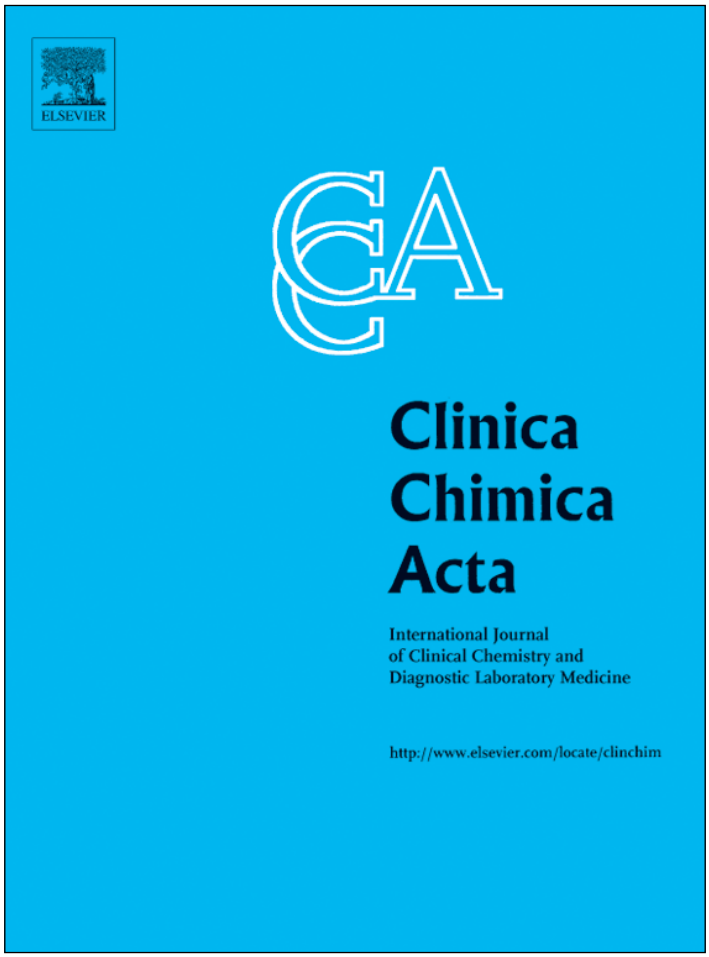
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Evaluation of the biochemical, inflammatory and oxidative profile of obese patients given clinical treatment and bariatric surgery

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ABSTRACT

Background: We investigated the biochemical and inflammatory parameters as well as biomarkers of oxidative stress in morbidly obese patients before and after bariatric surgery and clinical treatment.
Methods: This study was conducted using 60 individuals (10 men and 50 women) distributed into 3 groups: the control group, 20 non-diabetic obese patients given clinical treatment, the bariatric group, 20 non-diabetic obese patients given a Roux-en-Y bypass gastroplasty, and the bariatric diabetic group, 20 diabetic obese patients given a Roux-en-Y bypass gastroplasty. Measurements were made before and 1, 3, 6, and 12 months after surgery and clinical treatment.
Results: We showed a significant decrease in body weight, body mass index (BMI) and waist circumference, accompanied by a decrease in the lipid profile and glucose and glycated hemoglobin concentrations in the groups that received bariatric surgery. The concentrations of lipid peroxidation, carbonyl protein and NPSH, as well as superoxide dismutase (SOD) and catalase (CAT) activity, significantly decreased in both groups after surgery. The concentrations of inteleukin-6, inteleukin-1, TNF-α and resistin were also significantly lower, while adiponectin concentrations significantly increased 12 months after bariatric surgery. No significant alterations were observed in the biochemical, inflammatory or oxidative parameters of the control group.
Conclusions: Our findings demonstrate a decrease in body mass and a subsequent improvement in biochemical, metabolic and anthropometric parameters in patients given bariatric surgery. This may contribute to the reduction of oxidative damage in these patients and consequently a reduction in the risk of the development and progression of multiple co-morbidities associated with obesity.

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1. Introduction

Obesity is a chronic multifactorial disease that has reached epidemic proportions throughout the world, as well as a relevant risk factor for diseases such as type 2 diabetes, cardiopathies, hypertension, cerebral vascular accident, osteoarthritis, polycystic ovary syndrome (PCOS), and certain types of cancer [1–3]. As a consequence obesity has become an increasing source of morbidity and mortality worldwide. In Brazil, around 38 million Brazilians over the age of 20 are overweight. Data from the Brazilian Institute of Geography and Statistics (IBGE) shows an increase in obesity among adults from both sexes [4].

Obesity is defined as the deposition of abnormal or excessive fat in the adipose tissue [5]. Adipose tissue is an endocrine organ that produces and releases a large amount of bioactive peptides called adipokines, which directly contribute to the development of metabolic abnormalities, especially insulin resistance, alterations in vascular biology and lipoprotein metabolism, and tumor development [6–8]. Among all the adipokines, IL-6, TNF-α, resistin, leptin (pro-inflammatory), and adiponectin (anti-inflammatory) have received special attention in the specialist literature. High concentrations of these adipokines leads to a chronic inflammatory state in the organism that impacts several bodily functions, leading to pathologies associated with increased body fat [6–9]. In addition, the production of reactive oxygen species (ROS) by the endoplasmatic reticulum of adipocytes, which stimulate an influx of macrophages into the adipose tissue, is considered as one possible cause of the increased levels of cytokines and ROS observed in obesity [10–11].

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The increased generation, or the decrease in the scavenging or metabolism, of ROS is defined as oxidative stress [11]. The most commonly recognized effect of oxidative stress is the oxidation and damage of macromolecules such as proteins, lipids, DNA, and enzymes involved in energy production, thereby contributing to cellular injury, energetic deficit, and the acceleration of cell death through apoptosis and necrosis. Recently, studies have suggested that oxidative stress may play an important role in the pathogenesis and development of obesity-related comorbidities [11–13]. In fact, obese individuals show higher concentrations of plasma isoprostanes, plasma malodialdehyde, skeletal muscle 4-hydroxynonenal, and plasma protein carbonyls [11–14].

