VSG).

Meal-stimulated GLP-1 levels increased after both procedures reaching significantly higher levels after RYGB ($p=0.0001$). GIP response to MMT decreased to a similar extent after the 2 interventions ($p=0.977$). Both fasting and post-meal ghrelin concentrations were markedly suppressed after VSG and significantly lower than RYGB ($p=0.013$ to $p=0.035$). The improvement of insulin sensitivity and beta-cell function was significantly associated with weight loss ($p=0.014$ to $p=0.035$), while no relation was found with the changes in GI hormones. In conclusion, in morbidly obese T2DM patients, RYGB and VSG result in similar improvements of the glucose status in the face of different GI hormonal pattern. Weight loss is the key determinant of diabetes remission one year after surgery.

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Introduction

▼ The increasing epidemic of obesity and type 2 diabetes (T2DM) is long recognized as a major healthcare problem. Bariatric surgery has emerged as the most successful therapeutic option for morbid obesity, since it results in remarkable and sustained weight loss and a dramatic improvement of glucose control in patients with T2DM [1]. The improvement/resolution of T2DM is associated with the extent of weight loss and the type of surgery ranging from 55% after restrictive procedures to 95% after malabsorptive interventions [2]. The beneficial effects on glucose metabolism occur early after surgery, before any substantial weight loss, suggesting a role of weight loss-independent mechanisms, possibly related to changes in gastrointestinal (GI) hormones in response to ingested nutrients [3–5]. There is now ample evidence that both obesity and T2DM are associated with impaired secretion/action of GI hormones, namely glucagon-like peptide 1 (GLP-1) and glucose-depend-

ent insulinotropic polypeptide (GIP) [6] and that the restoration of a more physiologic GI hormone profile brought about by bariatric procedures may contribute to the improvement of glucose homeostasis.

Roux-en-Y gastric bypass (RYGB), one of the most widely performed bariatric techniques, creates a gastrojejunal anastomosis so that ingested food moves to the distal small intestine bypassing the duodenum and the proximal jejunum. For these characteristics, it is considered a mixed-malabsorptive procedure. RYGB has proven its clinical efficacy in obese patients with type 2 diabetes for more than 30 years, with a diabetes remission of ~75% [1]. Vertical sleeve gastrectomy (VSG) is a more recent procedure that involves the excision of most of the stomach while maintaining intestinal anatomy. It is considered a merely restrictive procedure although it is associated with marked reduction of plasma ghrelin concentrations due to the removal of the gastric fundus. VSG results in remarkable weight loss and metabolic improvement, reaching a rate of T2DM

remission similar to that of RYGB, but without the potential complications inherent to intestinal bypass procedures [7]. Previous studies have examined the effects of the 2 procedures with regard to diabetes remission or the changes in GI hormones, but limited information is available on the contribution of intervention-specific changes in GI hormonal pattern to the remission of diabetes. To this end, in this prospective study we compared the changes in insulin sensitivity, insulin secretion, and post-meal GI hormone levels in obese patients with T2DM 1-year after VSG or RYGB, to evaluate the hormonal and metabolic mechanisms involved in weight loss and remission of T2DM.

Materials and Methods

Selection and description of participants

The study group included 33 obese patients with T2DM (M/F: 14/19; mean age: 46 ± 9 years, BMI: 44 ± 8 kg/m²), who were on a waiting list for bariatric surgery. Inclusion criteria included: age 30–65 years, body mass index (BMI) >40 or ≥ 35 kg/m² with uncontrolled T2DM under medical treatment, no contraindications to VSG or RYGB. The choice of surgical procedure was made by the patient together with the surgeon after a full explanation of the risks and benefits of each procedure. In total, 14 subjects underwent RYGB and 19 subjects underwent VSG. All participants were examined by a multidisciplinary and integrated medical team consisting of a diabetologist, a bariatric surgeon, a psychiatrist, and a dietician. The clinical and metabolic evaluation of participants were conducted at the Department of Clinical Medicine and Surgery of Federico II University while surgical procedures were performed at the Department of Surgery, San Giovanni Bosco Hospital, Naples.

