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The relation between pro-oxidant antioxidant balance and glycolipid profile, 6 months after gastric bypass surgery

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Abstract

Background: Morbid obesity is a chronic disease that contributes to increased oxidative stress. Gastric bypass surgery is the gold standard method in treating co-morbidities.

Objectives: The objective of this study was to evaluate the relation between pro-oxidant antioxidant balance (PAB) as one measure of oxidative stress and glycolipid profile 6 months after gastric bypass surgery.

Setting: Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran.

Methods: Thirty-five morbidly obese patients with body mass index ≥35 kg/m^2 with co-morbidities or ≤40 kg/m^2 were randomly recruited. The PAB assay was used to estimate oxidative stress. Anthropometrics and glycolipid profile were collected at recruitment and 6 months after surgery. Statistical analysis was performed using SPSS 16 software.

Results: The study showed a significant postoperative reduction in serum PAB values compared with the baseline ($P < .001$). All anthropometric and several glycolipid parameters significantly reduced after surgery ($P < .001$), while serum high-density lipoprotein cholesterol was unaffected. Repeated measures analysis of variance showed that postoperative PAB values were affected by gastric bypass surgery ($F = 12.51$, $P = .001$). Regression analysis demonstrated medication usage controlling co-morbidities ($\hat{\beta} = -.6$, $P = .002$) and fasting blood glucose ($\hat{\beta} = .41$, $P = .04$) as independent factors in predicting PAB values 6 months after surgery.

Conclusions: Gastric bypass surgery can reduce PAB values in favor of antioxidants 6 months after the operation. Accordingly, fasting blood glucose after gastric bypass surgery can be an independent factor in predicting PAB values. (Surg Obes Relat Dis 2017;▮:00–00.) © 2017 American Society for Metabolic and Bariatric Surgery. All rights reserved.

Keywords: Obesity; Morbid; Oxidative stress; Gastric bypass; Pro-oxidant antioxidant balance

The prevalence of obesity and its complications are globally increasing [1]. Extreme or class III obesity is a chronic disease with a body mass index (BMI) ≥40 or ≥35 kg/m^2 with co-morbidities, in which gastric bypass surgery is the gold standard treatment method [2].

According to the World Health Organization's report in 2015, while nearly 28% of adults were obese worldwide, approximately 26% of the Iranian adult population suffered from obesity [3]. Although oxidative stress can be a consequence of obesity, it can also be a trigger of obesity

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[4]. Several studies demonstrated that people after weight reduction associated with increased physical activity had lower levels of oxidative stress because of a reduction in tissue insulin sensitivity [5,6]. In addition, a direct association among oxidative stress markers, inflammatory markers, hyperglycemia, and hyperlipidemia has been reported [7,8].

Although surgery may potentially contribute to an increased production of proinflammatory cytokines and reactive oxygen species [9], reduction in oxidative stress has been reported within the first week after surgery [10]. There are several methods to determine antioxidant or oxidant status in human body. Evaluating plasma concentrations of individual antioxidant molecules and total antioxidant capacity [11], direct assessment of free radical production [12], or estimating the end products of oxidative damage [13] have all been used. These surveys have only Q4 evaluated one part of the total pro-oxidant and antioxidant capacities and are indirect, time wasting, and expensive [14]. According to the main definition of oxidative stress [15], pro-oxidant antioxidant balance (PAB) assay (an inexpensive and easy to perform method) evaluates the pro-oxidant burden and the antioxidant capacity in 2 varied oxidation–reduction reactions and identical circumference coincidently [16]. It has been validated previously [17]. In an enzymatic reaction, the colorless 3, 3′, 5, 5′- tetra methyl benzidine is oxidized to its colored cation by peroxides; in a chemical reaction, reduction of its colored cation to the colorless compound by antioxidants occurs. The photometric absorbance is then compared with the absorbance given by a series of standard solutions that are made by mixing different proportions of hydrogen peroxide as a representative of pro-oxidant with uric acid as a representative of antioxidant reference [16].

To our knowledge, this is the first study in which serum pro-oxidant antioxidant balance has been determined in morbidly obese patients before and after gastric bypass surgery. We also tried to ascertain the effects of certain predictors on 6-month postoperative PAB values.