The effect of ROS is balanced out by the antioxidant action of non-enzymatic antioxidants, as well as by antioxidant enzymes. The most efficient enzymatic antioxidants involve superoxide dismutase (SOD) and catalase (CAT), while non-enzymatic antioxidants include non-proteic thiol, vitamin C, and vitamin E [11–14]. These antioxidant defenses are extremely important as they represent the direct removal of free radicals, providing maximal protection for biological sites [11–14].

The endemic extent of overweight individuals and obesity, and the associated comorbidities, has led to the development of therapies aimed at weight loss. Morbid obesity remains largely resistant to diet, exercise, and medication, but generally responds well to bariatric surgery [15,16]. In fact, bariatric surgery, using the Roux-en-Y gastric bypass (RYGB) procedure, demonstrates the most encouraging results in the treatment of patients with morbid obesity and type 2 diabetes by effectively reducing body weight and improving insulin sensitivity [16,17]. Moreover, a substantial majority of obese patients with diabetes, hypertension, and other cardiovascular complications experience complete resolution or improvement of these pathogeneses [17–19].

2. Materials and methods

2.1. Study population

This was a prospective controlled clinical study (May 2010 to June 2013) carried out at the University Hospital of the Federal University of Santa Maria, Rio Grande do Sul, Brazil. The study protocol was approved by the Human Ethics Committee of the Federal University of Santa Maria (number 23081.010115/2009-00). All of the participants in this study signed a Term of Free and Informed Consent and were informed of the objectives and methods of the study. The study involved 60 individuals (10 men and 50 women) distributed over three groups. The control group consisted of 20 non-diabetic obese individuals (3 men, 17 women) given clinical treatment. Their mean age was 39.2 ± 12.4 y, mean weight 122.9 ± 21.4 kg, and mean BMI 46.25 ± 7.3 kg/m^2. The clinical treatment included a balanced hypocaloric diet (1200 Kcal/day) and physical exercise, moderate intensity for 20–30 min, at least 3 times a week. The control group was examined during the basal period (3–15 days before the clinical treatment) and 1, 3, 6, and 12 months after the clinical treatment. The bariatric group consisted of 20 non-diabetic obese individuals (five men, 15 women) given a Roux-en-Y bypass gastroplasty (a gastrojejunal derivation, which is characterized by food restriction and malabsorption). Their mean age was 36.7 ± 10.5 y, mean weight 115.0 ± 20.3 kg, and mean BMI 43.09 ± 3.3 kg/m^2. The bariatric diabetic group consisted of 20 diabetic obese individuals (2 men, 18 women) given a Roux-en-Y bypass gastroplasty. Their mean age was 52.0 ± 10.7 y, mean weight 105.9 ± 15.2 kg, and mean BMI 44.1 ± 4.0 kg/m^2. The bariatric and bariatric diabetic groups were examined during the pre-surgical period, known as the basal period (3–15 days before surgery), and 1, 3, 6 and 12 months after surgery.

The inclusion criteria were morbid obesity, BMI ≥40 or 35 kg/m^2 to 39.9 kg/m^2, with comorbidities and a recommendation for bariatric surgery. The exclusion criteria were the presence of a psychiatric disorder (e.g. schizophrenia), smoking, alcohol or drug dependency, undergoing treatment involving antibiotics and/or anti-inflammatory or immunosuppressant drugs, and cancer or systemic diseases (e.g. systemic autoimmune diseases).

2.2. Clinical measurements

Anthropometric measurements with an emphasis to clinical markers of adiposity were obtained. Waist circumference (cm) was measured as the average distance between the last rib and the iliac crest, around the navel. All patients completed a clinical and epidemiological assessment evaluating physical exercise habits, smoking, hypertension, and treatment with statins and/or other drugs.

2.3. Sample collection

Blood samples were drawn after 12 h overnight fasting, using the venipuncture technique, into Vacutainer® (Becton Dickinson Vacutainers) tubes with sodium fluoride plus EDTA, citrate or no anticoagulant before and 1, 3, 6, and 12 months after surgery or clinical treatment. Blood collected with sodium fluoride plus EDTA was used to measure fasting glucose. Plasma EDTA was used to measure glycated hemoglobin (HbA1c), while the serum was used to assess the concentrations of total cholesterol, HDL cholesterol, triglycerides, insulin, creatinine, uric acid, and IL-6. The serum was also used to determine protein carbonyl and vitamin E concentrations. CAT and SOD activity was determined using whole blood collected in citrated vacutainer tubes and diluted in a 1:10 saline solution. For plasmatic thiobarbituric acid reactive substances (TBARS) and non-protein thiols, blood was collected using EDTA as an anticoagulant.

2.4. Biochemical measurements

Analysis of fasting glucose, glycated hemoglobin, total cholesterol, HDL cholesterol, triglycerides, uric acid, creatinine, and insulin was performed using standard methods from the Cobas MIRA® automated analyzer (Roche Diagnostics). LDL cholesterol was estimated using the Friedewald equation [20]. IL-6 was measured by capture ELISA following the instructions outlined by the manufacturer (eBIOSCIENCE).

2.5. Quantification of adipokines

Adiponectin (R&D Systems kit, sensitivity 0.25 ng/mL, intra-assay precision 3.9%, inter-assay precision 6.3%), resistin (R&D Systems kit, sensitivity 0.023 ng/mL, intra-assay CV 4.3%, inter-assay CV 7.5%), and serum ghrelin (DSL kit, sensitivity 0.07 ng/mL, intraassay and inter-assay CV 8%) were measured by ELISA using kits supplied by Diagnostic System Laboratories. Cytokine, TNF-a, IL-1, and IL-6 were assessed by enzyme-linked immunosorbent assay (ELISA) using commercial kits for humans (eBIO SCIENCE, intra-assay CV ≤15%; inter-assay CV ≤20%) in accordance with the manufacturer's instructions. The presence and concentration of the cytokines was determined by the intensity of the color measured by a micro ELISA reader.

