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IMPROVED INSULIN SENSITIVITY AFTER GASTRIC BYPASS CORRELATES WITH DECREASED TOTAL BODY FAT, BUT NOT WITH CHANGES IN FREE FATTY ACIDS

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Abstract

Background—Increased plasma free fatty acids (FFA) are considered one of the key elements in the pathogenesis of insulin resistance (IR) and type 2 diabetes (T2DM). We hypothesize that, in diabetic patients undergoing laparoscopic Roux-en-Y gastric bypass (LRYGB), a postoperative decrease in FFA will correlate with improved insulin sensitivity (Si).

Methods—30 obese (body mass index > 35 kg/m²) patients with a diagnosis of T2DM were studied preoperatively and 12 months after LRYGB in a prospective cohort study. Collected data included intravenous glucose tolerance test (IVGTT), total body composition by DEXA and plasma levels of FFA. Insulin sensitivity analysis from the IVGTT was estimated from minimal model analysis. Pre- and postoperative variables were compared using a paired sample t-test. Relationships between changes in variables were determined with Pearson's correlation test.

Results—Twelve months after LRYGB the study population showed a significant decrease in body mass index (BMI) ($P = 0.001$), FFA ($P = 0.03$), and total body fat ($P = 0.03$), with an increase in Si ($P = 0.001$). Postoperative changes in Si significantly correlated (Pearson's $r = -0.53$, $P = 0.01$) with change in total body fat, but not with changes in plasma FFA (Pearson's $r = -0.22$, $P = 0.31$).

Conclusions—Our study challenges the notion that IR is mediated to a significant degree by changes in plasma FFA concentration. Instead, changes in adiposity and consequently changes in adipokines release can be the key players in determining remission of T2DM after RYGB.

Keywords

Bariatric surgery; Laparoscopic Roux-en-Y gastric bypass; Free Fatty Acid; Insulin sensitivity; Insulin Resistance; Total body fat; adiposity

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INTRODUCTION

Obesity often causes IR and has been shown to influence the severity of IR in type 2 diabetes (T2DM)¹⁻³. Levels of plasma free fatty acids (FFA) are considered one of the key elements in the obesity-related pathogenesis of IR and T2DM⁴. Several studies have shown that increased FFA levels were associated with increased levels of IR in obese individuals, although the interpretation of the causal relationship between these two variables is still debated. For some authors, the increased FFA levels, seen in obese individuals is due to increases in FFA release⁵ and decreases in FFA clearance⁶. Increased concentrations of FFA has been proven to induce IR through several mechanisms: reduced glucose transport in skeletal muscle⁷, increased hepatic glucose production⁵, inhibition of the insulin receptor substrate-1 signaling pathway^{8,9} and activation of the proinflammatory nuclear factor- κ B pathway¹⁰ in insulin-responsive peripheral tissues. On the other hand, for other authors, the increased FFA levels could be the consequence of excessive lipolysis and lipoprotein lipase activity, secondary to the adipose tissue IR and hyperinsulinemia seen in obese individuals^{11,12}.

It has been demonstrated that bariatric surgery can achieve excellent long-term weight loss and improve obesity-related comorbidities, quality of life, and survival¹³⁻¹⁵. Two large nonblinded, randomized, clinical trials comparing laparoscopic Roux-en-Y gastric bypass (LRYGB) with medical therapy for the treatment of diabetes, showed that bariatric surgery resulted in better glucose control, with rates of hyperinsulinemia and the homeostasis model assessment-estimated insulin resistance index markedly improved as compared with medical therapy alone^{16,17}. Recently, gastric bypass has been shown to increase both Si and pancreatic beta-cell function, whereas, despite comparable weight loss, sleeve gastrectomy has been shown only partially restore the Si with no improvement in the pancreatic beta-cell function¹⁸. Insulin sensitivity improves within days after gastric bypass surgery, likely secondary to reduced stimulation of the entero-insular axis by caloric restriction^{19, 20}. However, the mechanisms responsible for the long term improved Si with resolution of T2DM after gastric bypass are still not well understood, but the preferential loss of fat is considered to play a key role²⁰.

Patients undergoing bariatric surgery have been also shown to have decreased FFA levels one-year after operation^{21,22}. Therefore, it could be hypothesized that the decreased FFA levels after bariatric surgery may play a role in mediating the improved Si with resolution of T2DM through insulin receptor signaling pathways.

The aim of our study is to determine if a postoperative decrease in FFA correlates with the improved Si seen in T2DM patients undergoing LRYGB.

