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Original article

Changes in oxidative stress markers and cardiometabolic risk factors among Roux-en-Y gastric bypass patients after 3- and 12-months postsurgery follow-up

Sônia Lopes Pinto, M.Sc.[a,b,*], Leidjaira Lopes Juvanhol, Ph.D.[b], Leandro Licursi de Oliveira, Ph.D.[c], Rodolfo Castilho Clemente, M.Sc.[a], Josefina Bressan, Ph.D.[b]

[a]*Nutrition Course of the Federal University of Tocantins, Palmas, Tocantins, Brazil*
[b]*Department of Nutrition and Health, Universidade Federal de Viçosa, Viçosa, Minas Gerais, Brazil*
[c]*Department of General Biology, Universidade Federal de Viçosa, Viçosa, Minas Gerais, Brazil*

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Abstract

Background: Evidence shows potential reduction in oxidative stress after Roux-en-Y gastric bypass. However, this outcome can vary, with postsurgery time, type of markers significantly altered, and possible relation with cardiometabolic risk markers, thus indicating the need for more studies.
Objective: To evaluate changes in oxidative stress and its relation with cardiometabolic risk markers in Roux-en-Y gastric bypass patients after 3 and 12 months postsurgery.
Setting: Federal University of Viçosa, Brazil.
Methods: All data were collected before surgery and after 3 and 12 months postsurgery. Biochemical data were collected, and insulin resistance was determined by homeostasis model assessment of insulin resistance, triglyceride/glucose index, and triglycerides/high-density lipoprotein cholesterol. Additionally, catalase, superoxide dismutase, ferric-reducing antioxidant power, nitric oxide, carbonylated protein, and malondialdehyde were analyzed.
Results: After 3 months postsurgery, excess weight loss was 46%. It increased to 82% after 12 months. We observed a significant reduction in levels of serum insulin, triglycerides, homeostasis model assessment of insulin resistance, triglyceride/glucose index, and triglycerides/high-density lipoprotein cholesterol indices and nitric oxide, throughout the entire study period. Also, reduced levels of total cholesterol, low-density lipoprotein, serum glucose, malondialdehyde, and superoxide dismutase were observed at 3 and 12 months postsurgery compared with baseline. On the other hand, reduction in ferric-reducing antioxidant power occurred only at 3 months postsurgery. We also observed that nitric oxide was positively correlated with triglycerides, percent excess weight loss, total cholesterol/high-density lipoprotein cholesterol, and triglyceride/glucose index.
Conclusion: Roux-en-Y gastric bypass is able to reduce oxidative stress, insulin resistance, and improve lipid profile after 3 and 12 months postsurgery. Furthermore, changes in oxidative stress and cardiometabolic risk markers are correlated. (Surg Obes Relat Dis 2019;■:1–8.)

Key words: Oxidative stress; RYGB; Insulin resistance; TyG index; Nitric oxide

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*Correspondence: Sônia Lopes Pinto, M.Sc., Nutrition Course of the Federal University of Tocantins, Palmas, Quadra 109 North, NS-15 Avenue, ALCNO-14, Block Bala2, CEP: 77001-090, Palmas, Tocantins, Brazil.

E-mail address: sonialopes@uft.edu.br (S.L. Pinto).

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Obesity promotes the reduction of antioxidant defense capacity, which contributes to oxidative stress, which can lead to the development of chronic diseases [1]. Conditions related to obesity, such as increased levels of insulin, free fatty acids, and glucose concentration, can increase the production of reactive oxygen species (ROS), creating an imbalance in the antioxidant defense system, also known as oxidative stress [2]. Studies highlight the role of adipose tissue in the production of ROS via inflammation. Increased ROS in the adipose tissue has been associated with increased expression of NADPH oxidase and reduced expression of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT) [1,3].

There is a close relationship between oxidative stress and the development of insulin resistance (IR). For instance, in animal models, the inhibition of NADPH oxidase drastically reduces oxidative stress and is capable of reversing IR [2]. Accordingly, improved insulin sensitivity associated with a reduction of oxidative stress has been investigated mainly for weight loss [4].