2.6. Determination of lipid peroxidation

Lipid peroxidation was estimated by measuring TBARS in serum samples according to a modified method of Jentzsch [21]. Briefly, 200 μL of serum was added to the reaction mixture containing 1 mL of 1% ortho-phosphoric acid and 0.25 mL alkaline solution of thiobarbituric acid-TBA (final volume 2.0 mL) followed by 45 min heating at 95 °C. The results were expressed as MDA per nmol/mL of serum.

2.7. Carbonylation of serum protein

The carbonylation of serum proteins was determined by a modified Levine's method [22]. The absorbance of the supernatant at 370 nm was measured using a spectrophotometer. Carbonyl content was calculated

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Table 1
Clinical characteristics of patients before bariatric surgery and clinical treatment. Patients were divided into: control (n = 20), bariatric (n = 20), bariatric diabetic (n = 20) groups. Each column represents mean ± SD.

Patients	Control	Bariatric	Bariatric diabetic
Age	39.2 ± 12.4	36.7 ± 10.5	52.0 ± 10.7
Men	15%	25%	10%
Women	85%	75%	90%
Diabetes mellitus	–	–	100%
Hypertension	56,25%	27,3%	90%
Dyslipidemias	25.0%	45.5%	80%
Osteoarthritis	37,5%	9%	40%
Anxiety/stress	75%	81.8%	100%
Depression	12,5%	45,5%	80%
Apnea	25%	27,3%	80%

using 22 × 103 mmol/cm as the molar extinction coefficient, and the results were expressed as nanomoles of carbonyl groups per milligram protein.

2.8. Superoxide dismutase (SOD) and catalase (CAT) activities

SOD activity in whole blood was performed according to the method of Misra and Fridovich [23]. In this method, SOD present in the sample competes with the detection system for radical superoxide. A unit of SOD is defined as the amount of enzyme that inhibits by 50% the speed of oxidation of adrenalin. The oxidation of adrenalin leads to the formation of the colored product, adrenochrome, which is detected by spectrophotometer. SOD activity is determined by measuring the speed of adrenochrome formation, observed at 480 nm, in a reaction medium containing glicine-NaOH (50 mM, pH 10) and adrenalin (1 mM). The SOD activity was expressed in USOD/mg protein.

The determination of the CAT activity was carried out in accordance with a modified method of Nelson and Kiesow [24]. This assay involves the change in absorbance at 240 nm due to CAT-dependent decomposition of hydrogen peroxide. An aliquot (0.02 mL) of blood was homogenized in potassium phosphate buffer, pH 7.0. The spectrophotometric determination was initiated by the addition of 0.07 mL in an aqueous solution of hydrogen peroxide 0.3 mol/L. The change in absorbance at 240 nm was measured for 2 min. The CAT activity was calculated using the molar extinction coefficient and the results were expressed as nmol/mg protein.

2.9. Determination of non-protein thiols

Non-protein thiols were assayed in serum by the method of Ellman [25] with some modifications. Aliquots (0.1 mL) of serum were added to a phosphate buffer 0.3 mol/L (0.85 mL), pH 7.4, and the reaction was read at 412 nm after the addition of 10 mM 5–5 V-dithio-bis(2-nitrobenzoic acid) (DTNB) (0.05 mL). Results were expressed as nmol NPSH/mL of serum.

2.10. Protein determination

Protein was determined by the coomassie blue method according to Bradford [28] using bovine serum albumin as standard.

2.11. Statistical analysis

Statistical analysis was performed using GraphPad Prism 5.0 (GraphPad Prism 5.0 Software Inc.). Data were analyzed statistically using a 2-way ANOVA followed by a Duncan's multiple range test. All data were expressed as the mean ± standard error. Differences were considered significant when was $p < 0.05$.

3. Results

Table 1 shows the results for BMI, body weight, and waist circumference before and 1, 3, 6, and 12 months after bariatric surgery and clinical treatment. There were no significant differences in BMI between the groups before the treatments. All patients were classified as morbidly obese, with a BMI >40 kg/m^2. The BMI of the control group remained unaltered throughout treatment, indicating that the clinical treatment was not effective in reducing body weight. Both surgical groups showed a significant decrease in BMI over time, reaching around 25 kg/m^2 after 12 months, showing the efficacy of bariatric surgery in terms of weight loss. The mean abdominal circumference for all groups before the treatments was >120 cm (Table 2). The clinical treatment had no effect on abdominal circumference. However, bariatric surgery significantly reduced abdominal circumference to around 80–88 cm. In addition, there was a significant reduction in the risk of complications.

Fasting glucose and glycated hemoglobin concentrations before and after bariatric surgery are shown in Table 3. Fast glucose concentrations were higher in the bariatric diabetic group (around 170 mg/dl) compared to the other groups, confirming the diagnosis of diabetes in these patients. One month after surgery, fast glucose concentrations decreased to normal concentrations (99 mg/dl) and remained in this range throughout the 12 months after surgery. In the bariatric diabetic group, a significant fall in glycated hemoglobin (HbA1c) concentrations occurred between the pre and postsurgical periods. No significant differences in HbA1c concentrations were observed in the control or bariatric groups.

As can be seen in Table 3, there were no significant differences in total and LDL cholesterol concentrations between the groups before treatment. The control group showed no significant differences in

Table 2
Body mass index (BMI), body weight and abdominal circumference before and 1, 3, 6 and 12 months after bariatric surgery and clinical treatment. Patients were divided into: control (n = 20), bariatric (n = 20), bariatric diabetic (n = 20) groups. Each column and row represents mean ± S.D. Duncan's multiple range test: different capital letters in the same column indicate a statistical difference among control, bariatric and bariatric diabetic groups ($p < 0.05$); different lowercase letters in the same row indicate a statistical difference among the different times within the same group ($p < 0.05$).

