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Original article

Postprandial hypertriglyceridemia predicts improvement in insulin resistance in obese patients after bariatric surgery

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Abstract

Background: Morbidly obese patients have associated diseases, such as diabetes, hypertension, hyperlipidemia, and cardiovascular disease. Bariatric surgery improves these obesity-related comorbidities, including insulin resistance. Evidence has shown that patients with morbid obesity have postprandial hypertriglyceridemia (HTG) and that this type of HTG is related to the degree of insulin resistance. Also, bariatric surgery produces a dramatic reduction in triglyceride levels. However, it is unknown whether patients with postprandial HTG have a different clinical evolution after bariatric surgery. The setting of our study was a university hospital.

Methods: We studied 57 morbidly obese patients who had mild or severe postprandial HTG after fat overload (<30 mg/dL or >90 mg/dL increase in triglycerides, respectively). All the patients underwent bariatric surgery. After surgery, the anthropometric and biochemical variables and the Homeostasis Model Assessment of Insulin Resistance were measured for 1 year at 0, 15, 30, 45, 90, 180, and 365 days after surgery.

Results: The patients with more severe postprandial HTG had a greater percentage of change in the Homeostasis Model Assessment of Insulin Resistance at 30, 90, and 180 days after surgery than the patients with less severe postprandial HTG. Multiple regression analysis showed that the postprandial triglyceride levels predict the variation in the Homeostasis Model Assessment of Insulin Resistance index, more so than did traditional variables, such as anthropometric, inflammatory, or hormonal data.

Conclusion: The postprandial HTG level might be the best predictor of improved insulin resistance in morbidly obese patients after bariatric surgery. (Surg Obes Relat Dis 2011;xx:xxx.) © 2011 Published by Elsevier Inc. on behalf of American Society for Metabolic and Bariatric Surgery.

Keywords: Bariatric surgery; Morbid obesity; Postprandial hypertriglyceridemia; Insulin resistance

Morbid obesity is an increasingly prevalent health problem. Morbidly obese patients often have associated disorders, including type 2 diabetes, hypertension, obstructive sleep apnea, hyperlipidemia, coronary heart disease, and congestive heart failure.

One possible treatment of morbid obesity is bariatric surgery. This surgery not only results in a significant weight decrease, but also in metabolic changes, independent of the weight variation. Important evidence exists for the meta-

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bolic effect of this surgery, because it produces a drastic decrease in insulin resistance within the first few days after surgery [1]. However, the mechanisms by which bariatric surgery produces these metabolic changes remain unclear.

Up to 50% of morbidly obese patients undergoing bariatric surgery have documented hyperlipidemia [2]. Individuals with morbid obesity have a high prevalence of the metabolic syndrome, and the metabolic syndrome is associated, not only with greater baseline triglyceride levels, but also with a greater prevalence of postprandial hypertriglyceridemia (HTG) [3]. Postprandial hyperlipidemia is associated more closely than fasting hyperlipidemia with cardiovascular risk [4].

There is a high flow and availability of fatty acids in subjects with obesity and the metabolic syndrome, and this high flow of fatty acids results in ectopic storage in tissues not prepared for it, an effect known as lipotoxicity. This situation produces metabolic intermediaries, such as ceramides, diacylglycerol, inflammatory cytokines, and oxidative stress that interfere with insulin signaling, generating insulin resistance [5]. Weight loss after bariatric surgery has also been shown to improve the lipid profile of patients with hyperlipidemia [6–8].

The postprandial hyperlipidemia experienced by morbidly obese patients is related to the degree of insulin resistance. In addition, bariatric surgery produces a dramatic reduction in triglyceride levels; however, at present, it is unknown whether patients with postprandial hyperlipidemia have a different clinical evolution after bariatric surgery. The aim of the present study was to examine the relationship between the postprandial hyperlipidemia response and insulin resistance evolution in morbidly obese patients after bariatric surgery.