Bariatric surgery is considered the most effective treatment for severe obesity because it promotes greater weight loss and resolution of co-morbidities [5]. Evidence shows that a reduction in oxidative stress after Roux-en-Y gastric bypass (RYGB) may be related to significant weight loss and reduced subclinical inflammation. However, little is known about its relation with cardiometabolic risk factors. In addition, studies in the literature are not unanimous with regard to variations in oxidative stress and cardiometabolic risk after bariatric surgery because these changes are time-dependent [4,6,7]. Therefore, the aim of this article was to evaluate changes in oxidative stress markers and cardiometabolic risk after 3 and 12 months of RYGB and explore the possible relations between changes in these markers.

Methods

Sample

This study is an observational prospective study of patients (nonsmokers and both sexes) who underwent RYGB. The study was conducted at the Outpatient Nutrition Clinic of the Federal University of Tocantins, in the city of Palmas, Tocantins, Brazil. The inclusion criteria in the study were as follows: age >20 and <60 years, underwent RYGB bariatric surgery for the first time, and were willing to report to the outpatient nutrition clinic at 3 and 12 months postsurgery for data collection. The exclusion criteria were individuals who had undergone other surgical procedures and smokers. The follow-up care of the patients lasted 12 months after the surgery. All data were collected in the following 3 phases between February 2017 and September 2018: before surgery and after 3 and 12 months postsurgery. This study was approved by the Ethics and Research Committee of the Federal University of Viçosa/MG. Before data collection, all patients signed an informed consent form.

Anthropometry and body composition

Weight was measured on an electronic digital scale (Welmy, São Paulo, Brazil) with a capacity of 300 kg and a precision of 100 g. Height was measured using a 2-m stadiometer attached to a wall without skirting. Both measures were performed according to techniques recommended by Jellife [8]. Body mass index (BMI) was calculated based on weight and height.

Waist circumference was measured from the midpoint between the lower costal margin and the iliac crest in the midaxillary using a flexible inelastic 2-m tape divided into centimeters [9]. Neck circumference (in cm) was measured at mean height, between the cervical spine, and the neck. In men with laryngeal prominence (Adam's apple), the measurement was taken just below its elevation [10].

To analyze the effect of bariatric surgery on weight, parameters derived from weight loss were calculated, such as excess weight (EW), given by preoperative weight (kg) − ideal weight (kg), considering a reference BMI = 24.9 kg/m^2. We also calculated percentage excess weight loss (%EWL) as absolute weight loss (kg) / EW × 100.

Body composition was evaluated using 4-electrode bioimpedance equipment (310 Biodynamics model, New York, USA) according to manufacturer's instructions. Body fat was expressed as a percentage and lean body mass (in kilograms).

Oxidative stress markers

Biological sample

To evaluate oxidative stress, the following markers were investigated: nitric oxide (NO), malondialdehyde (MDA), carbonylated protein, ferric-reducing antioxidant power (FRAP), SOD, and CAT. Blood samples were collected in a specialized laboratory after 12 hours of fasting during the preoperative period and 3 and 12 months postsurgery. Plasma and erythrocyte samples were separated and stored at −80°C until the time of analysis. All markers were analyzed using plasma samples, except for CAT, where erythrocyte was used.

Nitric oxide

NO was measured based on nitrite (NO_{2-}) metabolite according to the Griess method described by Guevara et al. [11]. This assay determines NO concentration via nitrite formed from the spontaneous reaction of NO and O_2. The product was read in a spectrophotometer at 570 nm, and NO was expressed in micromoles per milliliter.

Malondialdehyde

MDA was determined according to the method described by Jentzsch et al. [12] using a thiobarbituric acid reactive

substance assay. In this method, thiobarbituric acid reacts with MDA, a byproduct of lipid peroxidation in cell membrane, to form a chromophore. The absorbance of the chromophore at 535 nm was read in a spectrophotometer and MDA was expressed in nanomolar per milliliter.

Carbonylated protein

Carbonylated protein was determined according to Levine et al. [13], where 2,4-dinitrophenylhydrazine dye binds to damaged residues of protein forming hydrazone, which presents a maximum absorbance at 370 nm. Carbonylated protein was expressed in nmol/mL of plasma.