Groups/time	0	1 month	3 months	6 months	12 months
Body weigth (kg)					
Control	122.97 ± 6.25^{aA}	122.22 ± 9.67^{aA}	121.73 ± 8.45^{aA}	127.33 ± 10.45^{aA}	122.89 ± 10.62^{aA}
Bariatric	115.90 ± 6.75^{aA}	99.45 ± 4.67^{abB}	92.63 ± 14.67^{bB}	82.81 ± 8.76^{cB}	73.49 ± 4.56^{dB}
Bariatric DT	105.90 ± 10.53^{aA}	93.20 ± 9.76^{abB}	86.90 ± 8.98^{bB}	76.20 ± 4.45^{cB}	70.80 ± 7.87^{dcB}
Body mass index (BMI kg/m^2)					
Control	46.25 ± 2.12^{aA}	45.58 ± 2.12^{aA}	45.62 ± 2.99^{aA}	49.34 ± 2.67^{aA}	48.38 ± 2.96^{aA}
Bariatric	43.09 ± 1.95^{aA}	37.54 ± 3.41^{abA}	34.54 ± 4.32^{bA}	30.71 ± 1.95^{bB}	27.33 ± 2.01^{bcB}
Bariatric DT	43.40 ± 3.65^{aA}	38.57 ± 3.12^{abA}	31.97 ± 2.95^{bB}	31.50 ± 2.67^{bB}	25.41 ± 1.65^{bcB}
Waist circumference (cm)					
Control	133.19 ± 5.29^{aA}	134,33 ± 5.66^{aA}	132.00 ± 7.24^{aA}	131.50 ± 9.87^{aA}	132.40 ± 6.24^{aA}
Bariatric	123.00 ± 4.78^{abA}	107.27 ± 4.32^{bB}	97.45 ± 3.52^{cB}	91.81 ± 3.63^{cB}	83.21 ± 4.01^{cB}
Bariatric DT	121.22 ± 3.53^{abA}	108.55 ± 2.43^{bB}	89.77 ± 10.22^{cB}	90.44 ± 2.06^{cB}	82.77 ± 9.57^{cB}

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Table 3
Fasting glucose, glycated hemoglobin, cholesterol LDL, cholesterol HDL and triglycerides levels before and 1, 3, 6 and 12 months after bariatric surgery and clinical treatment. Patients were divided into: control (n = 20), bariatric (n = 20), bariatric diabetic (n = 20) groups. Each column and row represents mean ± S.D. Duncan's multiple range test: different capital letters in the same column indicate a statistical difference among control, bariatric and bariatric diabetic groups ($p < 0.05$); different lowercase letters in the same row indicate a statistical difference among the different times within the same group ($p < 0.05$).

Groups/time	0	1 month	3 months	6 months	12 months
Glucose fast (mg/dl)					
Control	115.66 ± 6.33^{aA}	103.90 ± 4.42^{aA}	105.87 ± 3.35^{aA}	101.11 ± 1.93^{aA}	102.12 ± 3.41^{aA}
Bariatric	101.60 ± 3.59^{aA}	91.30 ± 2.45^{bA}	91.22 ± 2.01^{bA}	87.00 ± 1.86^{bB}	87.22 ± 3.53^{bB}
Bariatric DT	164.50 ± 4.22^{bB}	97.37 ± 2.92^{bA}	95.33 ± 1.75^{bA}	95.00 ± 3.39^{bA}	85.87 ± 4.11^{bB}
Glicated hemoglobin (mmol/L)					
Control	6.35 ± 1.34^{aA}	6.44 ± 0.67^{aA}	5.75 ± 0.42^{aA}	5.78 ± 0.46^{aA}	6.13 ± 0.32^{aA}
Bariatric	5.38 ± 0.50^{aA}	5.20 ± 0.82^{aA}	5.12 ± 0.62^{aA}	5.10 ± 0.61^{aA}	5.12 ± 0.49^{aA}
Bariatric DT	7.43 ± 0.269^{aA}	6.34 ± 0.45^{aA}	5.59 ± 0.36^{bA}	5.55 ± 0.91^{bA}	5.66 ± 0.56^{bA}
Cholesterol total (mg/dl)					
Control	226.20 ± 7.76^{aA}	199.40 ± 11.34^{aA}	203.87 ± 5.40^{aA}	200.88 ± 6.12^{aA}	210.11 ± 10.56^{aA}
Bariatric	216.80 ± 10.6^{aA}	164.36 ± 11.14^{bB}	154.30 ± 7.92^{bB}	146.00 ± 7.54^{bB}	157.80 ± 9.62^{bB}
Bariatric DT	220.00 ± 8.36^{aA}	189.10 ± 13.07^{bA}	164.60 ± 10.4^{bB}	154.30 ± 7.86^{bB}	160.22 ± 9.30^{bB}
HDL cholesterol (mg/dl)					
Control	48.50 ± 0.95^{aA}	44.18 ± 2.25^{aA}	43.42 ± 2.91^{aA}	49.66 ± 1.72^{aA}	47.37 ± 3.93^{aA}
Bariatric	43.66 ± 4.50^{aA}	41.70 ± 2.22^{aA}	45.00 ± 2.14^{aA}	50.50 ± 2.34^{bA}	49.61 ± 1.40^{bA}
Bariatric DT	44.12 ± 2.89^{aA}	41.50 ± 4.70^{aA}	47.37 ± 1.99^{aA}	53.77 ± 1.41^{bA}	59.40 ± 2.92^{bA}
Triglycerides (mg/dl)					
Control	153.50 ± 20.50^{aA}	183.42 ± 28.42^{aA}	114.37 ± 7.40^{bA}	138.87 ± 6.88^{aA}	148.57 ± 10.8^{aA}
Bariatric	220.00 ± 17.6^{aB}	109.90 ± 8.25^{bB}	112.20 ± 10.6^{bA}	109.37 ± 12.92^{bA}	97.90 ± 13.16^{bB}
Bariatric DT	206.28 ± 19.3^{aB}	145.20 ± 10.7^{bA}	112.50 ± 9.84^{bA}	100.80 ± 9.15^{bA}	99.20 ± 8.77 ^{cB}