MATERIAL AND METHODS

Study design and Data collection

A prospective cohort study was designed. We studied 30 morbidly obese (body mass index [BMI] > 35 kg/m²) patients with a diagnosis of T2DM preoperatively and 12 months after LRYGB as previously described²³. Inclusion criteria included clinical diagnosis of T2DM

diabetes mellitus according to the American Diabetes Association criteria²⁴ with HbA1c • 10.0%, BMI • 35 kg/m² in accord with the 1991 NIH obesity surgery consensus conference criteria and stable weight for the previous 3 months²⁵, and age between 18 and 60 years. Exclusion criteria were history of cardiovascular heart disease, malignancy, uncontrolled hypertension, previous esophageal, gastric, pancreatic, small bowel, or large bowel surgery, tobacco use, or significant psychiatric disorder.

Collected data included weight, height, 3 hours frequently sampled intravenous glucose tolerance test (IVGTT), body composition by dual-energy X-ray absorptiometry (DEXA) and plasma levels of FFA. BMI was calculated as weight (kilograms) divided by height (square meters). DEXA was used to study the body composition and total fat and lean mass were measured. We used the minimal model analysis of Bergman to estimate the Si from the 3 hours frequently sampled intravenous glucose tolerance test²⁶. FFA were assayed by an enzymatic colorimetric method.

The LRYGB procedure was performed using a laparoscopic five/six port technique. We transected the jejunum at 50 cm distal to the ligament of Treitz and performed a stapled side-to-side jejunojejunostomy anastomosis, creating a 100 cm Roux limb. Then, we created a 15-ml proximal gastric pouch, and performed an ante-colic, retro-gastric Roux-en-Y gastrojejunostomy with linear stapler technique.

Statistical analysis

Patient's characteristics were summarized using mean \pm SD. Pre- and postoperative variables were analyzed by two-sides paired sample Student t test. Pearson's correlation test was used to determine the association between changes in variables. The SPSS statistical software program (version 20) was used for all analyses. P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

The study's cohort included 30 type 2 diabetic patients (20 female) underwent LRYGB. Mean age was 48 ± 8 years. As shown in Table 1, preoperative BMI was 43.4 ± 4.3 kg/m² and mean BMI at 12 months was 31.2 ± 4.6 kg/m². Using a paired T test, twelve months after LRYGB the study population showed a significant decrease in BMI (P = 0.001), FFA (P = 0.03), and total body fat (P = 0.03). As shown in Figure 1, there was a statistically significant increase in Si (P = 0.001) one-year after LRYGB.

As shown in Table 1, postoperative changes in Si significantly correlated (Pearson's $r = -0.53$, $P=0.01$) with change in total body fat, but not with changes in plasma FFA (Pearson's $r = -0.22$, $P= 0.31$).

DISCUSSION

We have demonstrated that patients with type 2 diabetic patients have a significant decrease in BMI, FFA and total fat mass and a significant increase in Si twelve months after LRYGB. We also have found a correlation between the increased Si and the decrease in total body fat

measured by DEXA one-year after LRYGB. However, interestingly and according to the fact that levels of FFA do not mediate the association between adiposity and Si²⁷, we have found that one-year after LRYGB there is no correlation between the increased Si and the decrease in FFA.

At present, we did not find in the literature any studies reporting the relationship between the decreased FFA levels and the improved Si in the long term after LRYGB.

As pointed out by Miller et al.²⁷, in spite of the fact that FFA have been shown to be associated both with measures of adiposity (BMI, visceral adipose tissue [VAT], and subcutaneous adipose tissue [SAT]) and with Si, this association is not mediated through FFA. They found that adiposity measures explained only approximately 1% of the variance in FFA, arguing that adiposity is not a strong predictor of FFA in our population and that therefore we should not expect circulating levels of FFA to mediate the relationship between adiposity and Si. Moreover, they underlined how levels of obesity may not strongly correlate with levels of circulating FFA due to the influence of several other factors, such as physical activity, dietary intake, overall FFA trafficking and metabolism. Miller et al.²⁷ did not find that increasing levels of FFA mediated the relationship between obesity and increased levels of adiposity and Si, despite demonstrating a very strong association between adiposity and Si. Likewise, we didn't find a correlation between the increased Si and the decrease in FFA after LRYGB, despite demonstrating a correlation between the increased Si and the decrease in total body fat after LRYGB. These results challenge the notion that the decreased levels of FFA after LRYGB mediate the improvement of IR and the resolution of T2DM after LRYGB and indicate that other factors might play a more significant role in the relationship between obesity and Si (i.e. changes in adiposity and changes in gut-hormones).