Methods

Subjects and study design

We undertook a 1-year, prospective, follow-up study involving morbidly obese patients undergoing bariatric surgery using biliopancreatic diversion with the Scopinaro procedure [9]. The study included 57 severely morbidly obese persons (24 men and 33 women; body mass index [BMI] 52.83 ± 7.41 kg/m^2). All the patients had been diabetic for >10 years. Data collection was done at 15, 30, 45, 90, 180, and 365 days after surgery. Patients taking lipid-lowering drugs or medication for the treatment of carbohydrate metabolism abnormalities were not included. All the participants gave informed consent, and the ethics and research committee reviewed and approved the study.

High-fat meal

One week before surgery, the subjects underwent a 50-g fat overload with a preparation (patent no. P201030776) after fasting for 12 hours. At baseline and 3 hours after the high-fat meal, blood samples were obtained from the antecubital vein and placed in Vacutainer tubes (BD Vacutainer, London, UK). The preparation of 100 mL contains 50 g fat, of which 30% are saturated, 49% are monounsaturated, and 21% are polyunsaturated. Only water was permitted during the process, and no physical exercise was undertaken [10].

Laboratory measurements

The blood samples were obtained from the antecubital vein and placed in Vacutainer tubes (BD Vacutainer). The serum was separated by centrifugation for 10 minutes at 4000 rpm and immediately 1 aliquot was frozen at −80°C until analysis and another was used to measure the metabolic parameters. The serum glucose, cholesterol, triglyceride, and high-density lipoprotein cholesterol levels were measured in a Dimension AutoAnalyzer (Dade Behring, Deerfield, IL) using enzymatic methods (Randox Laboratories, Crumlin, County Antrim, UK). The low-density lipoprotein cholesterol level was calculated using the Friedewald equation. Insulin was quantified using a radioimmunoassay (BioSource International, Camarillo, CA). Leptin and adiponectin were analyzed using enzyme-linked immunosorbant assay kits (Diagnostic System Laboratories, Webster, TX, and DRG Diagnostics GmbH, Marburg, Germany, respectively). The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was calculated from the fasting insulin and glucose levels using the following equation: HOMA-IR = fasting insulin (μIU/mL) × fasting glucose (mmol/L)/22.5 [11].

Statistical analysis

The results are presented as the mean ± SD. The patients were divided into those with low (<30 mg/dL increase in triglycerides) or high (>90 mg/dL increase in triglycerides) postprandial HTG after fat overload. These values correspond to the postprandial triglyceride differences at the 25th and 75th percentiles. The Student *t* test was used for comparisons between the 2 study groups and the Friedman test for comparisons of related samples during follow-up after surgery. Multiple linear regression analysis was performed to evaluate which variables contributed more to the changes in the insulin resistance rate after bariatric surgery. The values were considered statistically significant when $P < .05$. The analyses were performed using the Statistical Package for Social Sciences, version 15.0 for Windows (SPSS Iberica, Madrid, Spain).

Results

The biologic and anthropometric variables of the 2 study groups are listed in Table 1. No significant differences were found in the study variables, except for the postprandial plasma triglyceride levels, which were greater in the patients with postprandial HTG. This group also had increased very-low-density lipoprotein plasma levels (21.82 ± 11.20 mg/dL versus 31.45 ± 18.70