total and HDL cholesterol concentrations before and after the clinical treatment. Total and HDL cholesterol were significantly lower 1, 3, 6, and 12 months after surgery in the bariatric and bariatric diabetic groups compared to the basal period (Table 2). No significant differences in HDL cholesterol concentrations were observed among the groups before and 1, 3, and 6 months after surgery or clinical treatment. However, cholesterol HDL concentrations increased significantly in the bariatric diabetic group 12 months after surgery. Triglyceride concentrations were significantly elevated (>200 mg/dl) in the bariatric and bariatric diabetic groups before surgery (Table 3). These concentrations showed a significant reduction 1 month after the surgery and remained within the reference limits during the post-surgical period.

Insulin, HOMA IR, HOMA β, resistin, and ghrelin concentrations showed a significant decrease 12 months after bariatric surgery in both diabetic and non-diabetic patients (Table 4). No significant difference in these parameters was observed in patients before and after clinical treatment.

As can be seen in Table 5, inteleukin-6, inteleukin-1, and TNF-α concentrations significantly decreased 12 months after bariatric surgery in both diabetic and non-diabetic patients. However, adiponectin concentrations showed a significant increase 12 months after surgery in these patients. No significant difference in inteleukin-6, inteleukin-1, and TNF-α concentrations was observed in patients from the control group.

Table 6 shows the results obtained for lipid peroxidation. No significant difference in TBARS or carbonyl group concentrations were observed in the control group. TBARS and carbonyl group concentrations decreased significantly 6 and 12 months after bariatric surgery in the bariatric group. In the bariatric diabetic group a significant reduction in TBARS concentrations was observed 3, 6, and 12 months after surgery. TBARS concentrations were also higher before and 1 month after surgery compared to the other groups, indicating that diabetic obese individuals show a greater degree of lipoperoxidation. As can be seen in Table 6, the bariatric diabetic group showed a significant reduction in carbonyl protein concentrations 3, 6, and 12 months after surgery. In addition, carbonyl protein concentrations were significantly higher in the bariatric diabetic group before surgery compared to the control and bariatric groups.

No significant difference in CAT and SOD activity was observed in the control group before and after treatment. SOD activity showed a significant increase at 3, 6, and 12 months after surgery in both the bariatric and bariatric diabetic groups (Table 7). In the bariatric group, CAT activity increased gradually 3, 6, and 12 months after surgery. In the bariatric diabetic group this increase was observed from 1 month after surgery. It is important to note that CAT activity in the bariatric diabetic group was significantly lower before surgery compared to the other groups.

Similar to the SOD and CAT activity, both diabetic and non-diabetic patients that received bariatric surgery showed a significant increase in NPSH levels 3, 6, and 12 months after surgery (Table 6). NPSH levels

Table 4
Insulin, HOMA IR, HOMA β, resistin and ghrelin levels before and 12 months after bariatric surgery and clinical treatment. Patients were divided into: control (n = 20), bariatric (n = 20), bariatric diabetic (n = 20) groups. Each column and row represents mean ± S.D. Duncan's multiple range test: different capital letters in the same column indicate a statistical difference among control, bariatric and bariatric diabetic groups ($p < 0.05$); different lowercase letters in the same row indicate a statistical difference among the different times within the same group ($p < 0.05$).

Groups/time	0	12 months
Insulin (μU/mL)		
Control	23.26 ± 4.57^{aA}	21.46 ± 5.67^{aA}
Bariatric	19.33 ± 2.33^{aA}	6.26 ± 1.28^{bB}
Bariatric DT	21.86 ± 1.92^{aA}	5.50 ± 1.23^{bB}
HOMA IR (mmol/L·μU/mL)		
Control	6.62^{aA}	5.39^{aA}
Bariatric	4.83^{aA}	1.34^{bB}
Bariatric DT	6.08^{aA}	1.28^{bB}
HOMA β (mmol/L/μU/mL)		
Control	162.58^{aA}	203.31^{aA}
Bariatric	185.57^{aB}	96.89^{bB}
Bariatric DT	188.44^{aB}	90.16^{bB}
Resistin (ng/mL)		
Control	70.86 ± 1.90^{aA}	69.86 ± 2.19^{aA}
Bariatric	69.00 ± 2.09^{aA}	51.13 ± 2.77^{bB}
Bariatric DT	73.06 ± 2.35^{bA}	58.13 ± 2.22^{bA}
Ghrelin (pg/mL)		
Control	41.40 ± 2.18^{aA}	43.60 ± 3.33^{aA}
Bariatric	45.86 ± 1.80^{aA}	33.60 ± 1.09^{bB}
Bariatric DT	44.46 ± 1.82^{aA}	32.53 ± 1.49^{bB}

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Table 5
Inteleukin-6, inteleukin-1, TNF-α and adiponectin levels before and 12 months after bariatric surgery and clinical treatment. Patients were divided into: control (n = 20), bariatric (n = 20), bariatric diabetic (n = 20) groups. Each column and row represents mean ± S.D. Duncan's multiple range test: different capital letters in the same column indicate a statistical difference among control, bariatric and bariatric diabetic groups ($p < 0.05$); different lowercase letters in the same row indicate a statistical difference among the different times within the same group ($p < 0.05$).

