




Research Article

Chemerin, Inflammatory, and Nitrooxidative Stress Marker Changes Six Months after Sleeve Gastrectomy

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Background. Chemerin is a chemokine known to be increased in morbidly obese (MO) patients and correlated with markers of inflammation and nitrooxidative stress. We aimed to evaluate the changes of serum chemerin six months after laparoscopic sleeve gastrectomy (SG) and to assess if these changes are accompanied by variations of inflammatory and nitrooxidative stress markers. **Material and Methods.** We investigated the levels of chemerin, high-sensitive C-reactive protein (hsCRP), tumor necrosis factor alpha (TNF- α), nitrite and nitrate (NOx), total oxidant status (TOS), total antioxidant response (TAR), and oxidative stress index (OSI) in a group of 24 MO patients submitted to SG before and six months after surgery. The MO group was compared with 20 controls. **Results.** hsCRP ($p < 0.001$), NOx ($p < 0.001$), TOS ($p < 0.001$), TAR ($p = 0.007$), and OSI ($p = 0.001$) were significantly different between the two groups. Six months after surgery, we noticed significant changes (42.28% decrease) of hsCRP ($p = 0.044$) and OSI ($p = 0.041$) (31.81% decrease), while no significant changes were observed for chemerin ($p = 0.605$), TNF- α ($p = 0.287$), NOx ($p = 0.137$), TOS ($p = 0.158$), and TAR ($p = 0.563$). **Conclusions.** Our study showed no significant changes of chemerin, and except for hsCRP and OSI, no other inflammatory and nitrooxidative stress markers changed six months after surgery.

1. Introduction

Mounting evidence has demonstrated that excess adipose tissue is a source and a cause of chronic inflammation, oxidative stress, and adipokine dysregulation which are all interrelated and involved in development of metabolic complications [1, 2]. The first acute-phase protein to be described, C-reactive protein (CRP), produced by the liver and the adipose tissue, is a sensitive marker of inflammation known to be increased in obesity and involved in the pathogenesis of coronary heart disease and diabetes mellitus [3–5]. Tumor necrosis factor alpha (TNF- α) is a well-known inflammatory

marker produced by the macrophages of the stromal vascular tissue from the adipose tissue and has increased circulating levels in obesity-inducing insulin resistance [2, 3]. Furthermore, TNF- α determines oxidative stress leading to endothelial dysfunction and atherogenesis. High levels of TNF- α have been shown to increase the activity of inducible/inflammatory nitric oxide synthase (iNOS), the enzyme that induces large amounts of nitric oxide (NO) production that has cytotoxic effects and promotes apoptosis [6]. On the other hand, it has been shown that reactive oxygen species (ROS) enhance the production of proinflammatory cytokines and adhesion molecules [2, 7, 8].

Chemerin is a recently discovered chemokine known as a regulator of adipogenesis, inflammation, and glucose metabolism. The bulk of human data shows that obese patients display elevated chemerin levels which are positively correlated with markers of inflammation such as TNF- α and CRP, and thereby it might be used as an inflammatory marker. Also, chemerin seems to have a disruptive effect on glucose homeostasis and might be involved in the occurrence of type 2 diabetes and of other comorbidities [9–11]. Moreover, some authors have shown that insulin resistance seems to be a predictor of chemerin levels, independent of BMI [12].

Sleeve gastrectomy (SG) is a safe and effective as a standalone bariatric procedure with good weight loss results and effects on comorbidities explained by the reduction in adipose tissue mass and consecutive improvement of the inflammatory profile [13–15]. Studies that have addressed the dynamic of chemerin in relation with inflammatory markers, glucose homeostasis, and surgical weight loss have demonstrated various results. Some authors showed that the elevated plasma chemerin levels in morbidly obese (MO) patients decreased during the first year after gastric bypass, most prominently in the first 3 months when weight and fat mass loss, improvement of insulin sensitivity, and inflammatory markers were the strongest [16], while others showed no changes six months after both sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) [17]. As for the other inflammatory markers, while the change in TNF- α remains a controversial topic, CRP levels seem to improve significantly at 1 month after SG [15, 18].

