Erciyes Med J 2018; 40(3): 155-61 • DOI: 10.5152/etd.2018.0059

Evaluation of Oxidative Stress and Thiol-Disulfide Parameters According to the Body Mass Index in Adult Individuals

ORIGINAL ARTICLE

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ABSTRACT

Objective: In this study, the parameters of oxidative stress markers and thiol–disulfide homeostasis as a novel biomarker were evaluated in experimental groups of adult individuals, which were formed according to the body mass index (BMI).

Materials and Methods: A total of 165 adult patients were grouped as normal weight (BMI 18.5–24.9, n=39), pre-obese or overweight (BMI 25–29.9, n=47), obese (BMI 30–34.9; n=44), and severely obese (BMI >35, n=35). In addition to thiol–disulfide homeostasis parameters, the total oxidant status (TOS), total antioxidant status (TAS), oxidative stress index (OSI), ischemia-modified albumin (IMA), albumin, and ceruloplasmin levels were determined.

Results: Native thiol, total thiol, and native thiol/total thiol % levels were significantly decreased in the overweight, obese, and severely obese groups compared to the normal weight group ($p<0.001$). Disulfide levels were elevated in the overweight group compared to the normal weight group ($p<0.01$). While the TOS and OSI levels of the normal weight group were elevated compared to the overweight ($p<0.001$) and obese/severely obese groups ($p<0.05$), albumin levels of the normal weight group were reduced compared to other groups ($p<0.001$). The IMA levels of the overweight group were elevated compared to the normal weight and severely obese groups ($p<0.05$ and $p<0.001$, respectively). Ceruloplasmin levels of the severely obese group were increased compared to the normal weight and overweight groups ($p<0.001$ and $p<0.01$, respectively).

Conclusion: In our study, oxidative stress was increased in groups with a BMI greater than normal (≥25). In addition to this, the oxidative stress and thiol–disulfide homeostasis markers are observed to be further increased in the overweight group than the obese (≥30) group due to body's reaction to first inconsistency.

Keywords: IMA, TAS, thiol-disulfide homeostasis, TOS, ceruloplasmin

Cite this article as: Söğüt İ, Şenat Aydın A, Sağlam Gökmen E, Gün Atak P, Erel Ö, Görmüş DeGrigo U. Evaluation of oxidative stress and thiol/ disulfide parameters according to BMI in adult individuals. Erciyes Med J 2018; 40(3): 155-61.

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Submitted
09.04.2018

Accepted
23.07.2018

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INTRODUCTION

Obesity is caused by excessive lipid accumulation in the adipose tissue due to a positive energy balance, and it is a widely encountered problem, especially in developed or developing countries (1). Obesity is related to various factors, such as genetic susceptibility, hormonal changes, and environmental factors, meals high in calories and large portions, and sedentary lifestyle. Increased body fat is a risk factor that triggers several disorders. Diseases such as cardiovascular disorders, hypertension, type II diabetes, some cancer types, and asthma are known to be associated with obesity (2). The body mass index (BMI) is a simple classification criterion to assess the medical risks of obesity in adults. It is defined as the body weight in kilograms divided by the square of the height in meters (kg/m^2). According to the BMI, adults can be classified as underweight (<18.4), normal weight (18.5 to 24.9), overweight or pre-obese (25 to 29.9), obese class I (30 to 34.9), obese class II (35 to 39.9), and obese class III (>40).

Increased body weight has been reported to be associated with oxidative stress and cellular damage in numerous studies (3-4). Reactive oxidative stress (ROS) members such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), or hydroxyl radical (OH^-) and related peroxynitrite molecules ($ONOO^-$) are thought to cause cellular dysfunction by altering metabolic pathways, cell membrane, DNA, and protein structures. Reactive nitrogen, iron, copper, and sulfur types are also members of radical molecules. Superoxide anion, which is generated by detachment of a single electron from molecular oxygen, is a triggering factor in the formation of other ROS types (3-4). For example, obesity causes insulin resistance, hyperglycemia, and elevated free fatty acid levels. The increase in intracellular glucose levels stimulates the over-expression of the NADH and $FADH_2$, electron losses in mitochondrial inner membrane, and subsequent superoxide formation. Free fatty acids also disrupt adenine translocation, which leads up to superoxide production in the mitochondrial electron transport system. Increased body weight also puts a considerable burden on body muscles, causing increased muscle activity and subsequent formation of lipid hydroproxides due to

elevated electron transfer losses. All these disorders are followed by vitamin deficiencies and increased inflammation levels (5).

