

Evaluation of Oxidative Stress Status in Obese Patients after Bariatric Surgery

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ABSTRACT

This study aimed to evaluate the changes in oxidative stress markers in obese patients after bariatric surgery.

The study included a total of 90 obese adults, divided into two groups: those who underwent bariatric surgery (case, n=45) and those who did not (control, n=45). Parameters such as 8-hydroxy-2-deoxyguanosine (8-OHdG; oxidative DNA damage), NADPH oxidase 2 (NOX2), NADPH oxidase 4 (NOX4), and thiol-disulfide homeostasis were compared in both groups.

73.3% of the participants were female; age distribution was similar between groups (p=0.698). Body mass index (BMI) was lower in the case group compared to the control group (31.5±7.2 vs. 38.2±3.7 kg/m²; p<0.001). Native thiol levels were lower in the case group (135.9±55.6 vs. 154.3±38.0 µmol/L; p=0.014) and 8-OHdG was higher (7.6±1.8 vs. 6.5±2.1 ng/mL; p=0.015); NOX2 and NOX4 levels were similar. In the case group, those with a BMI change ≥13 kg/m² had higher native thiol levels (p=0.034) and lower 8-OHdG levels (p=0.045) than with a BMI change <13kg/m². A positive correlation was found between BMI change and native thiol levels (r=0.363; p=0.017). As the amount of weight loss increased, the disulfide/native thiol ratio decreased (r=-0.389; p=0.013) and the native/total thiol ratio increased (r=0.322; p=0.040).

Although overall oxidative stress markers (high 8-OHdG, low native thiol) were observed in obese patients who underwent bariatric surgery, improvements in oxidative stress markers were detected in those with greater BMI reduction. The findings suggest that effective weight loss after surgery may increase antioxidant capacity and reduce DNA oxidative damage. Long-term prospective studies are needed to clarify this relationship.

Keywords: Obesity, Bariatric surgery, Oxidative stress, 8-OHdG, NOX2, NOX4, Thiol-disulfide balance

Introduction

Obesity is a chronic disease characterized by the accumulation of fat in the body, resulting from the combined effect of environmental, psychological, genetic factors and individuals' lifestyles (1). This condition affects mitochondrial metabolism, increasing the production of reactive oxygen species (ROS) and the development of oxidative stress (2). This process usually occurs in two ways: In the first way, increased intracellular triglycerides lead to the accumulation of adenosine triphosphate (ATP) and a decrease in mitochondrial adenosine diphosphate (ADP). As a result, oxidative phosphorylation decreases and ROS production increases. This increase also triggers the inflammatory process (3). In the second way, hyperleptinemia stimulates the proliferation and activation of monocytes and macrophages, which trigger inflammation, as well as the production of interleukin-6 (IL-6) and

tumor necrosis factor alpha (TNF-α) (4, 5). Apart from these, body weight, fat amount, and lipid imbalances also cause oxidative damage and increase ROS production (6). ROS interacts with and damages all cellular components such as nucleic acids, proteins, and lipids. Oxidative stress resulting from this damage plays a role in the etiopathogenesis of diseases such as atherosclerosis, cancer, and diabetes (7, 8). Bariatric surgery is an important option in the treatment of obese patients, and oxidative damage can be reduced with this treatment (9). Oxidative damage resulting from increased ROS production in the body can be assessed by measuring thiol-disulfide homeostasis parameters, NOX4 (NADPH oxidase 4) and NOX2 (NADPH oxidase 2) enzymes, and 8-hydroxy-2-deoxyguanosine (8-OHdG) levels (10-12). Thiol groups support the antioxidant defense system, while disulfide bonds support oxidant balance. With oxidative stress, the thiol-disulfide balance shifts in favor of disulfide,

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and thiols decrease. Antioxidants in the body work to reduce oxidative damage by reducing disulfide chains (13). In adipose tissue, NOX4 is expressed from adipocytes and NOX2 from immune cells. NOX2 is an important enzyme that produces ROS; NOX4 is protective against obesity (10). 8-OHdG measurement is one of the most frequently used methods showing oxidative damage in DNA (11). In our study, we aimed to determine whether oxidative stress in obesity changes with bariatric surgical treatment. For this purpose, oxidative DNA damage (8-OHdG/10⁶ dG), endogenous oxidative damage (NOX2 and NOX4), and thiol levels were evaluated in obese patients who underwent bariatric surgery.

Materials and Methods

This research was approved by the Van Yüzüncü Yıl University Non-Interventional Clinical Research Ethics Committee with decision number 2023/01-13 dated 20.01.2023. The study was conducted with obese patients, both those who underwent laparoscopic sleeve gastrectomy surgery at least one year ago and those who did not, who applied to the Endocrinology and Metabolism Diseases Polyclinic of Dursun Odabaş Medical Center, Van Yüzüncü Yıl University Faculty of Medicine. 90 volunteer patients were included in the study. Patients with chronic diseases other than obesity and pregnant women were excluded from the study.