Methods

The Ethics Committee of Mashhad University of Medical Sciences approved the protocol for this pilot study. Data sampling was randomly conducted. Written informed consent was obtained from all participants.

Thirty-five morbidly obese patients, who were candidates for Roux-en-Y gastric bypass surgery, were admitted via the Surgery Clinic of Imam Reza Hospital, Mashhad, Iran, between September 2014 and February 2015. Inclusion criteria were in accordance with the indications for gastric bypass surgery [18]. Exclusion criteria were women who were planning to become pregnant within 12 months, lactating women, patients with autoimmune disease, those taking immunosuppressive or anti-inflammatory agents, smokers, alcoholic individuals, those who were following a specific diet or supplementation program 1 month before the surgery, and professional athletes because of their high metabolic status.

Two weeks before the planned surgical date and 6 months after surgery, blood samples were collected after a 12-hour fast. Biochemical tests including fasting blood glucose (FBG), serum lipid profile, and high-sensitivity C-reactive protein (hs-CRP) were determined by routine laboratory testing. To calculate insulin resistance, we used the homeostatic model assessment for insulin resistance algorithm (FBG mg/dL × Insulin mIU/L) / 405). A further blood sample (.5 mL) was collected from each participant and kept under refrigeration at −20°C to be compared with the samples that to be obtained 6 months after surgery.

Blood samples were centrifuged at 2000*g* for 15 minutes; the serum aliquots were separated and stored. The novel PAB assay was previously described by Alamdari et al. [16]. To compare oxidant burden and antioxidant capacity of each serum sample, we prepared 2 major solutions, standard and working. The standard solutions were prepared by mixing different proportions (0%–100%) of 500 μM hydrogen peroxide with 3 mM uric acid (in 10 mM NaOH).

The working solution was prepared by mixing specific amounts of tetra methyl benzidine, and its cation was immediately used. Two hundred milliliters of the working solution was added into the wells containing 10 mL of each sample, standard or blank (distilled water), and incubated in a dark place for 12 minutes at 37°C. Then, 50 μL of 2 M HCl was added into each well to stop the enzymatic reaction. The ELISA reader was used to measure the absorbance at 450 nm (with a reference of 570 or 620 nm wavelength). A standard curve was drawn for the standard samples and expressed as arbitrary Hamidi Koliakos unit, which shows the percentage of hydrogen peroxide in the standard solutions. The values of the measured samples were calculated in comparison to the values of standard curve and expressed as Hamidi Koliakos units [19]. In women of childbearing age, blood sampling was collected during the first week after the menstrual period [20]. Because gastric bypass patients have to take an appropriate multivitamin/ mineral supplement at least for 5 days a week [21], they were asked to discontinue their supplement 2 days before the second blood sampling.

Height and waist circumferences were measured using a standard protocol. Weight (in light clothes without shoes), BMI, and body composition were measured by bioelectrical impedance analyzer, Tanita-BC 418 (Tanita Corp., Tokyo, Japan). Six months after surgery, excess weight loss and excess BMI loss were calculated according to the described method [22].

Roux-en-Y laparoscopic gastric bypass surgery was performed by the same surgeon using a standard procedure [23]. Thirty days after surgery, for all patients a similar multivitamin/mineral supplement (Pharmaton, SA, Lugano, Switzerland) was prescribed. Individual differences such as sex [24] and medication usage for controlling co-morbidities, including insulin, metformin, aspirin, statins, and antihypertensive drugs were considered as confounding factors [25–27].

Statistical analysis

Data were analyzed using SPSS, version 16 (SPSS Inc., Chicago, IL). All variables were checked for normality using the one sample Kolmogorov-Smirnov test. Parametric and nonparametric data were presented as mean ± standard deviation or median (interquartile range), respectively. Paired sample *t* test and Wilcoxon test were used for the comparison of pre- and posttreatment variables. Repeated measures analysis of variance was used to evaluate within-patients and between-patients effects on pre- and 6-months postoperative PAB values. Partial correlation controlling for sex and medication usage was conducted to clarify the relation between PAB values and all anthropometric and glycolipid parameters at baseline and 6 months after surgery. Multiple hierarchical regression analysis was performed to determine the predictive validity of the associated variables on 6-month postoperative PAB values by controlling confounding variables. The significant level of the tests was .05.