The aims of this study were to assess the changes of chemerin 6 months after SG and to find out if these changes are accompanied by variations of inflammation and oxidative stress markers. We hypothesized that significant weight loss would be associated with reduction in inflammatory markers leading to diminished cardiovascular risk.

2. Materials and Methods

2.1. Study Groups. A group of 24 MO (16 female and 8 male) was recruited in a prospective manner from patients referred to bariatric surgery at the Second Surgical Clinic of Cluj-Napoca, Romania, between years 2014 and 2016. They all fulfilled the surgical criteria for bariatric procedures (BMI over 40 kg/m² or BMI between 35 kg/m² and 40 kg/m² with associated comorbidities) and were submitted to laparoscopic SG. The inclusion criteria were both sexes, age between 20 and 59 years, patients eligible for bariatric surgery with several dietary failures, and acceptance to participate to the study. Patients with inflammatory and infectious diseases or use of anti-inflammatory drugs, severe endocrine diseases (other than diabetes), hepatic or renal failure, mental illness, and malignancies were excluded from the study. In the MO group, 8 patients carried the diagnosis of type 2 diabetes, 9 had impaired fasting glucose, and the rest of them were within normal range of fasting blood glucose. None of the patients were on insulin treatment. A second group formed out of 20 normal-weight healthy subjects matched for age and gender with the first group was selected as a control group.

The study was approved by the Ethics Committee (number 503/15.12.2011), and written informed consent was obtained from all individual participants included in the study. The study was conducted in accordance with the ethical principles of the Helsinki declaration.

2.2. Study Design. The morbidly obese patients were evaluated anthropometrically and biochemically before and 6 months after SG. Anthropometrical measurements consisted of weight and height. Blood samples were collected after overnight fast and serum was obtained through centrifugation. The samples were run immediately or stored until analysis at -80°C . The study design included the measurements of chemerin, high-sensitive CRP (hsCRP), TNF- α , markers of nitrooxidative stress, fasting blood glucose, insulin, total cholesterol (TC), triglycerides, and HDL-C (high-density lipoprotein cholesterol). Low-density lipoprotein cholesterol (LDL-C) concentration was calculated by Friedewald formula [19].

2.3. Anthropometric and Laboratory Measurements. BMI was calculated according to the following formula: weight (in kilograms)/squared height (in square meters). The percent of excess BMI loss (%EBMIL) was calculated according to the following formula: %EBMIL = [(initial BMI – postop BMI)/(initial BMI – 25)] \times 100 [20]. Homeostasis model assessment of insulin resistance (HOMA-IR) was used to evaluate insulin resistance using the following formula: HOMA-IR = (fasting insulin $\mu\text{U/ml}$ \times fasting glucose mg/dl)/22.5 \times 18 [21]. A normal value was considered to be <2.5.

Fasting serum hsCRP levels were assayed using an automated system for chemiluminescence method (Immolute 1000, Siemens) and a commercially Immulite hsCRP kit (Siemens, Germany). Chemerin levels were determined using an ELISA kit (Abcam, Cambridge, United Kingdom), serum insulin using an ELISA kit (EMD Millipore, Burlington, Massachusetts, USA), and TNF- α levels using an ELISA method (Thermo Scientific, Waltham, Massachusetts, USA) according to the specific protocol of the manufacturer using an ELISA plate reader (Organon 230S, Netherlands). Coefficients of variation intra- and interassay for the tests were under 10%.