Oxidative damage is defined by inadequacy of the cellular antioxidant defense system in neutralizing increased ROS production (6-7). To prevent cellular damage that results from ROS, an array of mechanisms has aroused. Intracellular antioxidants are classified into two major groups as enzymatic (superoxide dismutase, catalase, glutathione peroxidase, thioredoxin, peroxiredoxin, and glutathion transferase) and non-enzymatic (lipoic acid, coenzim Q, vitamins C and E, thiol, glutathione, and ferritin, transferin, ceruloplasmin and albumin as proteins) types (6-7).

Total oxidant–antioxidant statuses, ceruloplasmin, and ischemia-modified albumin (IMA) are among important biomarkers of oxidative stress. Also, thiol-to-disulfide ratio appeared as a novel biomarker in patients with diabetes, cardiovascular diseases, cancer, and several other diseases (8-10). Thiol is a sulfidryl (-SH) group-containing organic compound that can bind C atoms. The plasma thiol pool is composed of albumin and other protein thiols, cysteinylglycine, cysteine, homocysteine, glutathione, and γ-glutamylcysteine (11).

In this study, the status of the thiol–disulfide balance as a novel biomarker and its harmony and compatibility with other oxidative damage markers were studied in experimental groups composed of adult individuals, which were formed according to their BMI.

MATERIALS and METHODS

The study was conducted on patients who were admitted to the polyclinic of internal medicine of İstanbul Bağcılar Training and Research Hospital, Health Sciences University. This cross-sectional study included 165 patients (104 females and 61 males) aged 18–60, without any history of heart and kidney deficiency, stroke, cerebrovascular diseases, and pregnancy. Patients' (selected with a simple random-sampling method) body weight expressed in kilograms was divided by the square of the body height for BMI after patients' body height and weight were measured. Patients were divided into four study groups as normal weight (BMI: 18.5 to 24.9; n=39), pre-obese or overweight (BMI: 25 to 29.9; n=47), obese (BMI: 30 to 34.9; n=44), and severely obese (BMI: ≥35; n=35). Serums were collected from blood samples taken from volunteers and kept at −80°C. Serum samples were then transported in cold chain (−20°C) to the Biochemistry Department of Ankara Yıldırım Beyazıt University Faculty of Medicine where analyses were performed. The study was conducted after an approval was received from the clinical research ethical committee of Istanbul Bilim University (29.11.2016/55-41).

The thiol–disulfide pair tests in the serum were determined using the method by Erel and Neselioglu (11), which is based on the principle of measuring the reduced thiol groups and existing native thiols (μmol/L) for the total thiol (μmol/L) amounts that were analyzed with 5, 5′-dithiobis-(2-nitrobenzoic) acid (DTNB). Disulfide amounts (μmol/L) were determined as half of the subtraction of native thiol from total thiol levels. Total antioxidant status (TAS, mmol Trolox eq/L), total oxidant status (TOS, μmol H_2O_2 eq/L), and oxidative stress index (OSI, arbitrary unit) were detected with commercial kits (Rel Assay Diagnostics, Gaziantep, Turkey) (12-13). A dark blue–green colored 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) radical is reduced to a colorless reduced-ABTS form with antioxidants. The change of absorbance at 660 nm is related with the TAS of the sample. Oxidants present in the sample oxidize the ferrous ioneo-dianisidine complex to the ferric ion. The ferric ion forms a colored complex with xylenol orange in an acidic medium. The change of absorbance at 530 nm is related with TOS of the sample. The OSI levels in the sample were detected as the ratio of the TOS level to TAS level. In our study, the ischemia-modified albumin level (IMA-ABSU) in serum was measured by a method reported by Das et al. (14), based on the spectrophotometric measurement (470 nm) of color production due to the reaction of albumin-cobalt with dithiothreitol. The reaction was performed by adding 50 μL 0.1% cobalt (II) chloride ($CoCl_2$,$6H_2O$), 50 μL 1.5 mg/mL dithiothreitol, and 1 μL of a 0.9% sodium chloride solution, respectively. Serum ceruloplasmin level (U/L) is automated, colorimetric, and based on the enzymatic oxidation of ferrous ion to ferric ion. Albumin levels (g/dL) were measured by a clinical biochemistry autoanalyzer (Roche, cobas 501, Mannheim, Germany).