Results

In our study, 35 patients (80% female and 20% male) with morbid obesity were recruited. Table 1 shows demographic data and reduction rate in excess weight and BMI after gastric bypass surgery. The mean age of patients was 39.42 ± 11.76 years. Medication users comprised 17.5% and 5.7% of the sample before and after surgery, respectively. Our study population approximately lost 28.44 ± 6.38% of their total weight and 64.12 ± 19.53% of their excess BMI during this period.

Table 2 summarizes changes in serum PAB, anthropometric, and several glycolipid parameters before and after surgery. Six months after surgery, there was significant reduction in serum PAB values, 58.69 ± 41.52 Hamidi Koliakos units compared with the baseline ($P < .001$).

The glycolipid variables showed significant changes ($P < .001$) except for serum high-density lipoproteins cholesterol (HDL-C) ($P = .6$) 6 months after operation. According to the repeated measures analysis of variance results, the within-patient effect of gastric bypass surgery was statistically significant (F = 12.51, $P = .001$). The main effects of confounding variables, sex (F = 2.67, $P = .11$) and pre- (F = .146, $P = .7$) and postoperative (F = 2.44, $P = .12$) medication usage, were not statistically significant. In addition, the between-patient effects of surgery and sex (F = 1.13, $P = .29$), surgery and pre- (F = .02, $P = .86$), and 6 months (F = .02, $P = .87$) postoperative medication usage were not statistically significant.

Correlations among PAB values and anthropometric and glycolipid parameters are shown in Table 3. At baseline, among anthropometric variables, the study demonstrated the highest direct correlation between PAB values and BMI (r = .39, $P = .02$). Six months after surgery, the highest direct correlation was observed between PAB values and weight (r = .47, $P = .005$). Among glycolipid parameters, the highest correlation was observed between PAB values and FBG at baseline (r = .5, $P = .003$) and 6 months after surgery (r = .55, $P = .001$).

Multiple hierarchical regression analysis demonstrated 6-month postoperative medication usage ($\hat{\beta} = -.6$, $P = .002$) and FBG status ($\hat{\beta} = .41$, $P = .04$) as significant predictor factors of PAB values 6 months after surgery (Table 4).

Table 1
Participants' demographic data and reduction rate in excess weight and BMI 6 months after surgery

Sex, female*	28 (80)
Age, yr†	39.4 ± 11.8
Medicine consumer* n (%)	
Baseline	6 (17.5)
6 months after surgery	2 (5.7)
Total weight loss† (%)	28.4 ± 6.4
Excess BMI loss† (%)	64.1 ± 19.5
Excess weight loss† (%)	63.9 ± 19.8

BMI = body mass index.
*Data are described as number (%).
†Data are described as (mean ± SD).

Discussion

The overall objective of this pilot study was to investigate whether there is a relation between PAB values and glycolipid profile in a small (n = 35) group of gastric bypass patients.

All patients had to intake supplementation as part of postoperative treatment protocol. We just had to instruct them to use the same supplement and offset it at least 2 days before the examination [21]. Furthermore, we identified few patients with compulsory consumption of medications controlling co-morbidities and could not ethically omit their medications before any metabolic improvement. Thus, we adjusted our analysis according to their effects and evaluated their possible effects on pro-oxidant and antioxidant levels [25,26,28].

Six months after surgery, we observed a decrease in the ratio between pro-oxidant and antioxidant, which may indicate a reduction in oxidative stress status. With respect to the repeated measures analysis of variance results, subjects' PAB values were affected by gastric bypass surgery, not by individual differences such as sex or medication usage. Several human and animal studies

Table 2
PAB, anthropometrics, and glycolipid profile changes in patients with morbid obesity before and 6 months after surgery