Total antioxidant capacity of plasma

Plasma antioxidant capacity was evaluated by the FRAP based on the reduction of Fe^{3+} to Fe^{2+} in the plasma by nonenzymatic antioxidants and subsequent complexation of Fe^{2+} with 2,4,6-tri (2-pyridyl) s-triazine to form a Fe^{2+} −2,4,6-tri (2-pyridyl)-s-triazine (2-pyridyl)-s-triazine chromophore, whose maximum absorbance can be measured in a spectrophotometer at 595 nm [14].

Superoxide dismutase

SOD activity was evaluated by its ability to catalyze the reduction of superoxide radical (O_{2-}) to hydrogen peroxide (H_2O_2) and O_2, using pyrogallol [15]. SOD was read in a spectrophotometer at 570 nm and expressed in unit per milliliter of plasma.

Catalase

The activity of CAT enzyme was determined by the method described by Hadwan et al. [16] with modifications. First, the erythrocytes were diluted in distilled water at a ratio of 1:500. Afterward, 10 μL of the sample was added to hydrogen peroxide for 3 minutes, and then ammonia molybdate was added. The prepared solution was read in a spectrophotometer at 374 nm and catalase activity was expressed in Kilo units.

Cardiovascular risk markers

We evaluated the serum concentration of glucose, insulin, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) by enzymatic colorimetric test. Casteli index was calculated considering total cholesterol (mg/dL) / HDL-C (mg/dL). Serum insulin concentration was determined by electrochemiluminescence immunoassay. All tests were performed in a third-party laboratory.

Three indices for the determination of IR were analyzed as follows: homeostasis model assessment (HOMA), TyG, and TG/HDL-C. The HOMA-IR index was calculated from the formula: fasting insulin (μU/L) × fasting blood glucose (nmol/L) / 22.5 [17]. IR was defined as HOMA-IR >2.71[18]. Triglyceride/glucose index (TyG) was calculated from TG and fasting glycemia by the formula (ln [fasting triglycerides (mg/dL) × fasting glycemia (mg/dL)]) / 2 [19]. TG/HDL ratio-C, in turn, was calculated by dividing TG (mg/dL) by HDL-C (mg/dL) [20].

The presence of metabolic syndrome was determined according to the International Diabetes Federation [21]. The diagnosis of diabetes and hypertension was defined through self-report confirmed by the use of medication. Dyslipidemia was defined according to the Updated Brazilian Dyslipidemia and Atherosclerosis Prevention Guidelines [22]. We also inquired about all medications used.

Statistical analysis

All data were analyzed in the Stata software (version 13.0, Texas, USA) and SPSS (version 20.0, Chicago, USA). Numerical variables were expressed in median and interquartile range, and categorical variables were expressed as absolute and relative frequencies. The Shapiro-Wilk test was performed to evaluate the normality of the numeric variables.

To evaluate differences in mean oxidative stress markers at baseline and after 3 and 12 months postsurgery, we used a repeated-measures analysis of variance test for variables that followed a normal distribution; for the others, a Friedman and Wilcoxon tests were used. For the categorical variables, the McNemar χ^2 test followed by Bonferroni's correction was performed.

We also performed the Spearman correlation analysis to test the relationships between changes in NO and cardiometabolic risk markers. The variations at 3- and 12-month follow-up were considered (Δ = value at 3 or 12 mo − baseline). For all analyses, $P < .05$ was considered statistically significant.

Results

This study included 58 patients with severe obesity who underwent RYGB. Mean age was 39.3 ± 9.3 years, and 70% were female. In the preoperative period, 76% of the patients used some type of medication. The most cited were antihypertensives (41.4%), hypoglycemic agents and/or insulin (29.3%), and antidepressants (12.0%). Among the women, 10% used contraceptives. After 12 months postsurgery, the median excess weight loss was 81.9%, body fat decreased to <30.0%, and median BMI was 28.1 kg/m^2 (Table 1).

For the clinical variables, we observed a reduction in insulin ($P < .001$) and TGs ($P < .001$) between the phases of the study. HDL reduced at 3 months postsurgery ($P < .001$) but increased from 3 to 12 months postsurgery ($P < .001$). On the other hand, TC, LDL, and glucose decreased at 3 and 12 months postsurgery compared with baseline ($P < .001$); however, there was no change from 3 to 12 months postsurgery ($P = .99$, $P = .401$, $P = .88$, respectively).