Nitrooxidative stress was evaluated by measuring serum nitric oxide (NO), total oxidative status (TOS), and total antioxidant response (TAR). NO concentration was measured indirectly using a colorimetric method for nitrite and nitrate (NOx) as final stable products. The principle of this method is the reduction of nitrate by vanadium (III) combined with detection by Griess reaction [22–24]. TOS and TAR as oxidative stress markers were analyzed using colorimetric methods, as well. TOS results were expressed in $\mu\text{mol H}_2\text{O}_2$ equiv./l [25, 26]. For TAR, the assay was calibrated with Trolox, and the results were expressed as mmol Trolox equiv./l [24–26]. The oxidative stress index (OSI) is an indicator of the degree of oxidative stress and is calculated by the ratio of the TOS to TAR [27].

Fasting blood glucose, TC, HDL-C, and triglycerides were measured using the standard enzymatic colorimetric method on an automatic analyzer (Prestige 24i, Tokyo Boeki, Japan).

2.4. Surgical Procedure. The greater curvature and fundus of the stomach were resected starting from the distal antrum, 2–3 cm cranial to the pylorus, to the angle of His. We used an Endo GIATM (Covidien, Medtronic, Minneapolis, MN, USA) laparoscopic stapler, with a 60 mm cartridge in order to divide the stomach and create a gastric tube parallel to and alongside a 34 CH bougie. The resected part of the stomach was extracted through the middle abdominal 15 mm port site.

2.5. Statistical Analysis. The normal distribution for each of continuous variables was verified separately for the control and MO group by quantile-quantile plot and normality tests (Shapiro-Wilk test, D'Agostino skewness test, and Anscombe-Glynn kurtosis test). In the descriptive statistics, we used the mean \pm standard deviation for variables with Gaussian distribution and median/interquartile interval (25th percentile–75th percentile) for variables with non-Gaussian distribution. The comparison between the groups (control and MO) was performed by parametric or nonparametric tests (Student *t*-test or Mann-Whitney *U* test). The analysis of repeated measures was performed using the Student *t*-test for the dependent groups or Wilcoxon signed-ranked test for the repeated measures of non-Gaussian characteristics. Because of the missing data, the number of subjects at every follow-up point being different, we used pairwise deletion in all the tests.

We used the multivariate analysis of variance (MANOVA) for repeated measures to evaluate the statistical significance of mean difference adjusted for variance-covariance of the studied characteristics. The independent factors were as follows: two studied time points (before and 6 months after surgery) and groups (control and MO patients). As post hoc analysis, we used univariate ANOVA test. The significance of linear correlations between the variables was tested by Pearson's coefficient.

The level of statistical significance for all two-sided tests was set at $p < 0.05$.

The statistical analysis was performed with the IBM SPSS v.19 (Armonk, NY: IBM Corp) and Statistica, version 6.

3. Results

Table 1 shows the anthropometric and biochemical characteristics of the controls and MO at baseline. As expected, we found significant differences, that is, higher levels in MO versus controls regarding mean weight ($t(23.43) = 11.74$, $p < 0.001$), BMI ($t(26) = 8.07$, $p < 0.001$), TC ($t(23) = 2.28$, $p = 0.032$), triglycerides (Mann-Whitney *U* test, $Z = 2.78$, $p = 0.004$), and HOMA-IR (Mann-Whitney *U* test, $Z = 2.52$, $p = 0.008$). The mean values of hsCRP (Mann-Whitney *U* test, $Z = 3.57$, $p < 0.001$), NOx (Mann-Whitney *U* test, $Z = 3.56$, $p < 0.001$), TOS (Mann-Whitney *U* test, $Z = 3.87$, $p < 0.001$), TAR (Mann-Whitney *U* test, $Z = 2.60$, $p = 0.007$), and OSI (Mann-Whitney *U* test, $Z = 3.03$, $p = 0.001$) were significantly different between the groups, that is, elevated mean values of hsCRP, NOx, TOS, and OSI in MO subjects as compared to the control group. Moreover and interestingly, mean values of TAR were higher in MO as compared

to controls. Regarding the mean values of chemerin (Mann-Whitney *U* test, $Z = 1.83$, $p = 0.07$) and TNF- α (Mann-Whitney *U* test, $Z = 1.84$, $p = 0.06$), we identified a tendency towards statistical significance between the two groups (increased levels in MO). There were no statistically significant differences of mean values of fasting blood glucose ($t(26) = 1.74$, $p = 0.093$), insulin ($t(22) = 1.27$, $p = 0.215$), HDL-C ($t(20) = 1.55$, $p = 0.135$), and LDL-C ($t(20) = 1.20$, $p = 0.242$) between controls and MO patients.