Antidiabetic treatment was oral hypoglycemic agents (OAD) in 24 patients, combined OAD plus bedtime insulin in 5 patients and diet alone in 4 patients. None was on multiple insulin injection regimen. Fourteen patients (74%) in VSG and 9 (64%) in RYGB were on antihypertensive drugs; 5 patients (36%) in the RYGB group and 3 patients (16%) in the VSG group were on hypolipidemic treatment.

The protocol was approved by the local Ethics Committee; all patients were informed of the risks and benefits of each procedure and provided written, informed consent before the study.

Study design

Before and one year after the bariatric procedure, anthropometric, clinical and routine laboratory parameters were collected together with data on medication use. On both occasions, in the morning after a 12-h overnight fast, a standard glucose tolerance test (OGTT, 75 g of glucose) was performed to evaluate insulin secretion and insulin sensitivity. The day after, a mixed-meal test (MMT) was performed to evaluate GI hormonal response. The week before the tests all patients consumed a standardized hypocaloric diet (1200Kcal) containing 52% CHO, 18% protein, 30% fat. To avoid possible confounders, OAD were withheld 2 days before the MMT, while long-acting insulin was discontinued for 24h.

Mixed meal test (MMT)

The liquid mixed meal (Resource® ENERGY Nestle Nutrition, 304kcal in total), containing 41 g carbohydrate (glucose), 13 g protein, and 9 g fat, was consumed within a maximum of 15 min. Blood samples were drawn through an indwelling cannula at

times 0, 30, 60, 90, 120, and 180 min for the measurement of glucose, insulin, active GLP-1 and total GIP concentrations at 0, 60, 120, and 180 min for the measurement of total ghrelin. Blood samples were collected in BD Vacutainer® EDTA Aprotinin Tube contained K3EDTA (1.6mg per ml blood) and Aprotinin protease inhibitor (50KIU per ml blood) and immediately centrifuged at +4 °C and 3000 rpm. Plasma samples were stored at –80 °C and rigorously kept at +4 °C during assay. The collection of blood samples with EDTA/Aprotinin under cooled conditions was appropriate to maintain GLP-1 and ghrelin stability as described by Di Marino et al. [8] and Tvarijonaviciute et al. [9].

Operative techniques

All operations were performed laparoscopically by the same surgery team, as previously described [10]. There were no major intra-operative complications or conversions to laparotomy.

Analytical procedures

Plasma glucose concentration was measured by the glucose oxidase method. Plasma insulin and C-peptide were determined by ELISA. Plasma lipids were measured by Roche Cobas analyzer using a colorimetric assay. HbA1c was measured by high-performance liquid chromatography [Diamat HPLC, Bio-Rad Laboratories (Canada) Ltd., Mississauga, Canada] [11].

Active GLP-1 was assayed by a nonradioactive, highly specific sandwich ELISA method (Merck-Millipore, Darmstadt, Germany) with 100% cross-reactivity with 7–36 amide and 7–37 glycine-extended, but no reactivity with 9–36 amide and 9–37 glycine-extended GLP-1 isoforms, GLP-2 or glucagon. Total GIP was assayed by a nonradioactive highly specific sandwich ELISA method with (Merck-Millipore, Darmstadt, Germany) 100% cross reactivity to human GIP (1–42) and GIP (3–42). Human total ghrelin (both intact and des-octanoyl forms) was assayed by a nonradioactive, highly specific sandwich ELISA method (Merck-Millipore, Darmstadt, Germany) with 100% cross-reactivity with des-octanoyl human ghrelin, 80% human ghrelin (active), and 70% canine ghrelin (active). The intra- and inter-assay coefficient of variation for the GLP-1 assay was $<5\%$ and for GIP and ghrelin assays was $<10\%$.