Table 1
Anthropometric characteristics of patients at baseline, and 3 and 12 months after Roux-en-Y gastric bypass

Variables	Baseline (n = 58)	3 mo (n = 58)	12 mo (n = 50)	*P* value
Weight, kg	112.5 (104.3–121.4)*	92.4 (83.2–103.2)†	77.2 (68.0–82.6)‡	<.001
WC, cm	122.7 (115.0–122.7)*	104.7 (98.7–115.2)†	92.0 (84.0–101.6)‡	<.001
NC, cm	41.5 (39.0–44.1)*	37.7 (35.8–40.1)†	35.0 (32.5–37.0)‡	<.001
BMI, kg/m^2	41.8 (38.2–46.4)*	33.7 (31.5–37.1)†	28.1 (25.1–31.2)‡	<.001
Weight loss, kg		20.9 (18.2–23.7)*	37.6 (31.9–44.1)†	<.001
%EWL		45.9 (39.9–53.5)*	81.9 (65.5–97.9)†	<.001
%BF	43.1 (38.9–46.0)*	38.0 (34.3–42.4)†	30.1 (25.5–35.8)‡	<.001
FFM, kg	63.5 (58.5–72.2)*	55.9 (50.8–62.5)†	52.6 (47.2–59.5)‡	<.001

WC = waist circumference; NC = neck circumference; BMI = body mass index; EWL = excess weight loss; BF = body fat; FFM = fat-free mass.

Values are median (interquartile range).

Analysis of variance was used for repeated measures followed by the Bonferroni post hoc for the variables with normality, and the Friedman and Wilcoxon test were used for the other variables. Different symbols indicate groups with statistically significant difference ($P < .05$).

Different symbols indicate a statistically significant difference ($P < .05$) between the groups.

Regarding the indices studied, we observed a reduction in HOMA-IR, TyG, and TG/HDL-C (all $P < .001$) between the phases of the study. The TC/HDL index reduced only at 12 months compared with baseline ($P < .001$). It was also noted that at 12 months postsurgery, no patient had diabetes, but 1 patient presented metabolic syndrome and IR (Table 2).

We observed that, among the markers of oxidative stress, only NO was reduced during all phases of the study ($P < .000$) (Fig. 1A). SOD and MDA decreased at 3 ($P = .04$, $P = .021$, respectively) and 12 months ($P = .006$, $P < .000$, respectively) in relation to baseline, but their values did not differ from 3 to 12 months ($P = .993$ and $P = .124$, respectively) (Figs. 1B,E). FRAP decreased only between the preoperative period and 3 months postsurgery ($P < .001$) (Fig. 1D). CAT and carbonylated protein showed no changes between the periods investigated ($P > .05$ for both) (Figs. 1C, 1G).

Correlation analysis was performed only for NO because it was the only oxidative stress marker that presented a more expressive reduction after RYGB. We observed that the variation observed at 12 months compared with baseline was directly associated with ΔTG (r = .79; $P < .001$), ΔTyG (r = .55; $P < 0.001$), ΔTC/HDL (r = .40; $P < .001$), and %EWL (r = .33; $P < .01$) (Fig. 2). We also analyzed the correlations considering 3 months postsurgery compared with baseline, and the results were very similar except for % EWL, which did not present a significant correlation

Table 2
Cardiometabolic risk factors in patients at baseline and 3 and 12 months after Roux-en-Y gastric bypass