Table 1
Distribution of biologic variables

Variable	ΔHTG <30 mg/dL	ΔHTG >90 mg/dL
Gender (n)		
Male	10	14
Female	20	13
Waist (cm)	141.75 ± 15.211	141.88 ± 14.177
Hip (cm)*	155.25 ± 13.441	148.44 ± 12.681
BMI (kg/m^2)	54.940 ± 7.428	52.406 ± 7.240
Triglycerides (mg/dL)	165.32 ± 114.92	143.55 ± 82.45
Postprandial triglycerides (mg/dL)*	172.96 ± 118.024	276.47 ± 80.988
HDL cholesterol	42.79 ± 8.304	43.76 ± 10.798
Cholesterol (mg/dL)	194.0 ± 35.46	186.15 ± 32.39
LDL (mg/dL)	128.432 ± 30.84719	113.735 ± 24.89424
VLDL (mg/dL)*	21.819 ± 11.200	31.453 ± 18.70192
Apolipoprotein AI (mg/dL)	155.95 ± 32.147	150.12 ± 19.37
Apolipoprotein B (mg/dL)	103.62 ± 20.836	109.82 ± 26.156
Bilirubin (mg/dL)	.378 ± .1634	.465 ± .2337
Alkaline phosphatase	73.07 ± 25.384	76.44 ± 20.490
Iron (μg/dL)	61.892 ± 26.453	89.60 ± 85.682
Glucose (mg/dL)	111.48 ± 51.125	124.85 ± 46.23
Insulin (μU/mL)	24.65 ± 21.51	22.82 ± 10.95
HOMA-IR	5.982 ± 4.77179	6.956 ± 4.033
HOMA-IS	41.829 ± 42.639	34.120 ± 28.791

ΔHTG = postprandial hypertriglyceridemia increase; BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein; HOMA-IR = Homeostasis Model Assessment of Insulin Resistance; HOMA-IS HOMA of insulin secretion.
* P <.05 indicates significant difference.

mg/dL) and a lower hip circumference than the patients with mild postprandial HTG (155.25 ± 13.44 cm versus 148.44 ± 12.68 cm).

Fig. 1A shows how the insulin resistance index and BMI changed during the follow-up period in the 2 groups. The greatest decrease in the HOMA-IR was found in patients with high postprandial HTG compared with those with less severe postprandial HTG at 30 days (percentage of change 21.06% ± 28.23% versus 46.81% ± 23.81%), 90 days (percentage of change 42.60% ± 25.25% versus 60.88% ± 23.14%), and 180 days (percentage of change 50.48% ± 20.56% versus 68.92% ± 15.94%) after surgery. No significant variations were seen in the rate of change in BMI between the 2 groups of patients with postprandial HTG. However, the hip circumference showed significant differences at 0 (155.25 ± 13.44 cm versus 148.44 ± 12.68 cm), 30 (142.52 ± 16.47 cm versus 136.09 ± 12.65 cm), and 365 (124.96 ± 10.37 cm versus 115.73 ± 13.40 cm) days after surgery (high postprandial HTG versus low postprandial HTG, respectively; Fig. 1B). No significant differences were found between the 2 groups of patients in the lipid variables during the follow-up period (Fig. 2), except for plasma free fatty acids (FFAs) at 180 days after surgery (.470 ± .147 mg/dL versus .356 ± .120 mg/dL; P < .05) and plasma triglyceride levels at 365 days after surgery (111.31 ± 44.33 mg/dL versus 82.25 ± 31.14 mg/dL; P <.05), both of which were higher in those with high postprandial HTG than in those with low postprandial HTG.

No significant differences were seen in the obesity-related hormonal and inflammatory variables measured, including adiponectin, leptin, and C-reactive protein (Fig. 3).

The Friedman analysis showed that had a significant decrease in the variables studied (HOMA-IR, BMI, hip circumference, C-reactive protein, leptin, FFA) and a significant increase in adiponectin and apolipoprotein AI after surgery.

The correlation studies between the baseline variables and the initial HOMA-IR levels detected positive correlations between both baseline and overload triglyceride levels and the HOMA-IR index (Fig. 4). Multiple regression analysis between the baseline variables possibly related to the changes in the HOMA-IR index was performed at 30 days after surgery, because this was the point after surgery showing the greatest change in the HOMA-IR. This analysis