Measurements

Weight loss was expressed as % change in BMI and as percent excess weight loss (%EWL) calculated by the following formula: $(\text{preoperative weight} - \text{current weight}) / (\text{preoperative weight} - \text{ideal weight}) \times 100$ [12]. Insulin sensitivity and insulin secretion indexes were derived from glucose, insulin, and C-peptide values measured every 30 min for 3 h during the OGTT. Insulin sensitivity was assessed as the oral glucose insulin sensitivity (OGIS), which has been validated vs. the hyperinsulinemic euglycemic clamp demonstrating a good correlation between the 2 measurements of insulin sensitivity [13]. Insulin secretion as total amount of the hormone released by the beta cells (ISR) was calculated from C-peptide with the deconvolution method [14]. Beta-cell function, which reflects the release of the hormone normalized to the glycemic stimulus, was assessed as “early” ($IGI_{30} = \text{ratio between incremental C-peptide concentration and incremental glucose concentration at 30 min}$) and “total” insulino-genic index ($IGI_{\text{total}} = \text{AUC}_{\text{Cpeptide}} / \text{AUC}_{\text{Glucose}}$). The interplay between insulin sensitivity and secretion, that describes the beta-cell adaptive response to changes of insulin sensitivity, was determined by the product $OGIS \times \text{AUC}_{\text{Cpeptide}}$ (adaptation index, AI) [15].

Table 1 Clinical and metabolic characteristics of participants before and one year after surgery.

	RYGB (n = 14)			VSG (n = 19)			RYGB vs. VSG
	Presurgery	One year	p-Value baseline vs. one year	Presurgery	One year	p-Value baseline vs. one year	p-Value at one year
Age (years)	49 ± 7	–	–	44 ± 10	–	–	–
Sex (M/F)	6/8	–	–	8/11	–	–	–
Weight (kg)	116 ± 20	78 ± 8	0.000	130 ± 29	90 ± 17	0.000	0.022
BMI (kg/m ²)	42 ± 6	28 ± 2	0.000	46 ± 9	32 ± 5	0.000	0.009
EWL (%)	–	78 ± 15	–	–	70 ± 23	–	0.259
ΔBMI (%)	–	–32 ± 10	–	–	–30 ± 7	–	0.546
T2DM duration (years)	5 ± 5	–	–	4 ± 4	–	–	–
Glucose (mg/dl)	166 ± 63	76 ± 8	0.000	140 ± 46	87 ± 18	0.006	0.184
HbA1c (mmol/mol)	65 ± 1	39 ± 0.1	0.003	60 ± 0.8	38 ± 0.1	0.004	0.759
Total cholesterol (mg/dl)	202 ± 26	167 ± 38	0.010	207 ± 57	211 ± 49	0.740	0.010
HDL-cholesterol (mg/dl)	44 ± 8	51 ± 10	0.009	44 ± 10	59 ± 16	0.004	0.089
LDL-cholesterol (mg/dl)	120 ± 25	91 ± 32	0.044	127 ± 48	136 ± 44	0.389	0.013
Triglycerides (mg/dl)	195 ± 76	114 ± 78	0.002	220 ± 120	101 ± 27	0.002	0.474
Therapy							
Diet alone (%)	2 (14)	13 (93)	0.017	2 (11)	17 (90)	0.003	0.800
OAD users n (%)	9 (64)	1 (7)	0.026	15 (79)	2 (10)	0.007	0.887
OAD + insulin users n (%)	3 (21)	0 (0)	0.098	2 (10)	0 (0)	0.167	0.809
Antihypertensive drug users n (%)	9 (64)	3 (21)	0.142	14 (74)	2 (10)	0.009	0.392
Hypolipidemic drug users n (%)	5 (36)	1 (7)	0.135	3 (16)	2 (10)	0.674	0.387

Data are expressed as means (± SD); RYGB: Gastric bypass; VSG: Vertical sleeve gastrectomy; BMI: Body mass index; EWL: Excess weight loss; T2DM: Type 2 diabetes mellitus; OAD: Oral antidiabetic drugs; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; HbA1c: Hemoglobin A1c

Estimation of insulin secretion was based on plasma C-peptide concentrations (prehepatic) to circumvent possible changes in insulin clearance after surgery, which may influence peripheral insulin concentrations. The hormonal responses to the mixed meal were evaluated as the incremental area under the curves (IAUC) for 3 h, calculated with the trapezoidal rule. IAUC was obtained by subtracting the basal area from the total AUC. The response of GLP-1 was also assessed as maximal increase (peak) during MMT. Partial T2DM remission was defined as HbA1c < 47.5 mmol/mol and fasting glucose < 125 mg/dl in the absence of antidiabetic medications. Complete remission was defined as a HbA1c < 42.1 mmol/mol and fasting glucose < 100 mg/dl in the absence of antidiabetic medications.