Six months after SG, we observed a significant change (a decrease was noticed) of the BMI ($t(17) = 7.41$, $p < 0.001$), hsCRP (Wilcoxon test, $Z = 2.01$, $p = 0.044$), and of OSI (Wilcoxon test, $Z = 2.04$, $p = 0.041$) mean values. The %EBMIL value was 64.36 ± 19.58 . However, we noticed no significant change of chemerin (Wilcoxon test, $Z = 0.51$, $p = 0.605$), TNF- α (Wilcoxon test, $Z = 1.06$, $p = 0.287$), NOx ($t(12) = 1.59$, $p = 0.137$), TOS (Wilcoxon test, $Z = 1.41$, $p = 0.158$), and TAR values (Wilcoxon test, $Z = 0.57$, $p = 0.563$) by the end of the study (Figures 1 and 2).

Using a 1 (group) \times 2 (time) design for MANOVA with repeated measures, we found no statistically significant time point changes (6 months after surgery versus baseline) on the blood lipids levels—TC, HDL-C, LDL-C, and triglycerides (Pillai's trace test: $F(3,7) = 1.2$, $p = 0.37 > 0.05$). When individual effect of each serum lipid were analyzed, we found no significant differences for TC (univariate ANOVA test, $F(1,9) = 0.12$, $p = 0.91 > 0.05$), HDL-C ($F(1,9) = 4.13$, $p = 0.73 > 0.05$), LDL-C ($F(1,9) = 0.86$, $p = 0.37 > 0.05$), and triglycerides ($F(1,9) = 0.029$, $p = 0.87 > 0.05$).

There was a statistically significant effect of time on the variables associated with blood glucose in general (MANOVA, Pillai's trace test: $F(3,12) = 7.6$, $p = 0.04 < 0.05$). Using post hoc analysis, we revealed a significant time effect on fasting blood glucose variable ($F(1,14) = 4.53$, $p = 0.052$), fasting insulin ($F(1,14) = 6.28$, $p = 0.025$), and HOMA-IR ($F(1,14) = 24.23$, $p < 0.001$) (Figure 2).

We observed a statistically significant linear correlation between changes of chemerin and those of TAR at 6 months after surgery ($r = 0.545$, $p = 0.04$), but no correlations were identified between chemerin variations and changes of BMI, TNF- α , hsCRP, NOx, TOS, and OSI.

4. Discussion

The present study was designed to analyze the hypothesis that increased levels of chemerin in a group of MO patients change 6 months after SG and that these changes run in parallel with changes of other inflammatory markers such as hsCRP, TNF- α , and nitrooxidative stress thus leading to a reduction of the cardiovascular risk. First of all, our results showed an important reduction of BMI (from 48.54 kg/m^2 to 34.69 kg/m^2) and a %EBMIL of 64.36% six months after SG. We observed no significant change in circulating chemerin and of TNF- α , NOx, TOS, and TAR, while a significant reduction of hsCRP and OSI was identified after surgery. Moreover, changes of chemerin correlated with changes of TAR, but they were independent of the variations of BMI, hsCRP, TNF- α , NOx, TOS, or OSI. Concerning

TABLE 1: Comparison of anthropometric and laboratory characteristics between groups.