Variables	Before surgery n = 35	After surgery n = 35	Difference between before and after surgery	P
PAB, Hamidi Koliakos units	150.6 ± 45.0	91.9 ± 36.6	58.7 ± 41.5	**<.001***
Weight, kg	127.56 ± 25.5	91.28 ± 20.45	36.28 ± 11.52	**<.001***
BMI, kg/m^2	47.06 ± 6.7	33.79 ± 6.54	13.27 ± 2.86	**<.001***
Waist circumference, cm	137.57 ± 19.41	107.16 ± 18.65	30.41 ± 15.25	**<.001***
Fat mass, kg	60.49 ± 14.48	33.91 ± 12.3	26.58 ± 2.16	**<.001***
Fat free mass, kg	65.4 ± 15.77	56.73 ± 14.22	8.66 ± 5.06	**<.001***
Fat trunk, %	45.2 (9.8)	36 (10.8)	10.8 (5.4)	**<.001**†
FBG, md/dL	99 (38)	85 (13)	11 (19)	**<.001**†
Insulin, mIU/L	19.5 ± 13.4	7.9 ± 5.4	11.7 ± 11.0	**<.001***
HOMA-IR, mg/L	3.6 (4.7)	1.4 (1.3)	2.3 (4.9)	**<.001**†
hs-CRP, mg/dL	9 ± 7.4	3.2 ± 4.4	5.6 ± 6.8	**<.001***
Cholesterol total, mg/dL	190.5 ± 31.8	160.9 ± 38.5	29.4 ± 40.8	**<.001***
Triglyceride, mg/dL	146.7 ± 73.5	100.5 ± 29.6	46.3 ± 70.8	**.001***
LDL cholesterol, mg/dL	109 ± 29.8	82.0 ± 23.6	26.6 ± 36.1	**<.001***
HDL cholesterol, mg/dL	40.9 ± 6.9	40.3 ± 7.2	0.7 ± 9.6	.6*

PAB = pro-oxidant antioxidant balance; BMI = body Mass Index; FBG = fasting blood glucose; HOMA-IR = homeostatic model assessment-insulin resistance; hs-CRP = C-reactive protein; LDL = low-density lipoproteins; HDL = high-density lipoproteins.
Parametric data are expressed as (mean ± SD). Nonparametric data described as median (interquartile range) values. Bold values are statistically significant.
*Paired sample t test.
†Wilcoxon test. $P < .05$ is statistically significant.

reported reduction in oxidative stress after gastric bypass surgery [10,29,30]. Considering to the results of Ueda et al. study [10], reduction in oxidative stress after gastric bypass surgery may be due to its influence on adipose tissues and oxidant balance.

The results of this study indicated that more than half of participants lost their excess weight within 6 months after the treatment. This is consistent with the findings of Netto et al. [31] and Wu et al. [32]. Furthermore, in this study, evidence suggested positive correlation between weight loss, improved body composition, and attenuating PAB values 6 months after surgery. These findings were in line with other investigations on gastric bypass and oxidative stress [33,34].

Several prospective studies demonstrated a significant reduction in hs-CRP, total cholesterol, triglyceride, and low-density lipoproteins cholesterol levels and a significant increase in HDL-C status after gastric bypass surgery [35–37]. Hormonal alternations may manage these changes in favor of lower triglyceride, cholesterol, and low-density lipoproteins cholesterol status and, in contrast, higher HDL-C levels [38]. For instance, bill acids [39] and

Table 3
Correlation between pro-oxidant antioxidant balance and anthropometrics and glycolipid profile in the baseline and 6 months after surgery

	PAB (Baseline)		PAB (6 months after surgery)	
Variable	r	P*	r	P*
Age, yr	−.07	.6	−.2	.2
Height, cm	−.06	.7	−.22	.2
Weight, kg	.33	**.05**	.47	**.005**
BMI, kg/m^2	.39	**.02**	033	**.05**
Fat mass, kg	.38	**.02**	.36	**.03**
Fat free mass, kg	.34	**.04**	.36	**.03**
Waist circumference, cm	.36	**.03**	.2	.2
Fat trunk, %	.1	.28	.19	.2
FBG, mg/dL	.5	**.003**	.55	**.001**
Insulin, mIU/L	.26	.1	.33	**.05**
HOMA-IR, mg/L	.4	**.01**	.4	**.01**
hs-CRP, mg/dL	.39	**.02**	.33	**.05**
Triglyceride, mg/dL	.2	.1	.08	.6
Cholesterol, mg/dL	.04	.7	.04	.8
LDL-C, mg/dL	−.12	.4	−.12	.5
HDL-C, mg/dL	.04	.7	−.16	.3

BMI = body mass index; FBG = fasting blood glucose; HOMA-IR= homeostatic model assessment-insulin resistance; hs-CRP = C-reactive protein; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.
Bold values are statistically significant.
*Partial correlation test is used.