Statistical analysis

All statistical analyses were performed using the statistical software package, SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation. Group comparisons were performed by the χ^2 test for categorical variables, the Wilcoxon test or the Mann-Whitney test. Time course effect of glucose and hormones was analyzed by general linear model (GLM) for repeated-measures with the aim of testing whether the changes in hormone levels between pre- and post-surgery differed among types of surgery at each time point of MMT (treatment × visit × min). GLM included weight loss as covariate. The association between changes after surgery was assessed by Spearman's correlation analysis. To analyze the role of factors associated with remission of diabetes, we compared the features of remitters and nonremitters. A logistic regression analysis was performed using remission as dependent variable and the factors significantly associated with remission as covariate. A p-value < 0.05 was considered statistically significant.

Results



Weight loss and metabolic control

Table 1 provides the main clinical and metabolic characteristics of participants before and one year after surgery. Age, BMI, duration of diabetes, glucose control, and lipid profile at baseline were similar between RYGB and VSG groups. At one-year, weight loss expressed as percent change in BMI was $-32 \pm 10\%$ after RYGB and $-30 \pm 7\%$ after VSG ($p = 0.546$). Likewise, excess weight loss (EWL%) was similar after the 2 interventions (78 ± 15 and $70 \pm 23\%$, $p = 0.146$). Glycemic control improved similarly in the 2 groups with a mean HbA1c reduction of 18–26 mmol/mol from baseline values. Fasting triglycerides levels fell markedly after both procedures; plasma total and LDL-cholesterol decreased after RYGB whereas they remained substantially unchanged after VSG (Table 1). The remission of diabetes (partial plus total) was achieved in 14 VSG patients (74%) and in 12 RYGB patients (86%) ($p = 0.28$). Antihypertensive medications were discontinued in all except 3 patients of the RYGB group and in 2 patients of the VSG group. Four patients of the RYGB group and one patient of the VSG group discontinued hypolipidemic treatment.

Insulin secretion and insulin sensitivity (OGTT)

Total insulin secretion (ISR) did not change, while beta-cell function improved to a similar extent one year after surgery ($IGI_{30} = 0.5 \pm 0.2$ and 0.4 ± 0.2 nmol/l/mg/dl and $IGI_{180} = 1603 \pm 1577$ and 1059 ± 952 nmol/l/mg/dl for RYGB and VSG, respectively) (Table 2). Insulin sensitivity (OGIS) was similar in the 2 groups, preoperatively and markedly improved after either procedures ($p < 0.001$ for both). Adaptation index (AI) increased to a similar extent after surgery with no difference between RYGB and VSG.

Glucose and hormone profile (MMT)

IAUC_{Glucose} decreased while IAUC_{Insulin} increased after surgery with no difference between interventions (Fig. 1).

Table 2 Insulin sensitivity and insulin secretion, and glucose and hormonal response to MMT before and one year after surgery.

	RYGB (n = 14)			VSG (n = 19)			RYGB vs. VSG pΔ
	Presurgery	One year	Δ	Presurgery	One year	Δ	
OGTT							
IGI 30 min (nmol/l/mg/dl)	0.2±0.1	0.5±0.2 **	0.3±0.2	0.2±0.02	0.4±0.2 *	0.2±0.2	0.406
IGI 180 min (nmol/l/mg/dl)	324±111	1603±1577 *	1279±439	281±190	1059±952 *	778±998	0.424
ISR (nmol/m ²)	65±21	58±18	-7±16	57±21	54±20	-3±21	0.681
OGIS (ml min ⁻¹ m ⁻²)	287±90	549±82 **	262±88	302±49	500±86 **	198±93	0.177
Adaptation index	0.5±0.2	0.7±0.3 *	0.2±0.2	0.4±0.2	0.7±0.3 *	0.3±0.3	0.390
MMT							
Fasting glucose (mg/dl)	173±50	96±13 **	-76±50	151±46	104±18 **	-47±39	0.080
IAUC glucose (mg/dl·180')	6246±5186	3016±3047	-3230±5710	8681±6678	3048±3490 **	-5633±4999	0.227
Fasting insulin (μU/ml)	30±18	11±4 *	-19±17	28±16	17±6 *	-11±17	0.203
IAUC insulin (μU/ml·180')	4313±2759	5118±2076	805±2808	7019±4343	5250±2866 *	-1769±2959	0.017
Fasting GLP-1 (pmol/l)	4.7±4.5	4.5±3.7	-0.2±5.1	3.1±1.8	3.9±2.9	0.8±3.2	0.579
IAUC GLP-1 (pmol/l·180')	27±130	2119±1200 **	2092±1266	85±142	235±278	150±319	0.000
GLP-1 30-min peak (pmol/l)	7±6	47±22 **	40±21	4±1	10±7 *	6±7	0.000
Fasting GIP (pg/ml)	108±130	42±19 *	-66±128	93±72	53±30 *	-40±54	0.501
IAUC GIP (pg/ml·180')	25344±15169	13234±4713 **	-12110±15733	34132±11527	21871±5619 *	-12261±9057	0.977
Fasting ghrelin (pg/ml)	391±264	443±169	52±290	457±262	200±41	-257±250	0.013
Ghrelin nadir (pg/ml)	309±72	278±38	31±75	334±64	167±12 *	167±61	0.035