Variables	Control*	Morbidly obese*	p value**
Age (years)	36.38 ± 6.3	42.15 ± 6.86	0.05
Weight (kg)	57.38 ± 6.74	136.85 ± 28.32	<0.001
BMI (kg/m ²)	21.34 ± 2.73	48.54 ± 9.27	<0.001
TC (mg/dl)	150 ± 22.82	187.35 ± 43.08	0.032
HDL-C (mg/dl)	40.18 ± 8.71	49.66 ± 15.81	0.135
LDL-C (mg/dl)	93.80 ± 19.34	112 ± 39.83	0.242
Triglycerides (mg/dl)	80.50 (69.50–89)	122 (116–173)	0.004
Fasting blood glucose (mg/dl)	90.75 ± 7.19	104.15 ± 21.06	0.093
Insulin (μU/ml)	6.84 ± 3.64	19.28 ± 19.09	0.215
HOMA-IR	1.43 (0.78–2.08)	3.31(2.66–5.05)	0.008
hsCRP (mg/l)	0.26 (0.10–0.48)	16.98(11.30–18.30)	<0.001
TNF-α (pg/ml)	19.52 (12.17–25.65)	25.64 (23.21–52.60)	0.06
Chemerin (ng/ml)	25.13 (21.73–29.95)	47.44(26.63–65.73)	0.07
NOx (μmol/l)	48.51 (44.80–53.74)	71.94 (68.46–76.91)	<0.001
TOS (μmol H ₂ O ₂ equiv./l)	19.26 (16.33–24.67)	93.19 (52.37–117.83)	<0.001
TAR (mmol trolox equiv./l)	0.62 (0.60–0.63)	0.88 (0.63–1.10)	0.007
OSI	31.39 (26.42–41.48)	142.27 (47.72–185.49)	0.001

BMI: body mass index; %EBMIL: excess body mass index loss; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HOMA-IR: homeostasis model assessment of insulin resistance; hsCRP: high-sensitivity C-reactive protein; TNF-α: tumor necrosis factor alpha; NOx: nitrites/nitrates; TOS: total oxidative status; TAR: total antioxidant response; OSI: oxidative stress index. *Mean ± standard deviation or median (interquartile interval: Q1–Q3); **Student for independent groups or Mann–Whitney's test.

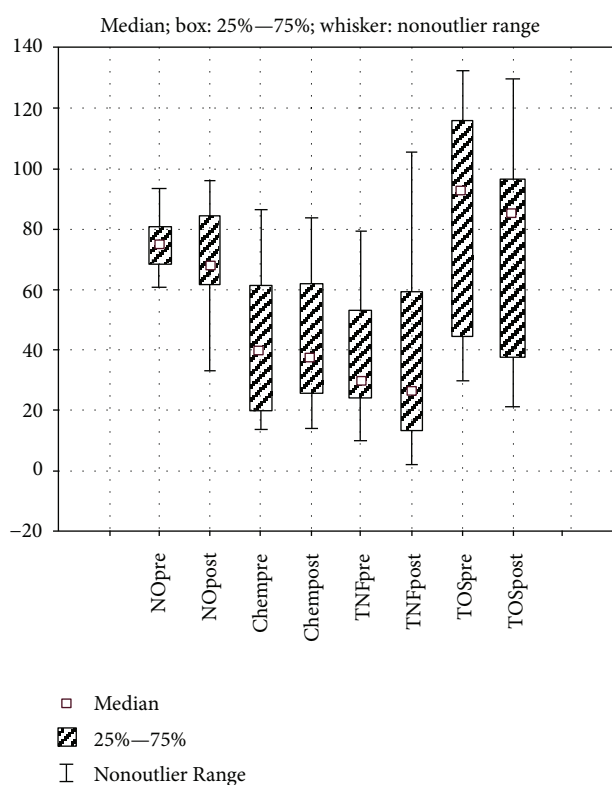


FIGURE 1: Evaluation of the changes of NOx, chemerin, TNF-α, and TOS values.