Table 4
Predictive validity of the correlated variables on pro-oxidant antioxidant balance values 6 months after surgery

Variable	B (SE)*	$\hat{\beta}$†	t statistic	P‡
Sex, female	45.66 (41.7)	.5	1.09	.2
Medication usage (yes)	−98.24 (27.6)	−.6	−3.55	**.002**
Weight, kg	.71 (2.85)	.3	.25	.8
BMI, kg/m^2	−4.28 (2.65)	−.7	−1.6	.11
Fat mass, kg	1.63 (3.57)	.55	.45	.65
Fat free mass, kg	.16 (2.27)	.06	.07	.9
FBG, mg/dL	1.42 (.67)	.41	2.12	**.04**
Insulin, mIU/L	.76 (1.19)	.11	.63	.52
hs CRP, mg/dL	.73 (1.3)	.08	.55	.58

BMI = body mass index; FBG = fasting blood glucose; hs-CRP = C-reactive protein.
Bold values are statistically significant.
*Unstandardized coefficient.
†Standardized estimated coefficient.
‡Multiple hierarchical linear regression is used.

glucagon like peptide 1 (GLP-1) [40] have been considered as factors affecting lipid profile after gastric bypass surgery.

In our observations, lipid profile except HDL-C status was significantly improved 6 months after surgery. Our results for lipid profile were in line with the findings of Netto et al. [31] and Rojas et al. [41]. A lengthier follow-up period may allow observation of probable significant improvement in HDL-C after surgery.

In the present study, hs-CRP showed direct association with PAB values 6 months after surgery. Some studies identified elevated PAB values as a cardiovascular disease risk factor aside from other factors [42–44]. So, this association between attenuated hs-CRP levels and PAB values after gastric bypass surgery can be related to the reduction in cardiovascular risk factor as a consequence of oxidative stress [45]. In addition, because some evidence has demonstrated protective effects of GLP-1 analogs on hs-CRP [46], changes in hs-CRP levels may be attributed to GLP-1 levels after surgery.

We observed significant improvement in glycemic profile 6 months after surgery. Early improvement in glycemic profile after gastric bypass surgery have been reported [47], but the precise mechanisms improving glucose hemostasis after gastric bypass surgery are still unclear. Bankoglu et al. [30] claimed that reduction in adipose tissues after surgery play an important role in improving tissues insulin sensitivity. Some studies have suggested that GLP-1 [48] and Roux loop [49] play an important role in glucose hemostasis after surgery.

In attempt to find the best predictors of 6-month postoperative PAB values, we observed that medication usage to control co-morbidities and lower the level of postoperative FBG can predict decreased PAB values.

In agreement with other studies, we observed that medications used for controlling co-morbidities had a potential effect in ameliorating oxidative stress [25,27]. Furthermore, the role of hyperglycemia in the development of oxidative stress has been described in several studies [50,51]. In describing one of the main mechanisms of hyperglycemia-induced oxidative stress, enhancement in tricarboxylic acid cycle, accumulation of nicotinamide adenine dinucleotide and flavin adenine dinucleotide, and consequently overproduction of superoxide radicals, have been mentioned [52]. Hyperglycemia, oxidative stress, and inflammation are 3 harmful related agents that initiate a cascade of intracellular signaling pathways and mediate insulin resistance permanently and therefore increase reactive oxygen species overproduction [53].

This study had 2 limitations. First, we had limitations for omitting multivitamin and medications that could potentially reduce the level of oxidative stress. Second, it was conducted as a pilot study with limited sample size. So, we hope that further studies with larger sample size and longer follow-up could better detect the relation between PAB values and glycolipid profile in patients undergoing gastric bypass surgery.

Conclusion

Our study demonstrated that gastric bypass surgery could reduce serum PAB values in favor of antioxidants and improve anthropometrics and glycolipid profile in patients with morbid or extreme obesity. It is of high importance to consider the reduction in fasting blood glucose after surgery as an important factor in reducing oxidative stress.

Disclosures

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

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