Data are expressed as means (±SD); OGTT: Oral glucose tolerance test; MMT: Mixed meal test; RYGB: Gastric bypass; VSG: Vertical sleeve gastrectomy; OGIS: Oral glucose insulin sensitivity; ISR: Insulin secretion rate; IGI: Insulinogenic index; AI: Adaptation index

*p<0.05, **p<0.001 vs. presurgery

Meal-stimulated GLP-1 concentrations were flat in all patients preoperatively. Following RYGB, both GLP-1 peak and IAUC increased markedly (p=0.001), while after VSG, the release of GLP-1, although increased compared to presurgery, was much lower than in patients operated of RYGB (p=0.0001). Meal GIP response after surgery decreased by 50% (p=0.001 after RYGB and p=0.05 after VSG) with no difference between interventions. Neither fasting nor nadir ghrelin during MMT changed after RYGB; in contrast, a marked suppression in both variables occurred after VSG with a significant difference between the 2 intervention (p=0.013 for fasting ghrelin and p=0.035 for nadir ghrelin concentrations) (◻ Fig. 1 and ◻ Table 2).

The increase in insulin sensitivity and beta-cell function was correlated with weight loss (R=0.425, p=0.014 and R=0.461, p=0.035, respectively) (◻ Fig. 2) while no association was found with GI hormone concentrations.

Discussion and Conclusion

In this study, we evaluated glucose homeostasis and the profile of GI hormones in severely obese patients with T2DM before and one year following either RYGB or VSG – 2 of the most frequently performed bariatric procedures – to gain insight into the physiological mechanisms behind weight loss and remission of T2DM. The 2 interventions resulted to be equally effective in terms of weight loss and improvement of glycemic control, with a similar rate of T2DM remission at 1 year (76% after VSG and 86% after RYGB). Actually, the 2 major determinants of glucose homeostasis, that is, beta-cell function and insulin sensitivity, improved to a similar extent after either procedures. Interestingly, total insulin secretion remained unchanged while beta-cell function increased significantly after surgery, indicating an amelioration of the pancreatic glucose sensitivity, since a similar secretion occurs with much lower blood glucose.

These results are in agreement with those of Keidar A et al. [16] and Nannipieri et al. [17] but differ from those of Kashyap et al.

[18], Lee et al. [19] and Schauer et al. [20] who demonstrated that RYGB is more effective than VSG in terms of metabolic improvement. Differences in the degree of weight loss achieved with the 2 procedures, study population, length of follow-up and experimental methods to assess metabolic functions may contribute to these variable results. A distinct GI hormonal pattern followed the 2 procedures. After RYGB, we found a marked increase in meal-induced GLP-1 response, a significant reduction in post-meal GIP and ghrelin response. Increased GLP-1 levels are well documented after RYGB, due to the accelerated nutrient entry into the small intestine [3, 4]. Data regarding GIP are more inconsistent, with some studies reporting an increased postprandial GIP level early after RYGB [21] and others no change [22] or even an early decline in fasting GIP levels in diabetic but not in nondiabetic patients [23]. This discrepancy may be due to differences in analytical methods to measure GIP (total vs. active form), the characteristics of the population studied (diabetics vs. nondiabetic), the length of the limbs of the Roux anastomosis and the duration of the follow-up.