Statistical Analysis

Statistical analyses were performed using the The Statistical Package for the Social Sciences (SPSS) 22.0 program (IBM Corp.; Armonk, NY, USA). For data that showed compliance with the normal distribution, the analysis of variance (ANOVA) test using the post-hoc Tukey test was applied, while for data for which the normal distribution did not fit, the Kruskal–Wallis ANOVA with the post-hoc Dunn's multiple comparison test was applied. Results were expressed as the mean±SD and median (minimum–maximum), $p<0.05$ was considered significant.

RESULTS

Demographic Information

Gender distribution in experimental groups was the following: in the normal weight group, there were 20 female and 19 male (n=39) subjects; in the pre-obese or overweight obese group, 20 female and 27 male (n=47); in the obese group, 18 female and 26 male (n=44); and in the severely obese group, 18 female and 19 male (n=35) subjects. The median (interquartile range) levels of ages of study groups were 44 (12), 44 (13), 44 (11.75), and 45 (10), respectively.

Thiol-Disulfide Homeostasis Variables (Table 1, Figure 1)

Overweight, obese, and severely obese groups were observed to have significantly elevated *native thiol* and *total thiol* (μmol/L, $p<0.001$) levels than in the normal weight group, while there was also a significant increase in *disulfide* (μmol/L) levels in the overweight group compared to the normal weight ($p<0.01$) and obese ($p<0.05$) groups. The normal weight group had significantly reduced *disulfide/total thiol* (%) levels ($p<0.001$, $p<0.01$, and $p<0.001$, respectively) and increased *native thiol/total thiol* (%) levels ($p<0.001$, $p<0.01$, and $p<0.001$, respectively) than the overweight, obese, and severely obese groups. The overweight group also had significantly elevated *disulfide/total thiol* (%) levels and decreased *native thiol/total thiol* (%) compared to the obese group ($p<0.01$ for both).

Oxidant and Antioxidant Variables (Table 2, Figure 2)

The TAS (mmol Trolox eq/L) levels of the overweight group showed a significant reduction when compared to the severely

Table 1. Thiol–Disulfide Homeostasis Variables

Groups → Variables ↓	Group 1 (Normal Weight-BMI: 18.5 to 24.9)	Group 2 (Overweight-BMI: 25 to 29.9)	Group 3 (Obese-BMI: 30 to 34.9)	Group 4 (Severely Obese-BMI: >35)	Test p	Post Hoc p
Native thiol (µmol/L)	388.5±58.18	297.5±47.67	322.4±47.62	303±51.85	p<0.0001	1-2*** p<0.001 1-3*** p<0.001 1-4*** p<0.001
Total thiol (µmol/L)	425.8±57.80	340.9±46.70	360.8±48.66	342.3±52.01	p<0.0001	1-2*** p<0.001 1-3*** p<0.001 1-4*** p<0.001
Disulfide (µmol/L)	18.68±3.76	21.72±4.99	19.20±3.88	19.66±3.68	p=0.0044	1-2** p=0.002 2-3* p=0.036
Disulfide/native thiol (%)	4.83 (4.12-5.65)	7.37 (5.80-8.87)	5.69 (4.93-7.22)	6.33 (5.08-8.04)	p<0.0001	1-2*** p<0.001 1-3** p=0.001 1-4*** p<0.001 2-3** p=0.006
Disulfide/total thiol (%)	4.40 (3.81-5.08)	6.42 (5.12-7.53)	5.11 (4.49-6.31)	5.62 (4.61-6.93)	p<0.0001	1-2*** p<0.001 1-3** p=0.001 1-4***p<0.001 2-3** p=0.005
Native thiol/total thiol (%)	91.2 (89.85-92.38)	87.16 (84.93-89.76)	89.79 (87.38-91.02)	88.77 (86.14-90.78)	p<0.0001	1-2*** p<0.001 1-3** p=0.001 1-4*** p<0.001 2-3** p=0.005