Groups/time	0	12 months
Inteleukin-6 (pg/mL)		
Control	287.93 ± 19.37^{aA}	253.53 ± 15.96^{aA}
Bariatric	241.26 ± 21.88^{aAB}	190.93 ± 14.58^{bB}
Bariatric DT	220.53 ± 18.44^{aB}	167.61 ± 12.68^{bB}
Interleukin-1 (pg/mL)		
Control	248.92 ± 17.17^{aA}	223.33 ± 17.17^{aA}
Bariatric	197.68 ± 11.44^{bB}	166.56 ± 10.21^{bB}
Bariatric DT	207.76 ± 9.38^{bB}	174.2 ± 6.82^{bB}
TNF-α (pg/mL)		
Control	318.26 ± 20.91^{aA}	285.26 ± 15.41^{aA}
Bariatric	266.13 ± 23.01^{aA}	210.06 ± 13.91^{bB}
Bariatric DT	251.76 ± 20.09^{aA}	204.92 ± 14.10^{bB}
Adiponectin (ng/mL)		
Control	50.60 ± 3.02^{aA}	53.13 ± 2.40^{aA}
Bariatric	46.33 ± 2.43^{aA}	77.93 ± 2.22^{bB}
Bariatric DT	53.80 ± 3.82^{aA}	80.13 ± 1.60^{bB}

were lower in diabetic patients before surgery compared to the other groups, increasing the susceptibility of these individuals to oxidative damage.

4. Discussion

Obesity is related to oxidative stress in various ways such as hyperglycemia, increased muscle activity, inadequate antioxidant defenses, lipid oxidation, chronic low grade inflammation, and hypertension [10,21–26]. An increase in oxidative stress derived inflammation has been hypothesized to be a major mechanism behind the pathogenesis and progression of obesity-related disorders [27]. In addition, the overproduction of ROS is responsible for an increase in circulating concentrations of proinflammatory cytokines, adipokines, and other inflammatory markers [10,11,28]. In this study, we evaluated the short and long term effects of bariatric surgery and clinical treatment on the development of the main variables related to diabetes and obesity, in particular inflammatory and oxidative parameters.

In our study both diabetic and non-diabetic patients given bariatric surgery showed significant decreases in body weight, BMI, and abdominal circumference (Table 2). The weight loss seen in patients after surgery was most intense over the first 3 months. These results are in accordance with reports that Roux-en-Y gastric bypasses can induce weight loss through a combination of mechanisms, including decreasing the capacity of the stomach, restricting the rate of emptying of the pouch, prohibiting the intake of high osmolar foods, and causing selective malabsorption of fat [29]. Another mechanism that could be associated with the decreases in body weight could be related to the significant decrease in ghrelin concentrations seen in both the bariatric and bariatric diabetic patients (Table 3) [30]. In fact, previous studies have demonstrated that a gastric bypass may disrupt ghrelin secretion, isolating ghrelin producing cells from direct contact with ingested nutrients, which normally regulates ghrelin concentrations [31,32]. Thus, this effect may contribute to the efficacy of the procedure in reducing weight, as ghrelin is an orexigenic hormone that has been implicated in both meal-time hunger and the long term regulation of body weight.

In relation to glycemia, the fasting plasma glucose concentrations before surgery were higher in the diabetic patients in our study (around 170 mg/dl), confirming the diagnosis of diabetes (Table 3). One month after surgery glucose concentrations decreased to normal concentrations (99 mg/dl) and remained in this range 12 months after surgery. These results are in line with several studies that have demonstrated that bariatric surgery can effectively and safely control diabetes in the short term and long term and even prevent its occurrence [30,32]. It is important to point out that restrictive procedures decrease food intake, leading to a reduction in glycemic load, and can contribute to weight loss and to the improvement of glucose control. Moreover, these results are directly linked to the increase in insulin sensitivity, and consequently the decrease in insulin resistance (HOMA-IR), observed in our study in both groups given bariatric surgery [33,34]. Thus, although our study found a significant decrease in insulin concentrations after bariatric surgery, it is plausible that massive weight loss and reduction of adipose tissue mass contributed to the increase in insulin sensitivity and consequently to the improvement in glycemic control in these patients.

In addition to the decrease in glucose concentrations, total cholesterol and triglyceride concentrations were also significantly lower at 1, 3, 6, and 12 months after surgery in both the bariatric and bariatric diabetic groups, while HDL cholesterol increased (Table 3). These results suggest an improvement in the lipid profile related to the improvement in fasting glucose, insulin resistance, weight loss, and waist circumference in patients given bariatric surgery [35]. This improvement in dyslipidemia was sustained with long term weight loss and was associated with a decrease in ectopic abdominal fat, which has long been recognized as inducing insulin resistance, subclinical inflammation, and cardiovascular risks specific to type 2 diabetes [36].

In this context, considering that inflammation is known to contribute to insulin resistance, we also investigated the plasma concentrations of inflammatory molecules before and after surgery. The elevation of inflammatory markers in obesity results from the endocrine activity of

Table 6
Lipid peroxidation (TBARS), carbonyl protein levels and non-protein thiols (NPSH) levels before and 1, 3, 6 and 12 months after bariatric surgery and clinical treatment. Patients were divided into: control (n = 20), bariatric (n = 20), bariatric diabetic (n = 20) groups. Each column and row represents mean ± S.D. Duncan's multiple range test: different capital letters in the same column indicate a statistical difference among control, bariatric and bariatric diabetic groups ($p < 0.05$); different lowercase letters in the same row indicate a statistical difference among the different times within the same group ($p < 0.05$).