Following VSG, a marked suppression of both fasting and post-meal ghrelin levels occurred as a consequence of gastric fundus removal; GLP-1 concentration increased although to a much lower extent than RYGB while GIP levels decreased by 50%. The finding that RYGB and VSG are equally effective on weight loss and metabolic improvement in the face of a different pattern of GI hormone profile, lead us to hypothesize that the changes in gut hormones are not the main determinant of the metabolic improvement, at least several months after surgery. However, since our evaluations were performed one year after surgery we cannot rule out that the changes in GI hormonal profile may have contributed to diabetes remission early after surgery. This hypothesis is in line with a recently published commentary, which underlined that the mechanisms behind the remission of diabetes after VSG or RYGB may differ in relation to the time at which they are studied. Early after surgery, the improvement of glycemic control is due to increased hepatic insulin sensitivity and to the improved beta-cell function conse-

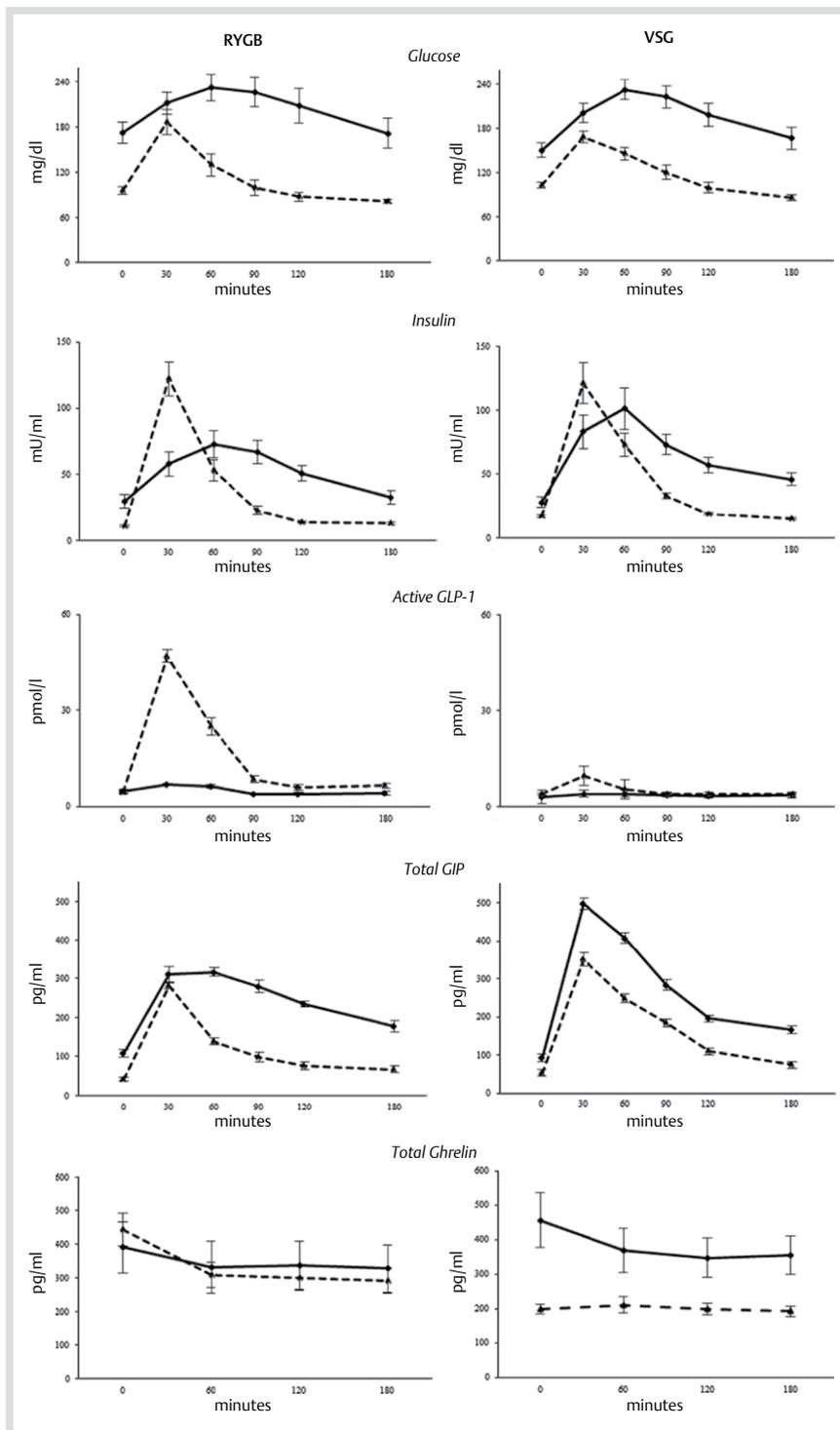


Fig. 1 Glucose, insulin, GLP-1, GIP, and ghrelin response to a mixed meal in RYGB and VSG subjects before (continuous line) and one year (dotted line) after surgery: Data are expressed as means (\pm SEM). GLM for repeated measures showed a significant meal effect for GLP-1 ($p < 0.001$). RYGB: Gastric bypass; VSG: Vertical sleeve gastrectomy; GLP-1: Glucagone-like peptide-1; GIP: Glucose-dependent insulintropic peptide.

quent to the exaggerated postprandial GLP-1 secretion. Later on, with progressive weight loss the improvement in peripheral insulin sensitivity becomes the prevalent mechanism [24]. On the other hand, a number of mechanisms have been highlighted which may contribute to the improvement of glucose tolerance after BS, including neural activation [25], modifications of intestinal microbiota [26], and changes in the expression of genes regulating glucose and fatty-acid metabolism induced by low nutrient availability [27].