Variables	Baseline (n = 58)	3 mo (n = 58)	12 mo (n = 50)	*P* value
Insulin, μUI/mL	15.3 (8.6–19.9)*	5.8 (4.5–8.4)†	3.7 (2.5–4.8)‡	<.001
Glucose, mg/dL	92.5 (85.7–102.0)*	84.0 (75.7–88.2)†	83.5 (79.0–87.0)†	<.001
TG, mg/dL	129.0 (95.5–173.0)*	91.5 (71.2–110.5)†	75.0 (52.0–86.0)‡	<.001
TC, mg/dL	179.5 (161.7–205.0)*	149.0 (130.5–173.5)†	156.2 (139.0–171.5)†	<.001
HDL-C, mg/dL	48.0 (39.5–55.5)*	39.7 (35.7–47.8)†	51.0 (45.7–59.5)‡	<.001
LDL-C, mg/dL	102.3 (85.7–123.2)*	89.3 (69.9–107.0)†	85.2 (69.5–97.7)†	<.001
TC/HDL-C	3.8 (3.1–4.6)*	3.5 (3.0–4.4)*	2.8 (2.4–3.3)†	<.001
HOMA-IR	3.7 (2.1–4.6)*	1.2 (.8–1.7)†	.7 (.5–.9)‡	<.001
TyG	8.6 (8.3–9.2)*	8.2 (7.9–8.5)†	7.9 (7.6–8.2)‡	.001
TG/HDL-C	2.5 (1.9–3.8)*	2.1 (1.6–2.8)†	1.4 (1.0–1.8)‡	<.001
Insulin resistance	46 (71.8%)*	7 (12%)†	1 (2%)†	
Metabolic syndrome	30 (46.9%)*	7 (12%)†	1 (2%)†	
Diabetes	17 (29.3%)*	3 (5.2%)†	0 (0%)	
Hypertension	24 (41.4%)*	4 (6.9%)†	2 (4.0%)†	
Dyslipidemia	30 (51.7%)*	43 (74.4%)†	16 (32.0%)*	

TG = triglycerides; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; HOMA-IR = homeostasis model assessment; TyG = triglyceride/glucose index.

Values are median (interquartile range) or n (%).

Analysis of variance was used for repeated measures followed by the Bonferroni post hoc for the variables with normality, and the Friedman and Wilcoxon test for the other variables. For the categorical variables, the McNemar χ^2 test followed by Bonferroni's correction was performed.

Different symbols indicate groups with a statistically significant difference ($P < .05$).