Groups/time	0	1 month	3 months	6 months	12 months
TBARS (ηmol MDA/mg protein)					
Control	20.56 ± 5.6^{aA}	18.08 ± 4.1^{aA}	20.01 ± 3.1^{aA}	19.08 ± 3.7^{aA}	21.0 ± 4.1^{aA}
Bariatric	22.45 ± 4.5^{aA}	20.51 ± 5.9^{aA}	15.96 ± 5.1^{bA}	12.45 ± 2.9^{bA}	9.46 ± 1.9^{bB}
Bariatric DT	25.62 ± 4.8^{aA}	27.50 ± 4.8^{aB}	17.56 ± 4.5^{bA}	13.23 ± 3.4^{bA}	11.35 ± 1.6^{aB}
Protein carbonylation (ηmol/mg of protein)					
Control	2.95 ± 0.5^{aA}	3.61 ± 0.3^{aA}	3.54 ± 0.4^{aA}	3.91 ± 0.9^{aA}	4.2 ± 1.2^{bA}
Bariatric	3.50 ± 0.93^{aA}	3.43 ± 1.0^{aA}	2.65 ± 0.2^{aA}	1.26 ± 0.1^{bB}	1.96 ± 0.3^{bB}
Bariatric DT	3.13 ± 0.1^{aA}	2.96 ± 0.3^{aA}	2.19 ± 0.7^{aB}	1.95 ± 0.6^{bB}	1.84 ± 0.5^{bB}
NPSH (μmol/mL plasma)					
Control	0.80 ± 0.1^{aA}	0.95 ± 0.1^{aA}	1.00 ± 0.3^{aA}	1.00 ± 0.2^{aA}	0.99 ± 0.6^{aA}
Bariatric	0.95 ± 0.3^{aA}	0.82 ± 0.2^{aA}	1.32 ± 0.5^{aA}	1.45 ± 0.4^{bAB}	1.67 ± 0.7^{bB}
Bariatric DT	0.70 ± 0.1^{aA}	1.15 ± 0.3^{aA}	1.45 ± 0.4^{bA}	1.75 ± 0.5^{bB}	1.60 ± 0.4^{bB}

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Table 7
Superoxide dismutase (SOD) and catalase (CAT) activity before and 1, 3, 6 and 12 months after bariatric surgery and clinical treatment Patients were divided into: control (n = 20), bariatric (n = 20), bariatric diabetic (n = 20) groups. Each column and row represents mean ± S.D. Duncan's multiple range test: different capital letters in the same column indicate a statistical difference among control, bariatric and bariatric diabetic groups ($p < 0.05$); different lowercase letters in the same row indicate a statistical difference among the different times within the same group ($p < 0.05$).

Groups/time	0	1 month	3 months	6 months	12 months
Superoxide dismutase activity (U SOD/mg protein)					
Control	18.8 ± 4.8^{aA}	19.8 ± 4.2^{aA}	20.96 ± 6.3^{aA}	18.6 ± 3.7^{aA}	21.4 ± 3.7^{aA}
Bariatric	15.5 ± 5.4^{aA}	17.1 ± 5.9^{aA}	20.6 ± 3.3^{aA}	27.5 ± 7.9^{bB}	30.3 ± 5.2^{bB}
Bariatric DT	19.6 ± 4.1^{aA}	20.0 ± 4.8^{aA}	26.5 ± 7.2^{bB}	29.6 ± 3.4^{bB}	29.6 ± 4.2^{bB}
Catalase activity (ηmol/mg of protein)					
Control	14.3 ± 2.5^{aA}	14.1 ± 3.0^{aA}	13.4 ± 1.4^{aA}	15.5 ± 3.3^{aA}	14.9 ± 1.9^{aA}
Bariatric	15.6 ± 3.2^{aA}	13.3 ± 2.0^{aA}	20.6 ± 2.9^{bB}	28.6 ± 4.1^{cB}	27.1 ± 3.3^{cB}
Bariatric DT	17.2 ± 4.1^{aA}	21.9 ± 1.3^{aB}	22.9 ± 3.7^{bB}	25.5 ± 6.6^{cB}	29.4 ± 3.7^{cB}

excess adipose tissue [7,9,11]. During the differentiation of preadipocytes into mature adipocytes, the latter become capable of producing a number of enzymes, cytokines, growth factors, and hormones involved in several metabolic events [37,38]. Among these adipokines, resistin has recently been found to participate in the inflammatory response, with increased concentrations of this molecule leading to the over production of glucose from the liver and inhibiting preadipocyte differentiation [38,39]. In the present study, resistin concentrations were markedly elevated in obese patients before surgery and showed a significant decrease 12 months after bariatric surgery in both diabetic and non-diabetic patients (Table 4). These results corroborate those obtained by Edwards et al. [40] and Jankiewicz-Wika et al. [41], who also found lowered plasma resistin concentrations 12 months after bariatric surgery, together with a decrease in insulin resistance. Furthermore, this decrease in resistin concentrations is associated with the reduction of abdominal obesity in these patients, as it is mainly secreted by adipocytes and macrophages found in visceral adipose tissue.

Interestingly, in our study decreases in resistin concentrations in bariatric patients was accompanied by decreases in the inflammatory markers IL-1, IL-6, and TNF-α and by an increase in anti-inflammatory molecules such as adiponectin (Table 5). In this context, it is important to point out that the pro-inflammatory effects of resistin have been attributed to its ability to activate NF-kB signaling pathways and subsequently to increase the expression of several pro-inflammatory cytokines, including IL-1, IL-6, and TNF-α, which can impair insulin signaling pathways and lead to insulin resistance [42–45].

Among the major mediators of the inflammatory response is TNF-alpha, which contributes to the deregulation of insulin-signaling pathways by the phosphorylation of the insulin receptor substrate-1 (IRS-1) protein in serine residues by kinases, which consequently prevents its interaction with the insulin receptor beta subunit [43]. In line with our results, previous studies have reported over expression of TNF-alpha in the adipose tissue of both human and animal models of obesity, as well as links between a decrease in TNF-alpha and a reduction in body weight and waist and hip circumferences [46–48].