Procedure: For the study, in addition to routine tests performed at the time of application, 1 ml of peripheral blood was collected from individuals into complete blood count and biochemistry tubes containing EDTA. Blood samples were centrifuged on the day of collection and stored at -40°C. Human NADPH Oxidase 2, NOX2 BT-LAB Kit (Bioassay Technology Laboratory Cat. No: E6898Hu), Human NADPH Oxidase 4, NOX4 BT-LAB Kit (Bioassay Technology Laboratory Cat. No: E4156Hu), Total Thiol Assay Kit (Rel Assay Diagnostics, clinical chemistry solutions LOT: TZ2301T REF: RL0192), Native Thiol Assay Kit (Rel Assay Diagnostics, clinical chemistry solutions LOT: TZ2301N REF: RL0185), and 8-OHdG (8-Hydroxydeoxyguanosine) ELISA Kit (Elabscience Cat. No: E-EL-0028) levels were determined using commercial ELISA kits on a BioTek EL & 800 instrument, following the instructions in the kit procedure. Results were determined using standard curves after endpoint reading at 450 nm.

Statistical Analysis: Descriptive statistics of the data included mean, standard deviation, median, minimum, maximum, frequency, and ratio. The distribution of variables was evaluated using the Kolmogorov–Smirnov test. Chi-square test was used for the analysis of qualitative independent data, the independent samples t-test or Mann–Whitney U test was used for the analysis of quantitative independent data, and Pearson and Spearman correlation analysis was used for correlation analysis. Data analyses were performed using SPSS 28.0 software. A significance level of $p < 0.05$ was considered significant.

Results

Of the 90 patients included in the study, 66 (73.3%) were women and 24 (26.7%) were men. The mean age of the patients was 42.0 ± 11.4 . 21 (23.3%) of the patients were smokers, while 69 (76.7%) were non-smokers.

The case group (n:45) consisted of patients who had undergone bariatric surgery, with a mean BMI of 31.5 ± 7.2 . The control group (n:45) consisted of non-surgically obese individuals with a mean BMI of 38.2 ± 3.7 . BMI was significantly lower in the case group than in the control group ($p: 0.001$). Native thiol levels were significantly lower in the case group than in the control group ($p: 0.014$). 8-OHdG levels were significantly higher in the case group than in the control group ($p: 0.01$) (Table 1).

In the case group, native thiol levels were found to be significantly higher in the group with a BMI change ≥ 13 kg/m² compared to the group with a BMI change < 13 kg/m² ($p: 0.034$). 8-OHdG levels were found to be significantly lower in the BMI change ≥ 13 kg/m² group compared to the group with a BMI change < 13 kg/m² ($p: 0.045$). The number of individuals who were within the first 4 years postoperatively was significantly higher in the BMI change ≥ 13 kg/m² group compared to the group with a BMI change < 13 kg/m² ($p: 0.002$) (Table 2).

A significant positive correlation was observed between BMI change and native thiol value ($p: 0.017$ $r: 0.363$) (Table 3).

A significant negative correlation was observed between the amount of weight loss and the disulfide/native thiol value ($p: 0.013$, $r: -0.389$). A significant positive correlation was observed between the amount of weight loss and the native/total thiol (%) value ($p: 0.040$, $r: 0.322$) (Table 4).

Table 1: Comparison of Age, Smoking Status, Gender, BMI, and Oxidative Stress Markers in Case and Control Groups

	Control Group			Case Group			P	
	Mean±SD/n (%)	Median		Mean±SD/n (%)	Median			
Age	41.9	±13.4	43.0	42.2	±9.0	41.0	0.698	m
Smoking Status	Yes	12	26.7	9	20.0		0.619	χ ²
	No	33	73.3	36	80.0			
Gender	Female	31	68.9	35	77.8		0.340	χ ²
	Male	14	31.1	10	22.2			
BMI (kg/m ²)	38.2	±3.7	37.5	31.5	±7.2	30.7	0.000	m
NOX2 (ng/ml)	4.3	±1.7	3.8	4.4	±2.2	3.5	0.890	m
NOX4 (ng/l)	165.2	±119.4	113.9	168.0	±149.1	119.4	0.610	m
Total Thiol (μmol/l)	279.2	±66.6	297.7	247.3	±81.2	248.3	0.052	t
Native Thiol (μmol/l)	154.3	±38.0	154.7	135.9	±55.6	112.3	0.014	m
Disulfide	65.7	±18.5	65.0	59.0	±22.0	59.9	0.139	t
Disulfide/Native Thiol(%)	43.1	±11.5	42.7	48.5	±23.4	43.1	0.503	m
Disulfide/Total Thiol (%)	22.7	±3.7	23.0	23.5	±5.4	23.1	0.466	t
Native/Total Thiol (%)	54.6	±7.4	54.0	54.3	±13.0	54.0	0.895	t
8-OHdG (ng/mL)	6.5	±2.1	6.3	7.6	±1.8	8.0	0.015	t

t: Independent samples t-test / m: Mann-Whitney U test / χ²: Chi-square test

Table 2: Comparison of Case Groups with BMI Changes Below 13 kg/m² and Above 13 kg/m² According to Variables