A significant reduction in fasting triglycerides occurred in our patients after either procedure, as reported in previous studies [10,28,29], whereas total and LDL-cholesterol decreased after

RYGB but not VSG. This finding is in line with recent studies demonstrating that bariatric procedures differentially affect cholesterol metabolism with malabsorptive procedures (biliointestinal bypass) providing a much greater reduction than restrictive surgery independent of weight loss and insulin resistance [30].

A weakness of this study might be the lack of patient randomization to the 2 types of operations. However, since the 2 procedures differ in terms of unwanted effects and frequency of monitoring during follow-up, the patient's preference should not be ignored. Noteworthy is the fact that the 2 groups were comparable for anthropometric and biochemical measures, as

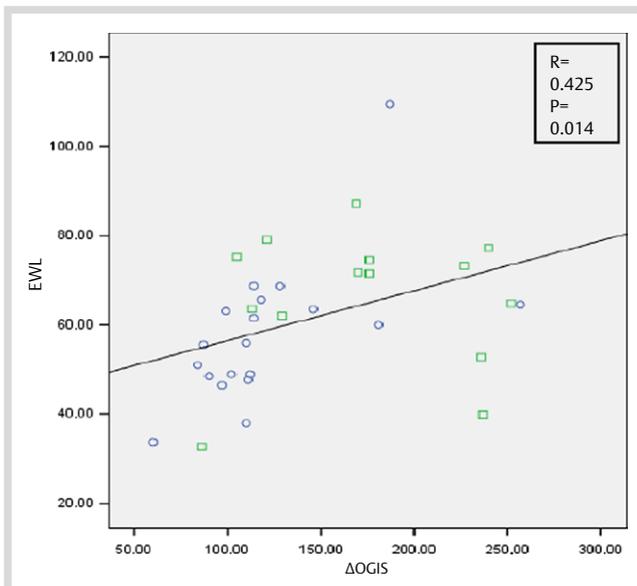


Fig. 2 Correlation between excess weight loss (EWL) and changes of insulin sensitivity (OGIS) in SG (circle) and RYGB (square) subjects. (Color figure available online only).

well as for medication use, thus minimizing the possibility of selection bias.

In conclusion, RYGB and VSG exert similar beneficial effects in terms of weight loss and remission of T2DM in the face of remarkable differences in GI hormone profile. These findings highlight the importance of weight loss and challenge a primary role of incretins in mediating the metabolic improvement achieved in obese patients with T2DM one year after VSG or RYGB.

Conflict of Interest

The authors declare no conflict of interest.

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