Showing similar effects upon the metabolism of carbohydrates and lipids to those of TNF-α, chronic exposure to elevated IL-6 concentrations, which were found in our study, is associated with the development of insulin resistance, diabetes mellitus, and cardiovascular disease [38] (Table 5). Among the damaging effects caused by exposure to IL-6 is a reduction of glucose transporter-4 and insulin receptor substrate-1 expression, as well as the suppression of adiponectin expression [28,42,43]. In fact, the results of our study demonstrated that elevated concentrations of IL-6 are accompanied by a decrease in adiponectin concentrations before surgery. However, with the significant weight loss after surgery, we observed a significant decrease in IL-6 concentrations, together with an increase in the circulating concentrations of adiponectin, which is an important inhibitor agent of the inflammatory process. Adiponectin is a peptide secreted by adipose tissue and its circulating concentrations are inversely proportional to the body mass index. It plays an important role in metabolic control by binding to two receptors of adiponectin (AdipoR1 and AdipoR2) [49,50,51]. Studies have indicated that in both liver and skeletal muscle, adiponectin reduced triglyceride content and improved insulin signaling by increasing the expression of genes involved in fatty acid oxidation [52]. Moreover, previous studies have shown that increases in insulin sensitivity, promoted by adiponectin, is associated with the inhibition of the expression of hepatic gluconeogenic enzymes and the rate of endogenous glucose production, resulting in decreases in both serum glucose and hepatic glucose production [49–53]. Thus, knowing the effects of adiponectin, it is plausible to suggest that the surgery, and the subsequent weight loss, culminate in the rise of the concentrations of this peptide and consequently in a number of metabolic benefits. It is important to note that the alterations in biochemical and inflammatory parameters observed in obese patients after the surgery are directly correlated with the results obtained for the oxidative stress biomarkers evaluated in this study.

Our results show an increase in TBARS levels, an important indicator of lipid peroxidation, as well as in protein carbonyl levels in all groups before surgery (Table 6). These results are consistent with other studies that related obesity to a state of chronic oxidative stress [27,46,54–56]. This increase in oxidative damage is associated to the important role adipose tissue plays in producing ROS. In obese states, increasing amounts of macrophages and lymphocytes reside in the adipose tissue and, in combination with adipocytes, may release ROS [10,11]. Moreover, obesity has been associated with increased expression of NADPH oxidase and a reduction in the expression of several antioxidant proteins [56]. In line with these data, in this study we observed a decrease in SOD and CAT activity in obese patients before treatment. The decrease in the activity of these enzymes can lead to an accumulation of the anion O_2, and thus H_2O_2, which through the Fenton reaction can generate highly reactive HO radicals that can cause lipoperoxidation as well as important protein and DNA alterations leading to cell dysfunctions and to the development of comorbidities associated to obesity [27].

However, levels of lipid peroxidation and protein carbonylation significantly decreased with weight loss in obese diabetic and non-diabetic patients who underwent surgery, along with an increase in SOD and CAT activity (Table 7). This elevation may be the result of improved antioxidant capacity in these patients and consequently a reduction in oxidative lesions [54,55]. It is important to point out that this increase in SOD and CAT activity 6 and 12 months after surgery can be related to an increase in the conditions that induce SOD and CAT synthesis, in particular the reduction of adipose tissue. Consistent with our results, some studies have found that 6 months after bariatric surgery there is a reduction in the oxidative stress of patients, associated with an increase in SOD and CAT activity [55,56,57]. These results differ from those reported by Murri [27], who found that total antioxidant capacity and the activity of CAT and SOD did not vary significantly during their study. In this context, it is important to note that data from previous studies have shown that CAT and SOD activity varies widely in obese patients [58]. These differences in the activity of antioxidant enzymes can be attributed to variations related to age, gender, and the degree and duration of the

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pathology as well as variations in the study models and types of surgeries used.

Similar to SOD and CAT activity, diabetic and non-diabetic patients that received bariatric surgery showed a significant increase in NPSH levels 3, 6, and 12 months after surgery (Table 6). Our data are comparable with those reported by Cabrera et al. [46] and Uzun et al. [59], who also found that GSH levels, the main non-protein thiol, significantly increased 6 and 12 months after surgery. It is important to note that weight loss can cause a reduction in ROS production, which consequently can lead to the restoration of NPSH levels in patients who have received bariatric surgery, as the depletion of this antioxidant in morbidly obese patients could be due to its increased utilization in removing H_2O_2 and other peroxides produced in excess due to oxidative stress and the inflammatory process. In this context, a decrease in ROS production, together with a reduction of adipose tissue, could contribute to the elevation of NPSH levels that in turn may result in the reduction of oxidative lesions and related pathologies in patients after surgery.

In contrast to the improvements in the biochemical, oxidative, and inflammatory markers in patients who received bariatric surgery, no significant differences were observed in patients that were given clinical treatment. It is important to point out that the patients given clinical treatment were provided with alimentary reeducation, with a balanced hypocaloric diet and frequent exercise. We recommended physical activity at least three times a week (moderate exercise, 4–7 kcal/min, for 20 to 30 min). As found in other studies, it is difficult to engage and maintain people in clinical treatment as it is too hard to change life habits and follow so many restrictions. The difficulty of putting into practice these medical recommendations, along with the lack of medications free of significant side-effects to help reduce weight and the compensatory mechanisms related to food intake, is a significant factor that influences the ineffectiveness of clinical treatment. Thus, we suggest that the absence of improvement in the parameters analyzed in the patients undergoing clinical treatment is directly related to these factors.

In conclusion, in this study we could show that before surgical treatment all obese patients showed indicators of systemic oxidative stress, accompanied by indicators of low antioxidant defenses and alterations in biochemical and inflammatory parameters. However, after bariatric surgery significant improvements in antioxidant defense were observed, associated with a reduction in oxidative lesions and inflammatory biomarkers. This improvement in the oxidative profile and biochemical parameters was proportional to the reduction in BMI and abdominal circumference. Thus, we suggest that a decrease in adipose tissue can lead to lower ROS levels and cytokine synthesis and liberation, resulting in a reduction in oxidative stress. These findings support the idea of adipose tissue as a potential therapeutic target in the prevention and control of pathogenesis related to obesity. Moreover, they reinforce the effectiveness of bariatric surgery in the treatment of morbid obesity and its complications, particularly diabetes mellitus.

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