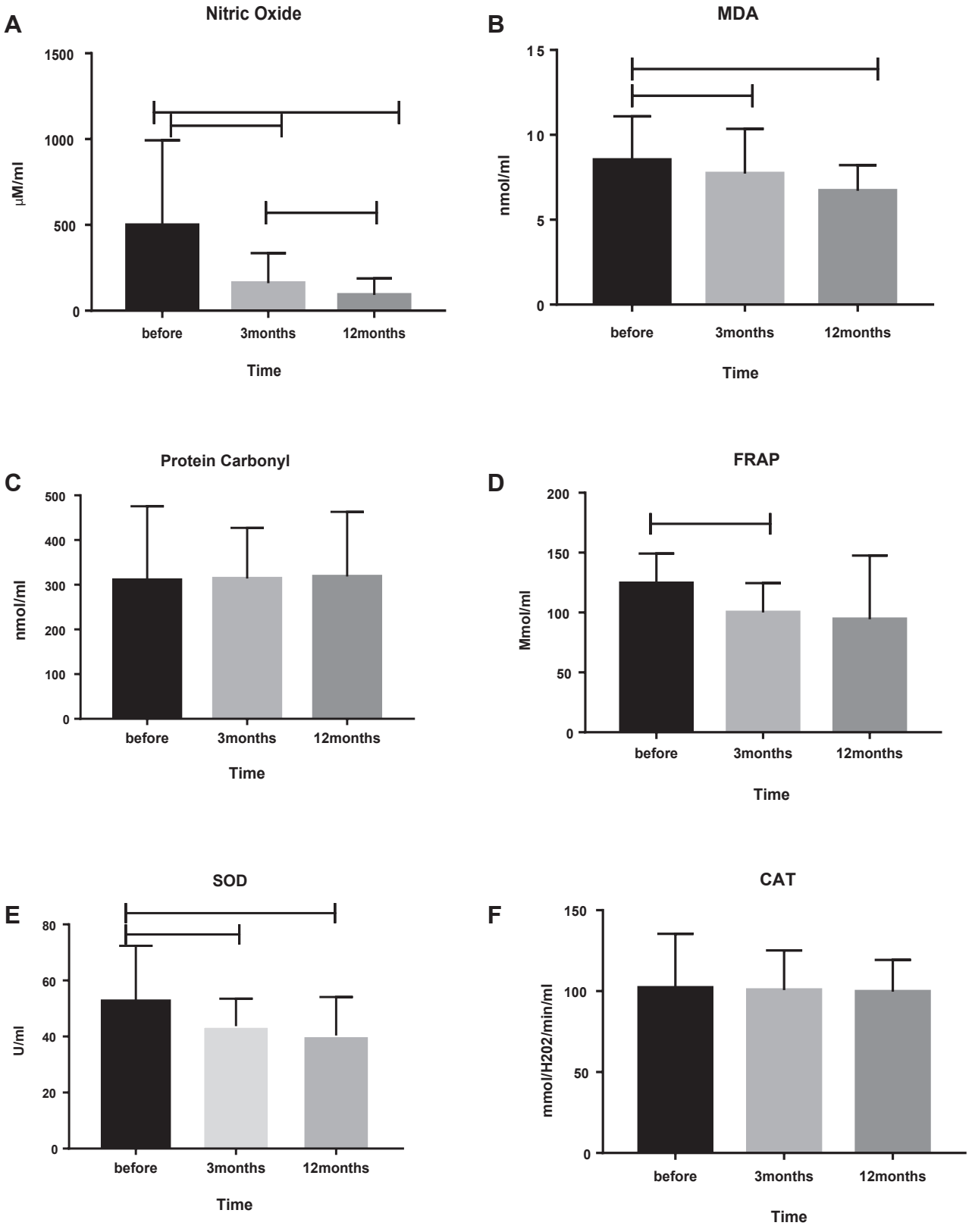

Fig. 1. Markers of oxidative stress in patients undergoing Roux-en-Y gastric bypass at baseline and at 3 and 12 mo after surgery. Values expressed as mean and standard deviation. Anaylsis of variance was used for repeated measures for the variables with normality, and Friedman and Wilcoxon test were used for the other variables. MDA = malondialdehyde; FRAP = ferric-reducing antioxidant power; SOD = superoxide dismutase, CAT = catalase.