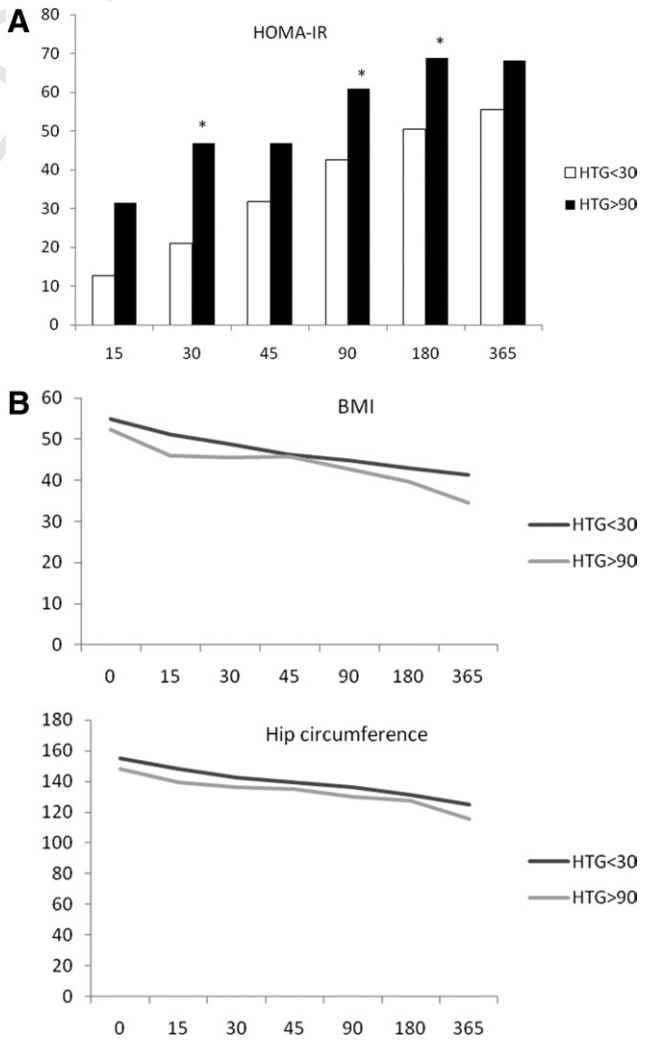

Fig. 1. (A) Percentage of variation in HOMA-IR in both study groups during 1-year follow-up period. (B) Course of anthropometric variables in both study groups during follow-up period.