	BMI Change <13		BMI Change ≥13		p			
	Mean±SD/ n (%)	Median	Mean±SD/n (%)	Median				
Age	44.0	±9.0	45.5	40.5	±8.9	41.0	0.205	t
Gender	Female	18	81.8	17	73.9		0.524	χ ²
	Male	4	18.2	6	26.1			
BMI (kg/m ²)	34.0	±8.3	31.7	29.2	±5.0	29.4	0.032	m
NOX2 (ng/ml)	4.9	±2.6	3.7	4.0	±1.7	3.5	0.910	m
NOX4 (ng/l)	184.9	±172.6	129.1	152.0	±124.9	114.7	0.639	m
Total Thiol (μmol/l)	229.5	±73.9	228.3	266.1	±86.2	277.6	0.152	t
Native Thiol (μmol/l)	117.7	±42.5	105.4	153.3	±61.7	147.3	0.034	t
Disulfide	58.7	±22.3	58.9	59.2	±22.4	61.4	0.944	t
Disulfide/Native Thiol(%)	53.5	±27.5	44.4	43.5	±17.8	42.4	0.344	m
Disulfide/Total Thiol (%)	24.6	±5.2	23.5	22.3	±5.4	22.9	0.186	t
Native/Total Thiol (%)	53.3	±15.1	53.5	55.3	±10.8	54.1	0.614	t
8-OHdG (ng/mL)	8.1	±1.5	8.4	7.1	±1.9	7.1	0.045	m
Postoperative time	≤ 4 Year	5	22.7	16	69.6		0.002	χ ²
	>4 Year	17	77.3	7	30.45			

t: Independent samples t-test / m: Mann-Whitney U test / χ²: Chi-square test

Table 3: Correlation Analysis of Oxidative Stress Markers Between Postoperative Time Elapsed, Weight Loss Duration, Weight Loss Amount, Weight Gain Duration, Weight Gain Amount, and BMI Change

		NOX2	NOX4	Total Thiol	Native Thiol	Disulfide
Postoperative	r	0.127	0.080	-0.059	-0.127	0.031
Follow-up Period	p	0.424	0.618	0.713	0.419	0.848
Weight Loss	r	0.152	0.157	0.134	0.141	0.004
Duration (Months)	p	0.337	0.328	0.402	0.368	0.979
Amount of	r	0.160	-0.066	0.014	0.200	-0.145
Weight Loss (kg)	p	0.313	0.683	0.929	0.198	0.371
Weight Gain	r	0.074	0.020	-0.026	0.066	-0.006
Period (Months)	p	0.642	0.900	0.870	0.672	0.973
Weight Gain	r	0.096	0.144	-0.180	-0.059	-0.173
Amount (kg)	p	0.547	0.369	0.260	0.706	0.287
BMI Change	r	0.062	-0.135	0.184	0.363	0.037
	p	0.698	0.398	0.249	0.017	0.821

Table 4: Correlation Analysis Between Oxidative Stress Markers and Post-operative Follow-up Period, Weight Loss Duration, Weight Loss Amount, Weight Gain Duration, Weight Gain Amount, and BMI Change

		Disulfide/ Native Thiol (%)	Disulfide/ Total Thiol (%)	Native /Total Thiol (%)	8-OHdG
Postoperative	r	0.074	0.074	-0.086	0.090
Follow-up Period	p	0.648	0.648	0.594	0.578
Weight Loss	r	-0.016	-0.016	-0.018	-0.152
Duration (Months)	p	0.924	0.924	0.909	0.344
Amount of	r	-0.389	-0.296	0.322	-0.014
Weight Loss (kg)	p	0.013	0.064	0.040	0.931
Weight Gain	r	-0.090	-0.051	0.090	0.155
Period (Months)	p	0.582	0.757	0.575	0.332
Weight Gain	r	-0.201	-0.134	0.169	0.210
Amount (kg)	p	0.213	0.408	0.291	0.188
BMI Change	r	-0.152	-0.225	0.127	-0.157
	p	0.350	0.162	0.430	0.326