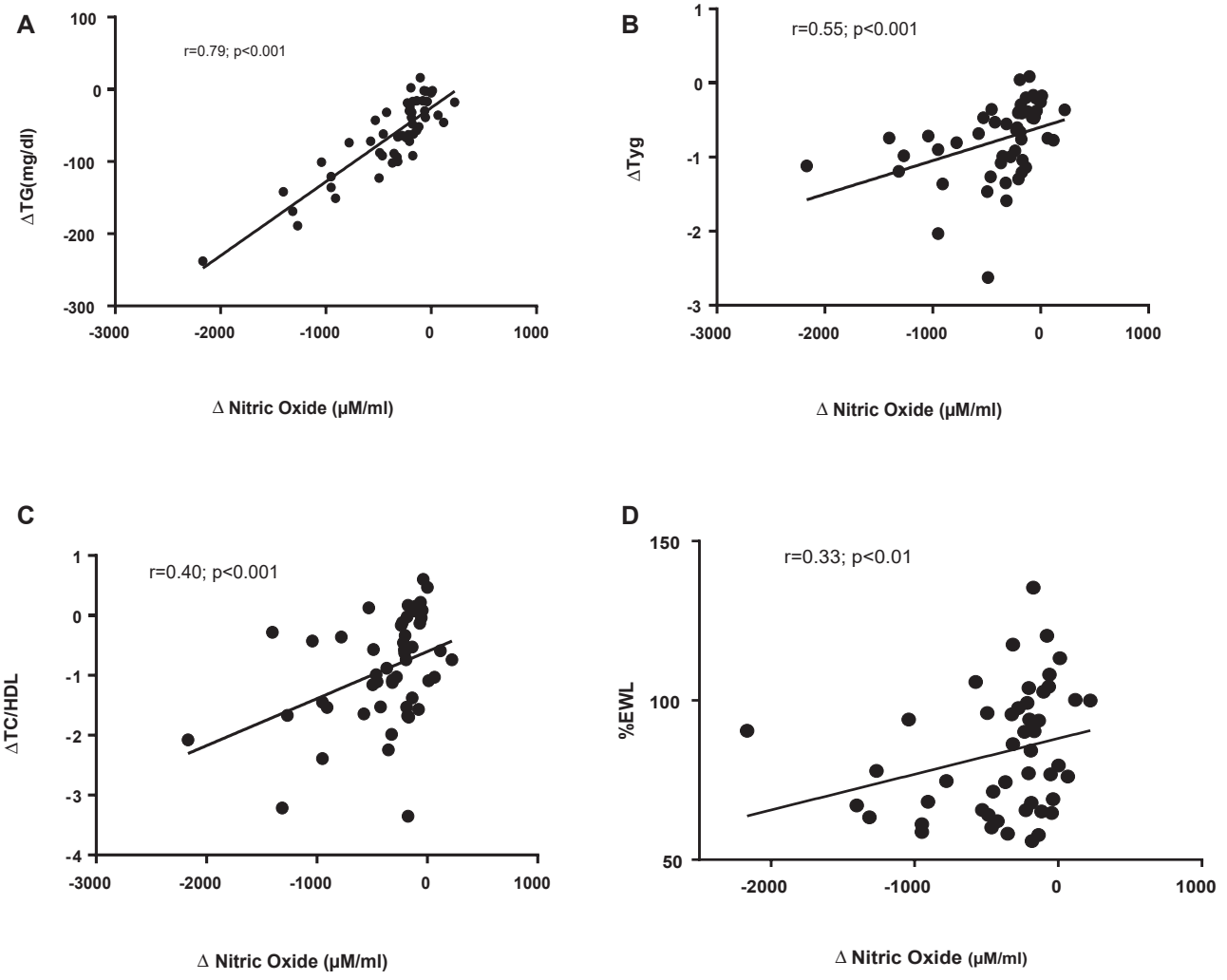

Fig. 2. Correlation between changes in serum nitric oxide values and cardiometabolic risk markers (Δ = 12 months Roux-en-Y gastric bypass – baseline). ΔTG = triglyceride; ΔTyG = triglyceride/glucose index; ΔTC/HDL = total cholesterol/HDL-cholesterol; %EWL = excess weight loss.

(ΔTG: r = .79; $P < .001$; ΔTyG: r = .61; $P < .001$; ΔTC/HDL: r = .31, $P = .018$).

Discussion

Among the oxidative stress markers studied, we observed a significant reduction in only NO after 3 and 12 months postsurgery (RYGB). At 12 months postsurgery, NO presented a positive and strong correlation with TG and a moderate correlation with %EWL, TyG, and TC/HDL, indicating a linear association between NO reduction after surgery and changes in these markers.

NO is a free radical produced from the oxidation of one of the 2 guanidino nitrogens of L-arginine to L-citrulline, a reaction catalyzed by NO synthase enzyme. An important source of NO is the adipose tissue, contributing greatly to its synthesis mediated by inducible NOS (iNOS) and endothelial (eNOS) enzymes. Evidence shows that NO has a central role in adipocyte physiology, regulation of energy metabolism, and control of body composition [23].

In addition to weight reduction promoted by bariatric surgery, the levels of proinflammatory cytokines are reduced; therefore, the synthesis of NO also decreases. In this study, we show that the higher the %EWL, the greater the reduction of NO. In addition, we observed a strong correlation between reduction of NO and reduction in serum TG and TyG indices, the latter being calculated from serum TG and glycemia concentrations. All these findings are possibly related to weight and fat reduction promoted by RYGB, resulting in a reduction of inflammation and a significant improvement in insulin resistance [7].

Similar to NO, MDA is an important marker of oxidative stress, which represents lipid peroxidation levels. We observed its reduction at 3 and 12 months postsurgery compared with baseline. Only 1 study in the literature

reported a reduction in MDA of RYGB patients at only 3 months postsurgery [4]. Most studies observed a decrease in MDA after 1 year postsurgery [6,7,24,25]. A possible explanation for our finding could be the high EWL observed among the patients, which was 47% at 3 months postsurgery and 83% at 12 months. The %EWL observed is higher than those found in other studies that evaluated MDA in RYGB patients [6,24]. Considering that MDA represents lipid peroxidation, it is expected that individuals who lose weight and leave the condition of obesity present reduced levels of MDA.