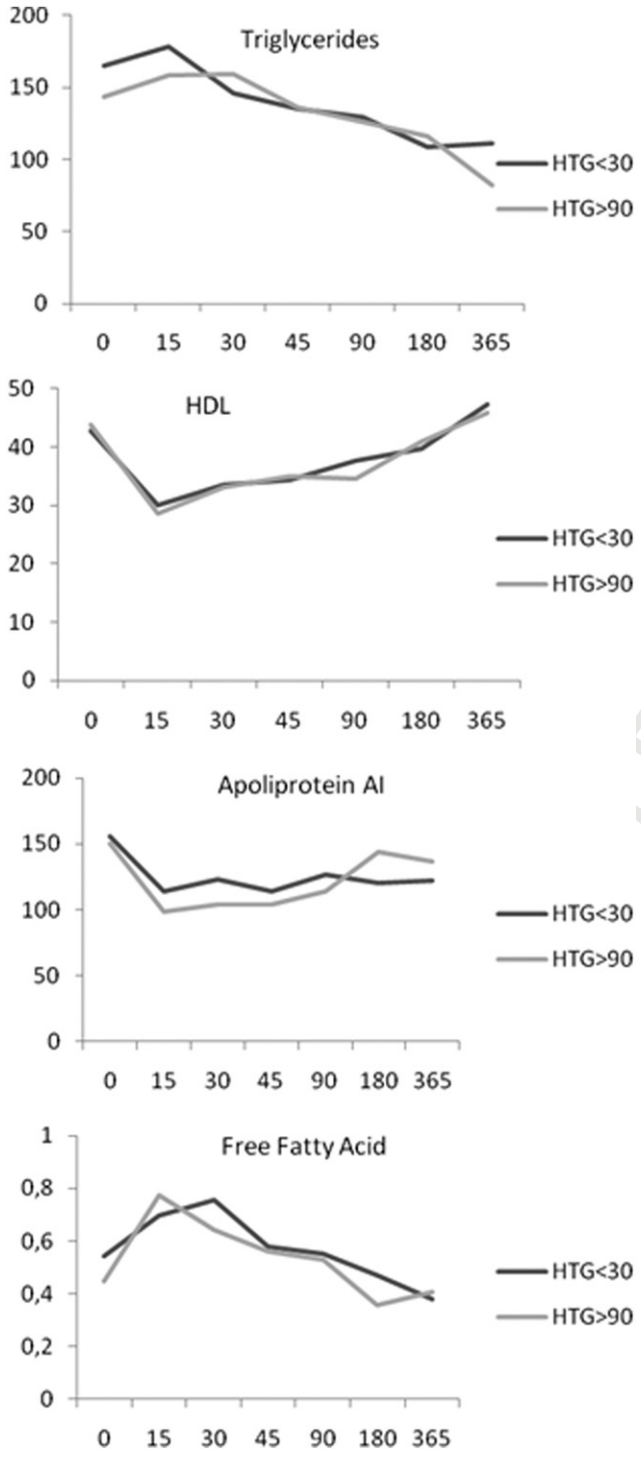

Fig. 2. Course of lipid variables in both study groups during follow-up period.

showed that the only variables predicting the variation in the HOMA-IR index after surgery were the postprandial triglyceride levels and the HOMA-IR index before surgery (Table 2).

Discussion

Insulin resistance in morbidly obese patients improved to a greater extent after bariatric surgery in those patients with more severe postprandial HTG than in those with mild postprandial HTG. Multiple linear regression analysis has irrefutably demonstrated that postprandial triglyceride levels predict the change in the degree of insulin resistance in patients undergoing bariatric surgery.

Malabsorptive surgery improves the lipid profile of patients undergoing bariatric surgery at the expense of the poorer absorption of fats. Nguyen et al. [8] observed an immediate reduction in plasma triglyceride levels 1 month postoperatively, compared with baseline levels, with a 63% reduction in the triglyceride levels at 12 months postoperatively. Brolin et al. [12] also reported that by 6 months