Data are presented as the mean±SD, median (minimum–maximum), BMI: body mass index, SD: standard deviation.
(* p<0.05, ** p<0.01, ***p<0.001)

obese group, normal weight group, and obese group (p<0.001, p<0.01, and p<0.05, respectively), while the TOS (µmol H_20_2 eq/L) levels of the normal weight group also showed a significant reduction when compared to the overweight group, obese group and severely obese group (p<0.001, p<0.01, and p<0.01, respectively). The normal weight group also displayed significantly lower *OSI* (arbitrary unit) levels than the overweight, obese, and severely obese groups (p<0.001, p<0.01, and p<0.01, respectively), while the overweight group had significantly higher OSI levels than the severely obese group (p<0.05). The overweight group displayed significantly higher *IMA-ABSU* levels when compared to the severely obese and normal weight groups (p<0.001 and p<0.01, respectively), while the obese group had significantly elevated IMA levels compared to the severely obese group (p<0.01). The normal weight group showed a significant increase in *albumin* (g/dL) levels when compared to the overweight group, obese group, and severely obese group (p<0.001). The severely obese group showed a significant increase in *ceruloplasmin* (U/L) levels when compared to the normal weight group and overweight group (p<0.001), while ceruloplasmin levels in the obese group were significantly increased compared to the normal weight group and overweight group (p<0.001 and p<0.01, respectively).

DISCUSSION

Obesity is a risk factor for various disorders such as cancer, cardiovascular diseases, non-alcoholic liver disease, hypertension lung problems, and diabetes (15). Obesity-related oxidative stress plays an important role in development of cellular damage. The fat accumulation rate is positively correlated with oxidative stress intensity. It is also known that oxidative stress is elevated with an increased BMI (16). In our study, the TOS and OSI levels were increased in groups with above-normal BMI (>25). Parallel to our results, the TOS and OSI levels of obese kids with non-alcoholic liver disease were also reported to be elevated (17). In another study on total oxidant and antioxidant statuses of children with obesity and metabolic syndrome, the TAS, TOS, and OSI levels were shown to be elevated with a BMI increase (18).

In addition, levels of ceruloplasmin, which is an acute phase reactant, were also observed to be elevated, which is paralleled with the BMI increase. This increase in ceruloplasmin levels with weight gain was found to be related to the 'OH radical, which is generated through the Fenton-type reaction of H_2O_2 and Cu^{+2} and low intensity protein oxidation. Ceruloplasmin was shown to be an oxidative marker (19), and elevated ceruloplasmin levels were found to be associated with atherosclerosis and cardiovascular diseases (20).

In our study, levels of albumin, which plays a key role in the transportation of antioxidants, and TAS were decreased especially in the overweight group. Kinoshita et al. also reported that increased oxidative stress is associated with decreased albumin levels (21). Hydroxyl radicals released from the Fenton reactions are directed to the targets that are important for protein conservation, due to high affinity of albumin to metal ions. High levels of albumin in plasma form the biggest thiol pool in circulation. These sulfidrile