In relation to the antioxidant enzymes, SOD and CAT, we observed a reduction in only SOD at 3 and 12 months postsurgery compared with baseline. SOD is an antioxidant enzyme that converts $O_{2\cdot}$ to hydrogen peroxide H_2O_2 and O_2 and thus controls the formation of free radicals. In obese individuals, chronic inflammation and oxidative stress stimulate greater synthesis of SOD as an adaptive response [26]. With regard to MDA and NO, this result is possibly a reflection of weight loss and reduced BMI, as there is a reduction in SOD activity because of the lower level of ROS and proinflammatory cytokines. However, findings on the behavior of SOD among bariatric surgery patients are controversial; both decreasing [25] and increasing [24] trends have been reported.

We evaluated total antioxidant capacity by FRAP and observed its reduction only after 3 months postsurgery (RYGB). Unlike other markers, FRAP is directly influenced by diet quality rather than weight loss. Therefore, the change observed in the first 3 months after surgery can be explained, at least partially, by the lower consumption and/or absorption of antioxidants, such as vitamin C, β-carotene, and α-tocopherol, which is expected after surgeries such as RYGB that are composed of a restrictive and malabsorptive procedure [5]. However, it should be noted that all patients in the study used daily multivitamin supplementation, which in turn may have directly interfered with the observed FRAP values. At 3 months postsurgery, there was a reduction in FRAP because the most significant dietary changes occur in this period; however, considering the use of multivitamins, it could have been even more expressive.

In relation to clinical and biochemical parameters, we observed a reduction in all the studied variables, especially at 3 months postsurgery. However, both serum insulin and TG levels, as well as HOMA-IR, TyG, TG/HDL-C, presented a significant reduction at 3 and 12 months postsurgery. RYGB is considered the gold standard for the treatment of severe obesity [5] because it promotes significant weight loss and metabolic improvement through hormonal mechanisms related to increased peptide YY and glucagon-like peptide 1 hormones. These hormones act in the stimulation of insulin production, which significantly improves IR [27].

A reduction in HOMA-IR after 3 months postsurgery [28,29] was also observed in other studies with RYGB patients. TyG is a recent index being investigated for its predictive capacity of cardiovascular diseases, especially because it is accessible [30,31]. We observed a significant reduction in TyG and HOMA-IR at all stages of the study. Similarly, the TG/HDL-C index also decreased at all stages of the study. Cazzo et al. [32] showed that TyG and TG/HDL-C of RYGB patients after 1 year postsurgery were associated with the reversal of metabolic syndrome, unlike HOMA-IR. Considering that the TyG and TG/HDL-C indices are constructed from routine examinations (glycemia, HDL, and TG), their use in clinical practice would be of great importance.

This study presents a limitation inherent to the study population. The patients were on multivitamin supplementation, a routine treatment after bariatric surgery, which may have influenced the results of the oxidation markers, as previously mentioned. Despite this limitation, the findings of the study contribute to the advancement of research related to the impact of bariatric surgery on oxidative stress and cardiometabolic risk factors, such as insulin resistance.

Significant changes in oxidative stress markers were observed at 3 months postsurgery. After this period, subtle modifications were observed until 12 months postsurgery. The same was observed for the clinical variables, such as insulin resistance, glycemia, and lipid profile. These findings are interesting because they suggest that the greatest impact of the surgery occurs in the short term, making the early postsurgery period the most crucial period to obtain success from the surgery. Although metabolic changes continue to occur after 3 months of surgery and up to 12 months, their rates are lower.

Conclusion

RYGB surgery showed its ability to reduce oxidative stress, improve IR and lipid profile, and reverse metabolic syndrome. These main changes were observed at 3 months postsurgery. In addition, changes in NO were associated with changes in TG, TyG, TC/HDL-C, and %EWL. We also found that TyG and TG/HDL-C indices and HOMA-IR presented the same tendency, indicating that the former could serve as a cost-effective predictor of IR in clinical practice, given that they can be calculated from routine medical test results.

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Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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