We have found a significant correlation between the increased Si and the decrease in total body fat measured by DEXA one-year after LRYGB. This correlation underlines the crucial role played by the fat tissue in both the pathogenesis of the obesity-related IR and its resolution after LRYGB, and justifies the relatively recent concept of fat tissue as an endocrine organ²⁸. A correlation between the changes in fat mass and the IR one-year after bariatric surgery had already been pointed out²⁹. Different fat depots have different effects on reducing Si, with intra-abdominal fat having a greater impact than peripheral fat^{30,31}, and with visceral abdominal fat having a greater impact than subcutaneous fat^{32,33}. Kelley et al.³³ suggested that plasma FFA levels might be a link mediating the relationship between VAT and skeletal muscle IR in obesity. In this scenario, an increased local production of FFA by VAT would mediate the IR seen in obese individuals: VAT has a high rate of basal lipolysis and respond poorly to lipolysis restraining insulin, resulting in inappropriately high delivery of FFA to the portal circulation that will lead to peripheral IR and beta-cell dysfunction³⁴. As mentioned early, Miller et al.²⁷ did not find that increasing levels of FFA mediate the association between increased levels of adiposity and Si. However, they found that FFA interact with VAT (but not with SAT) to influence levels of Si. They showed that in individuals with lower VAT, those with low FFA levels had improved levels of Si relative to those with high FFA levels. Therefore, Miller et al.²⁷ added another step in our understanding of the role played by FFA in mediating IR in obesity. VAT has been proven to be more insulin resistant than SAT³⁵, such that levels of FFA do not additionally impact

IR. Instead, in individuals with low VAT levels, increased FFA levels may additionally contribute to IR through the above-mentioned mechanisms of lipotoxicity. Unfortunately, we didn't include in our study-design a CT scan for differentiating between intra-abdominal fat (VAT and SAT) and peripheral fat. We could have divided our obese patients in those with high VAT and those with low VAT and we could have looked for the presence of a correlation between the decreased FFA levels and the increased Si in the first group after LRYGB.

Other limitations of our study were that we didn't collect data showing the duration of the diabetes prior the enrollment and that we did not perform an insulin suppression test in our obese patients in order to quantify the insulin resistance. It has been demonstrated that circulating plasma FFA levels in obese individuals are not a simple reflection of adiposity, but vary considerably as a function of whether the obese individuals are insulin resistant or insulin sensitive¹². Studying metabolic changes in obese individuals after sibutramine-assisted weight loss, McLaughlin et al.¹² showed that despite comparable decreases in FFA levels with weight loss in both insulin resistant or insulin sensitive groups, the insulin response fell significantly in association with weight loss only in the insulin resistant group. Based on this observation, if we had found a positive correlation between the decreased FFA levels and the increased Si in the insulin sensitive group after LRYGB, we could have speculated that, at least in insulin sensitive obese individuals, decreased FFA levels after LRYGB play a role in the improvement of Si and T2DM resolution after LRYGB.

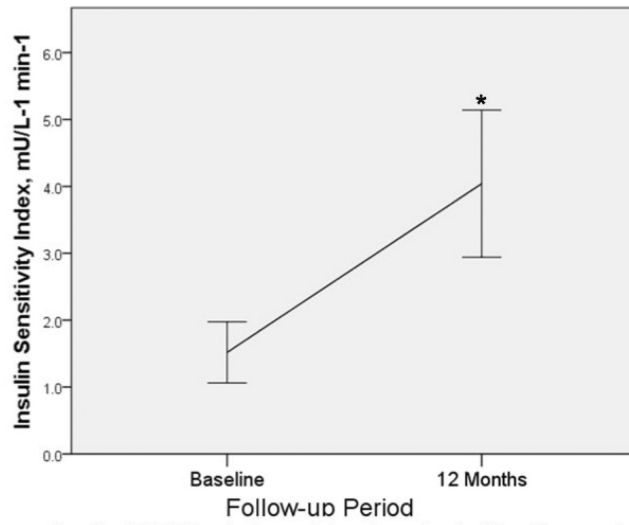
In conclusion, our study has demonstrated that one-year after LRYGB there is a correlation between the increased Si and the decrease in total body fat measured by DEXA and that there is no correlation between the increased Si and the decrease in FFA levels. Since we did not divide our obese population based on high/low levels of VAT or based on their response to an insulin suppression test, our findings do not imply that a decrease in FFA level after LRYGB are without a role in mediating the improvement of Si and the resolution of T2DM one-year after LRYGB. However, these data suggest that other factors produced by AT, such as adipokines, might play an important role in mediating obesity-related IR. Therefore, we believe that changes in adiposity, and consequently changes in adipokines, such as proinflammatory cytokines, leptin, adiponectin and resistin, are likely the key players in determining remission of IR and type 2 diabetes after LRYGB. Studying the profile of these adipokines after LRYGB was beyond the purpose of our study and further studies in this area are necessary.

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* Twelve months after RYGB the study population showed a significant increase in insulin sensitivity ($P < 0.05$).

Fig. 1.
Change in insulin sensitivity after LRYGB

Table 1

Change in Postoperative Variables Correlated to Insulin Sensitivity.

	Paired T-test			Correlation to Insulin Sensitivity
	Preoperative	12 Months Follow-up	P	
Body Mass Index	43.4±4.3	31.2±4.6	P = 0.001	P = 0.12
Total Fat (Kg)	66.7 ±82.1	27.0 ±46.2	P = 0.03	P = 0.01
Free Fatty Acids (µmol/L)	765±251	611±197	P = 0.03	P = 0.31

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