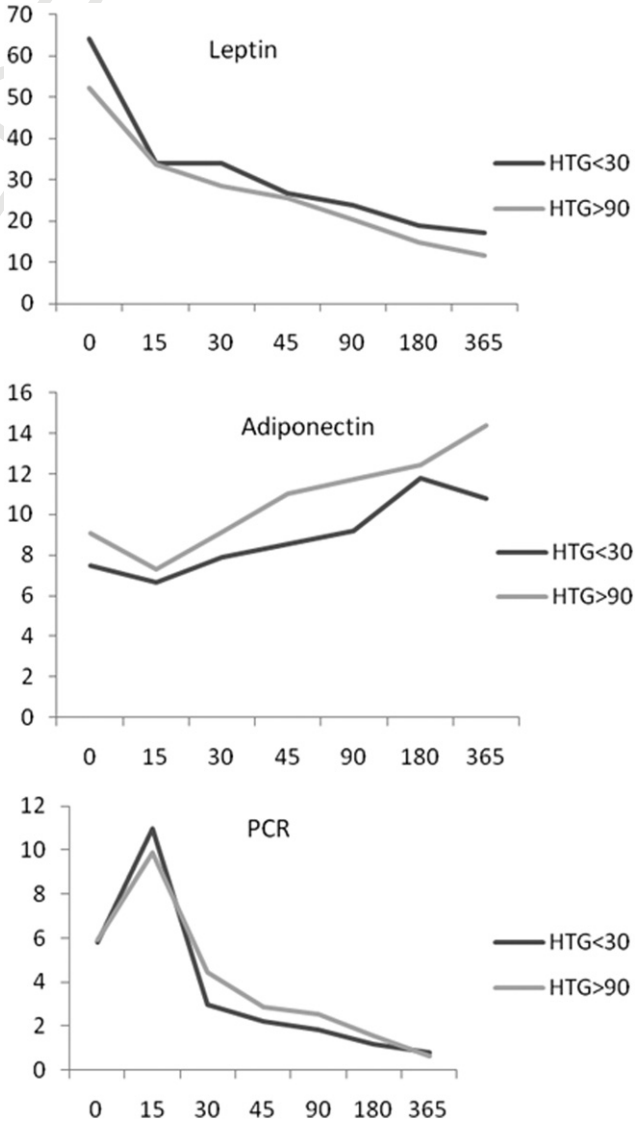

Fig. 3. Course of hormonal levels and inflammatory markers in both study groups.

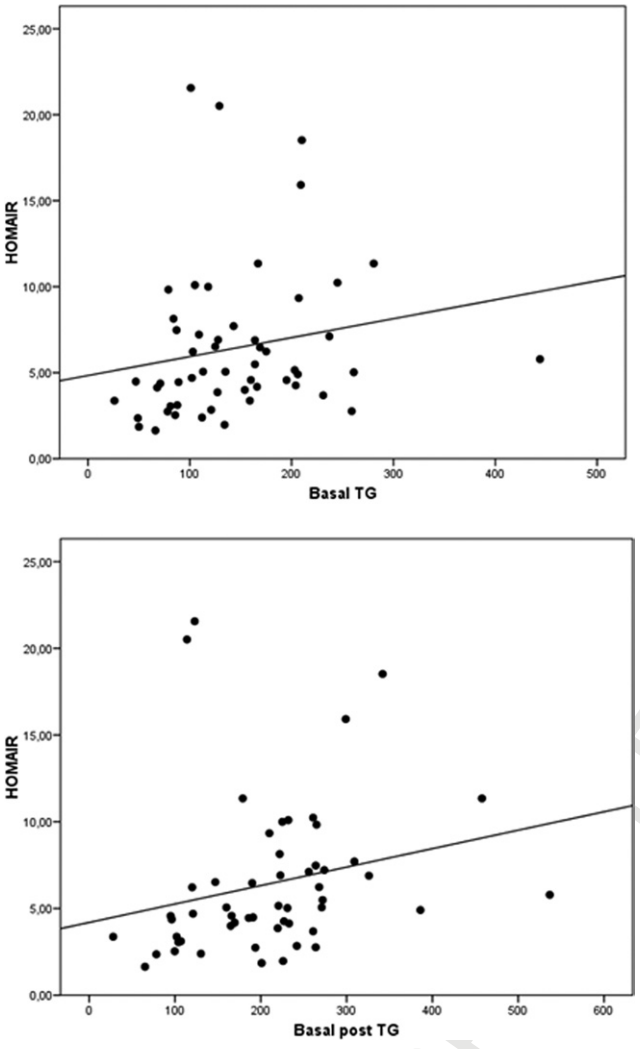

Fig. 4. Correlations between HOMA-IR index and baseline and postprandial triglycerides (r = .362 and r = .440, respectively).

postoperatively, patients who had undergone gastric restrictive surgery had a 50% mean reduction in plasma triglyceride levels. The Swedish Obesity Study found a 28% reduction in triglycerides in surgically treated subjects at 10 years after gastric bypass [13]. Our results showed a significant decrease in triglyceride levels at 1 month and 1 year after surgery. Mingrone et al. [14] analyzed the behavior of nonesterified fatty acids and triglyceride levels in operated patients and found that the decrease in nonesterified fatty acids appeared to be associated with the improvement in glucose oxidation, and the triglyceride decrease was associated with the increase in glucose storage.