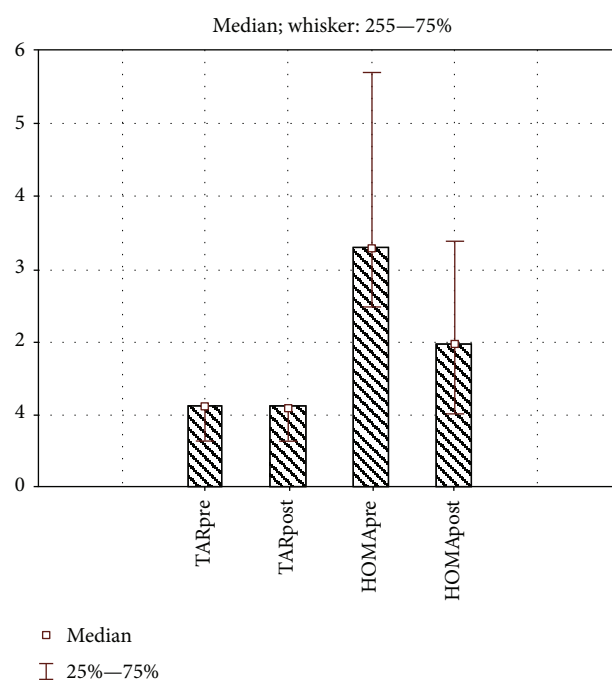


FIGURE 2: Evaluation of the changes of TAR and HOMA-IR values.

changes of fasting blood glucose, insulin, and HOMA-IR, they displayed a significant decrease six months after SG.

Emerging data has demonstrated that chemerin levels are elevated in obese patients [12, 16, 28–30]. Chemerin is a chemoattractant protein for macrophages being produced as a response to inflammation and may induce a positive

feedback for a continuous chronic inflammation. Still, precise data on the conditions that drive the increase of chemerin remain to be elucidated. Regarded as a marker of inflammation, chemerin is considered to be a possible link between obesity and the development of its metabolic comorbidities. Although it seems that chemerin might play a role in insulin sensitivity, the results remain conflicting [9].

Considering that chemerin is an inflammatory marker, we presumed that a postsurgical chemerin change/decrease would result in a reduced recruitment of macrophages in the adipose tissue leading to a diminished proinflammatory state and a lower cardiovascular risk. Still, in our study, six months after surgery, circulating chemerin levels which were increased at baseline as compared to the controls (with a tendency towards statistical significance between the two groups) did not change/decrease significantly and alongside with the important reduction of BMI. There were no correlations between the changes of BMI and those of chemerin. In agreement with our results, other authors showed in a group of MO with similar values of BMI and HOMA-IR as in our group of patients that did not change chemerin levels significantly 6 months after SG, but an important reduction was exhibited one year after surgery [17]. On the other hand, a significant early decrease of circulating chemerin levels, that is, at 3 months after RYGB, was demonstrated by some authors, showing that the reduction was correlated with a decrease in glucose and HOMA-IR [16]. Furthermore, Sell et al. demonstrated that the decrease of chemerin could still be observed between the first and the second year after surgery in the absence of further change in BMI, fat mass, HOMA-IR, leptin, or adiponectin [16]. Consistent with these data, Chakaroun et al. showed that besides an important surgical weight loss (1 year after RYGB) that induced a 25% reduction in chemerin serum concentrations, even a moderate weight loss as a result of a 6-month hypocaloric diet and furthermore even 12 weeks of exercise training before any appreciable changes in body weight induced a decrease of chemerin levels [12]. This reduction was independent of BMI changes and was predicted by reduced hsCRP and improved insulin sensitivity. Taken together, these results suggest that chemerin and inflammation may be associated independently of BMI [12].

Inflammatory cytokines seem to be involved in the upregulation of chemerin [31]. In this respect, Catalán et al. pointed out that elevated chemerin levels did not change one year after RYGB, but TNF- α treatment significantly enhanced the mRNA levels of chemerin in human visceral adipocytes [32]. In line with these results, we might speculate that the lack of significant change of TNF- α together with NOx despite the important decrease of hsCRP might explain the absence of chemerin variations.