Table 2. Oxidant and Antioxidant Variables

Groups → Variables ↓	Group 1 (Normal Weight-BMI: 18.5 to 24.9)	Group 2 (Overweight-BMI: 25 to 29.9)	Group 3 (Obese-BMI: 30 to 34.9)	Group 4 (Severely Obese-BMI: >35)	Test p	Post Hoc p
TAS (mmol Trolox eq/L)	1.0±0.088	0.89±0.153	0.97±0.142	1.02±0.126	p=0.0002	1-2** p=0.002 2-3* p=0.031 2-4*** p<0.001
TOS (μmol H_20_2 eq/L)	4.47 (3.80-5.81)	18.28 (8.47-46.02)	10.09 (4.41-32.08)	5.85 (4.62-42.52)	p<0.0001	1-2*** p<0.001 1-3** p=0.002 1-4** p=0.003
OSI (arbitrary unit)	0.44 (0.37-0.60)	1.89 (0.85-6.03)	1.01 (0.44-2.98)	0.62 (0.40-4.08)	p<0.0001	1-2*** p<0.001 1-3** p=0.004 1-4** p=0.004 2-4* p=0.042
IMA-ABSU	67.10 (61.80-72.10)	72.10 (66.10-77.20)	69.25 (62.98-73.48)	63.20 (55.50-70.20)	p<0.0001	2-4*** p<0.001 1-2** p=0.006 3-4** p=0.008
Albumin (g/dL)	5.01±0.202	4.77±0.192	4.77±0.217	4.80±0.175	p<0.0001	1-2*** p<0.001 1-3*** p<0.001 1-4*** p<0.001
Ceruloplasmin (U/L)	396.6 (297.4-448.3)	409.5 (357.8-487.1)	512.9 (426.7-605.6)	560.3 (491.4-655.2)	p<0.0001	1-3*** p<0.001 1-4*** p<0.001 2-3** p=0.001 2-4*** p<0.001

Data are presented as the mean±SD, median (minimum–maximum). BMI: body mass index, SD: standard deviation; TAS: total antioxidant status; TOS: total oxidant status; OSI: oxidative stress index; IMA: ischemia-modified albumin
(* p<0.05, ** p<0.01, ***p<0.001)

groups (–SH) act as antioxidants against the ROS damage (22). In addition to these, albumin is a binder of free fatty acids, and these fatty acids are reported to increase in obesity and subsequent lipid peroxidation (23). However elevated oxidative stress depletes albumin pool and its antioxidant capacity. The IMA levels increase due to the modification of albumin N-terminal part by ROS and free radicals. IMA is also considered as an oxidative stress, inflammation, and ischemia marker (24). Our result showed that the IMA levels were increased in overweight and obese groups compared to controls. Parallel to our results, a previous study also revealed that IMA levels were increased in overweight and obese groups, indicating IMA as an oxidative stress marker (23).

Oxidative stress occurs when antioxidant levels are lower than ROS levels in organisms. The balance of ROS levels is attempted by enzymatic and non-enzymatic antioxidants in the organism. Among the most important non-enzymatic antioxidants are thiols containing –SH groups (25). The serum thiol levels are indirect indicators of antioxidant levels. Thiols can make disulfide bonds and then be reduced to thiols reversibly. This dynamic thiol–disulfide homeostasis has an important role in the antioxidant ability, detoxification, and apoptosis. Disruption of this homeostasis is an indicator various disorders such as cardiovascular diseases, cancer, diabetes, and Alzheimer's (11, 26).

In our study, antioxidant parameters of thiol–disulfide homeostasis were lower, and oxidant parameters were higher in groups with above-than-normal BMI (>25). The thiol–disulfide homeostasis was determined to be shifted to disulfide formation. In addition to this, oxidative stress in the overweight group was observed to be higher than in the obese and severely obese groups. Parallel to our results, Elmas et al. measured dynamic thiol–disulfide homeostasis parameters in obese kids and reported that this dynamic equilibrium was shifted to disulfide formation in obese kids compared to controls (9). In addition, the thiol–disulfide balance of children with obstructive sleep apnea is impaired relative to the control group, and this is parallel to our results (27).

The adipose tissue formation in obese individuals was found to be associated with increased inflammation and oxidative stress levels, and decreased antioxidant levels (28). We also hypothesized that in groups with an above-normal BMI (>25), inflammation and oxidative damage were increased, while antioxidant levels are decreased. In our study, TOS, OSI, IMA, ceruloplasmin, and disulfide levels were elevated, while albumin and thiol levels were decreased. An interesting result observed in our study is that the oxidative stress levels in the overweight group were higher compared to the obese (>30) group. Organisms tend to be in a stable equilibrium state. When this equilibrium is disrupted, an organism attempts to rebalance it (29). Therefore, a possible explanation for our result is that the weight gain triggers oxidative stress, and the overweight group is more susceptible due to disruption in oxidant/antioxidant balance than obese and severely obese groups in which this disruption in oxidant/antioxidant balance was attempted to be reverted by the organism.