Mingrone et al. [14] also reported on a patient who underwent biliopancreatic diversion for chylomicronemia secondary to a familial deficiency of lipoprotein lipase and diabetes, who did not lose weight postoperatively. The patient, in fact, increased her weight after the operation, owing to an unrestricted diet rich in sugary and fatty foodstuffs, confirming that the lipid malabsorption and the lower plasma lipid levels, rather than the weight loss, cause the reversibility of the insulin resistance condition [14].

From our results, the improvement in insulin resistance after bariatric surgery might be due to the improvement in postprandial lipidemia after bariatric surgery, because the plasma triglyceride levels experienced a gradual decline during follow-up, which could be explained by a lower absorption of dietary fat after surgery.

The relationship between HTG and insulin resistance has been previously reported [15]. Obese subjects and those with type 2 diabetes have a high FFA flux that increases their availability to the tissues and leads to ectopic or nonadipose tissue storage of triglycerides [16]. This storage causes alterations in insulin signaling [17,18]. In addition, postprandial HTG is a metabolic risk factor associated with the metabolic syndrome and insulin resistance [19]. There is also an association between postprandial triglycerides and insulin resistance [20].

Worse triglyceride clearance after a fat overload is associated with elevated plasma FFA levels, and this high availability of FFAs in many cases might be the genesis of insulin resistance in peripheral tissues owing to the high availability of lipids. Other studies conducted in humans have confirmed a close relationship between chylomicron levels and insulin resistance [21–24]. In addition, our group recently reported that the jejunum lipid content is inversely related to plasma levels of chylomicrons and the HOMA-IR [25], and this content plays an important role in the synthesis and release of intestinal lipoproteins. Therefore, the function lost in this bowel segment after surgery or a reduced surface for fat absorption owing to the absence of this segment after bariatric surgery could result in an alteration in the physiology or metabolism of intestinal lipoproteins and, consequently, an alteration of factors involved in postprandial lipid metabolism and insulin resistance.

Another mechanism involved in the effects observed in the present study might be related to differences in the anthropometric variables measured. However, the study by Migrone et al. [14] found that lipid metabolism was respon-

Table 2
Multiple regression analysis

Variable	ΔHOMA-IR (R = .839; R^2 = .705)		
	β	P value	95% CI
Postprandial TG	.508	.044	.006–.387
HOMA-IR	.843	.001	4.997–16.315

HOMA-IR = Homeostasis Model Assessment of insulin resistance; CI = confidence interval; TG = triglycerides; FFA 3.0 = free fatty acids 3 hours after fat overload; FFA = free fatty acids.

Independent variables: FFA 3.0, baseline hip circumference, HOMA-IR, baseline FFA, systolic blood pressure, postprandial triglycerides, baseline waist circumference, baseline cholesterol, baseline body mass index, diastolic blood pressure, baseline triglycerides; dependent variable: percentage of variation in HOMA at 30 days after surgery.

sible for the improvement in insulin resistance after surgery and not the weight loss that occurred after this improvement. In our study, we observed no significant differences in these variables, including BMI and hip circumference, between the 2 study groups. Multiple regression analysis showed that postprandial triglyceride levels were closely related to the improvement in insulin resistance after surgery, regardless of the changes in weight. Another explanation for this improvement in insulin resistance associated with postprandial HTG could be the hormonal mechanisms involved in the physiology of adipose tissue and the tissue metabolic capacity. However, in our study, we observed no significant differences in these variables between the 2 study groups.

The fundamental limitation of our study was that we did not provide molecular mechanisms to explain the connection between postprandial HTG and the improved insulin resistance. However, we believe this important clinical finding opens up a new pathway for future studies of the variables able to predict the improvement in insulin resistance in obese patients undergoing bariatric surgery.

Conclusion

The results of our study have shown that postprandial HTG is the best predictor of improved insulin resistance in morbidly obese patients undergoing bariatric surgery, more so than other lipid, hormonal, and inflammatory variables. Because of the high number of morbidly obese patients, the clinical value of this finding could be important for determining the phenotype of patients who can be expected to obtain greater benefit from bariatric surgery.

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