Circulating CRP levels have been demonstrated to be significantly decreased at six months after SG [33], and some authors underlined the fact that the change in BMI was correlated with the difference between preoperative and postoperative CRP levels [34, 35]. However, in our group of patients, we did not observe such a correlation. On the other hand, decreased levels of CRP have been demonstrated by other authors to be present even earlier after SG, that is, after

one month, and these values were maintained at 6 months after surgery [15].

As for TNF- α circulating levels, medical data showed that the changes following bariatric surgery remain controversial and should be investigated through randomized trials [3]. We found no significant changes 6 months after restrictive surgery, which is in line with other studies that have demonstrated that reductions in BMI values between 40 kg/m² and 30 kg/m² slightly affect TNF- α levels in MO [36, 37]. In our group of patients, six months after surgery, the BMI mean value was 34.7 kg/m². However, we did notice a correlation between %EBMIL and changes of TNF- α . Hand in hand with our data, Pardina et al. showed that the expression of TNF- α did not vary with weight loss in the adipose tissue and liver despite the improvement in body weight and in most of the parameters associated with obesity comorbidities (insulin resistance and dyslipidemia), underlining that TNF- α does not reflect the improvement of inflammation during the first year after bariatric surgery [4]. Moreover, another study showed that there was a significant transitory increase of TNF- α levels at 3 months and a trend to increased levels at 6 and 12 months after gastric bypass, explained by the authors by the fact that TNF- α produced in the adipose tissue is not released into the circulation and therefore does not significantly contribute to the circulating TNF- α levels [18]. Furthermore, they underlined that the low levels of vitamin D (commonly noted following gastric bypass) might be another factor contributing to the elevated levels of TNF- α [18]. Last but not least, Pardina et al. explained that although the number of monocytes, the predominant source of TNF- α , decreases with weight loss, there is no correlation between this reduction and the changes in TNF- α [4]. Furthermore, as showed by the same authors, it seems that TNF- α is not involved in the lowering of hsCRP in plasma since it did not appear to be affected by the weight loss [4].

When examined 6 months after SG, besides a significant reduction of BMI and weight, our MO patients underwent no significant changes of nitrooxidative stress markers (NOx, TOS, and TAR). There was, however, a significant decrease of OSI. The levels of NOx as an expression of iNOS activity highly stimulated within the increased number of macrophages, and as an inflammatory marker, were demonstrated elsewhere to be elevated in MO patients [24]. Previously, we showed a slight transitory tendency of NOx to increase and of TAR to decrease 6 months after bariatric surgery but with no significant changes by the first year after the surgical intervention as compared to the baseline. The lack of significant change of nitrooxidative markers observed in our present study (except for OSI) might be explained by the persisting elevated levels of TNF- α 6 months after SG. On the other hand, a recent study showed that an improvement of weight and metabolic profile after laparoscopic SG was accompanied in parallel by a progressive recovery of antioxidant enzyme activities and the decline of oxidative byproducts. More precisely, they observed significant changes in antioxidant enzymes and in other markers of oxidative stress with some mean values reaching control levels as early as 3 months postsurgery [38]. We may conclude that there is no unique pattern for the nitrooxidative stress after SG, but it

is worth evaluating it in order to try to reduce it with exogenous antioxidant therapy when necessary.

The main limitation of the present study was that it addressed a small sample of patients. Because of the missing data, the conclusions concerning the changes of the studied parameters must be regarded with precaution. Further studies with a larger number of obese/MO subjects and a longer follow-up time are needed in order to confirm the trend of the repeated measures and correlations between the changes of the studied variables.

In conclusion, we observed that 6-month surgical weight loss through SG was not associated with significant changes of the inflammatory marker chemerin. Furthermore, except for hsCRP and OSI, there were no important variations of other markers of inflammation and oxidative stress.

Ethical Approval

All procedures involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration.

Consent

Informed consent was obtained from all participants included in the study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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