Discussion

Obesity leads to increased oxidative load and insufficient antioxidant capacity. Reducing fat mass with bariatric surgery in obesity provides metabolic improvement in addition to cosmetic benefits. Thiol groups and disulfide bonds, 8-OHdG, NOX2, and NOX4 measurements can be used to evaluate the balance of the oxidant and antioxidant systems. A decrease in thiol groups and an increase in disulfide bonds are expected

with oxidative stress. Antioxidants in the body help prevent oxidative damage in this way (13). In nuclear and mitochondrial DNA, 8-OHdG is one of the dominant forms of free radical-induced oxidative lesions and is one of the frequently used parameters in demonstrating oxidative damage (11). NOX2 is a subunit of the NADPH oxidase enzyme complex. It plays a role in the production of reactive oxygen species and the development of atherosclerosis (14, 15). NOX4 is an enzyme found in all aerobic organisms that protects the vascular system against inflammatory stress (16).

Studies have shown that total thiol levels are lower in obese individuals compared to normal-weight individuals. A negative correlation was found between BMI and total thiol levels (17-19). In our study, native thiol levels were found to be statistically significantly lower in the surgically obese group compared to the non-surgical obese group. In the surgical group, a significant negative correlation was observed between the amount of weight loss and disulfide/native thiol, and conversely, a significant positive correlation was observed between the amount of weight loss and native thiol/total thiol. The significantly lower native thiol levels in the surgical group indicate increased oxidative stress in this group. In subgroup analyses of the surgical group conducted to investigate the reason for this, native thiol levels were found to be significantly higher in those with a greater decrease in postoperative BMI compared to those with a lesser decrease in postoperative BMI.

In the study conducted by Kocael A. et al. on morbidly obese patients and non-obese healthy individuals who underwent laparoscopic band ligation, serum 8-OHdG levels, a marker indicating oxidative DNA damage, were similar between the groups, while urine 8-OHdG levels were significantly higher in morbidly obese patients compared to controls. Six months after surgery, weight, BMI, and serum-urine 8-OHdG levels were found to be significantly decreased in morbidly obese patients (20). In our study, consistent with our thiol results, serum 8-OHdG levels were found to be statistically significantly higher in individuals who underwent bariatric surgery compared to non-surgical obese individuals. These results confirm the presence of oxidative stress in our obese patients who have undergone surgery. Similar to thiol analyses, 8-OHdG levels were also found to be significantly lower in the group with a greater reduction in BMI compared to the group without a reduction in BMI, in the subgroup analysis. This can be interpreted as indicating that strict BMI control in those who have undergone surgery may reduce oxidative stress and DNA damage. The previously mentioned correlation analyses also highlight the importance of medical follow-up, dietary adherence, and exercise for weight control in the post-surgical period.

A study in mice genetically ablation-treated with NOX4, a protective factor against inflammatory stress, reported increased visceral fat accumulation and susceptibility to diet-induced obesity and early-onset insulin resistance. Increased levels of

NOX2, an oxidative stress marker, and ROS production, due to hyperglycemia and hyperlipidemia, have also been shown to contribute to insulin resistance because protein kinase B reduces insulin activation (10, 21). Due to these relationships, NOX2 and NOX4 levels investigated in non-surgical obese and surgically obese patients were found to be similar in both groups. No difference was found in subgroup analyses. Based on this result, it can be considered that thiol and 8-OHdG measurements are more sensitive than these enzymes in determining oxidative stress.

In our study, oxidative stress markers were found to be higher in patients who underwent bariatric surgery compared to non-surgical obese patients. Several factors may explain this situation. Our study included obese patients who had undergone surgery at least one year prior, and their average BMI was 31.5, still within the obesity range. This average indicates non-compliance with diet, which can lead to surgical failure even if the surgery is successful. Insufficient adherence to medical recommendations, such as necessary vitamin supplements, may also have contributed to oxidative stress. Supporting this, we found that the group with a greater decrease in BMI had a significantly shorter medical follow-up period compared to the other group, meaning their surgeries were more recent. This result may mean that the patients had better follow-up and adherence to medical recommendations due to their more recent surgeries. We interpreted our results as indicating that treatment non-compliance in bariatric surgery patients, including lifestyle modifications, leads to higher levels of oxidative DNA damage and oxidative stress, even compared to non-surgical obese individuals.

The relatively small sample size, the lack of long-term follow-up, the cross-sectional nature of the study, and the absence of a comparison with the preoperative status of obese patients who underwent surgery are weaknesses of our study. Long-term, prospective studies with a large number of participants are needed to demonstrate the contribution of bariatric surgery to the treatment of obesity. Although lifestyle modification is emphasized at every opportunity in the treatment of obesity, our study is the first to show that medical non-compliance after obesity surgery can harm the patient.

In conclusion, postoperative medical follow-up, treatment, and dietary adherence were identified as the main factors reducing oxidative stress in bariatric surgery patients.

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