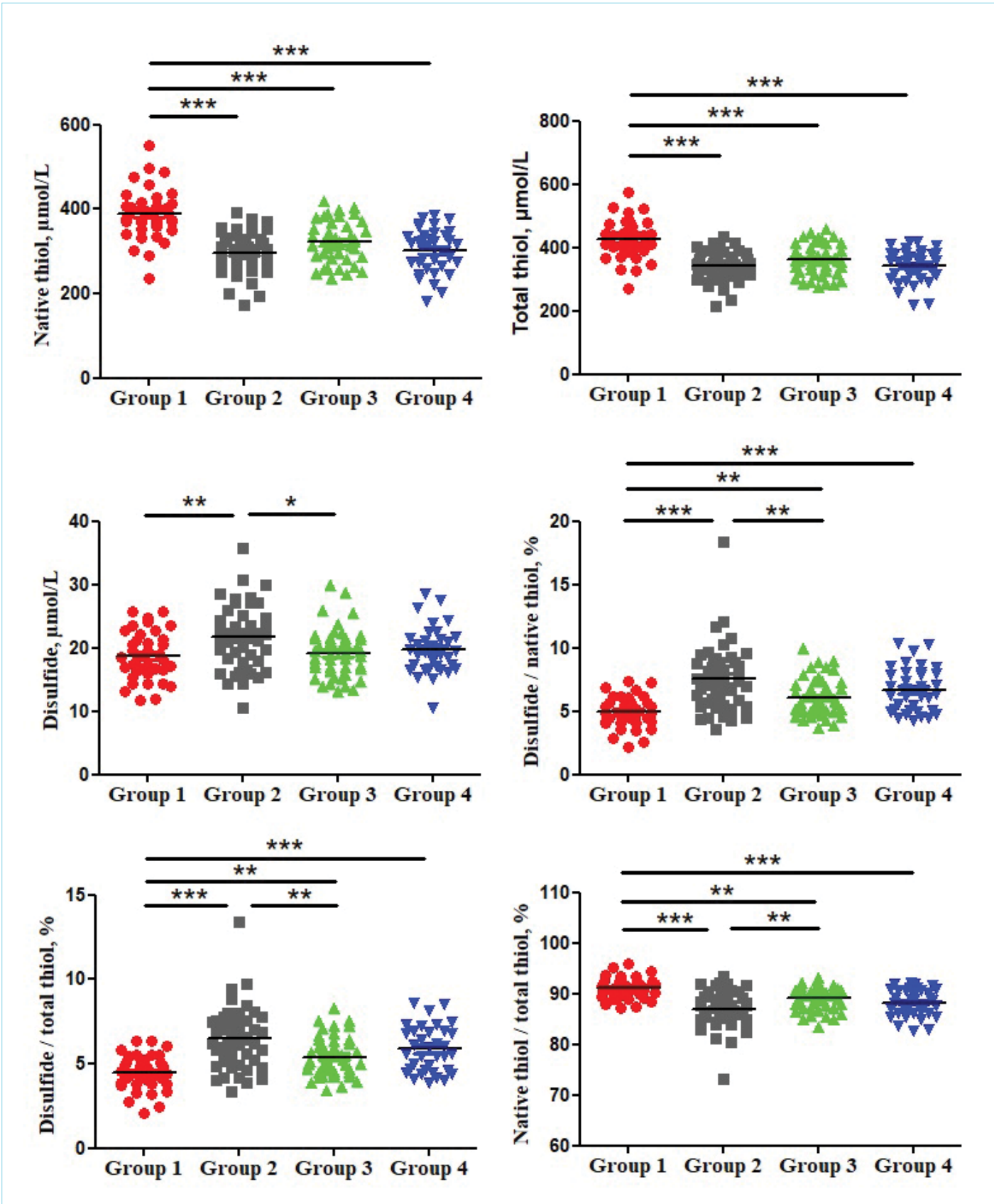

Figure 1. Thiol–disulfide homeostasis variables. Group 1 (normal weight; BMI: 18.5 to 24.9); Group 2 (overweight; BMI: 25 to 29.9); Group 3 (obese; BMI: 30 to 34.9); and Group 4 (severely obese; BMI: >35)
* p<0.05, ** p<0.01, ***p<0.001

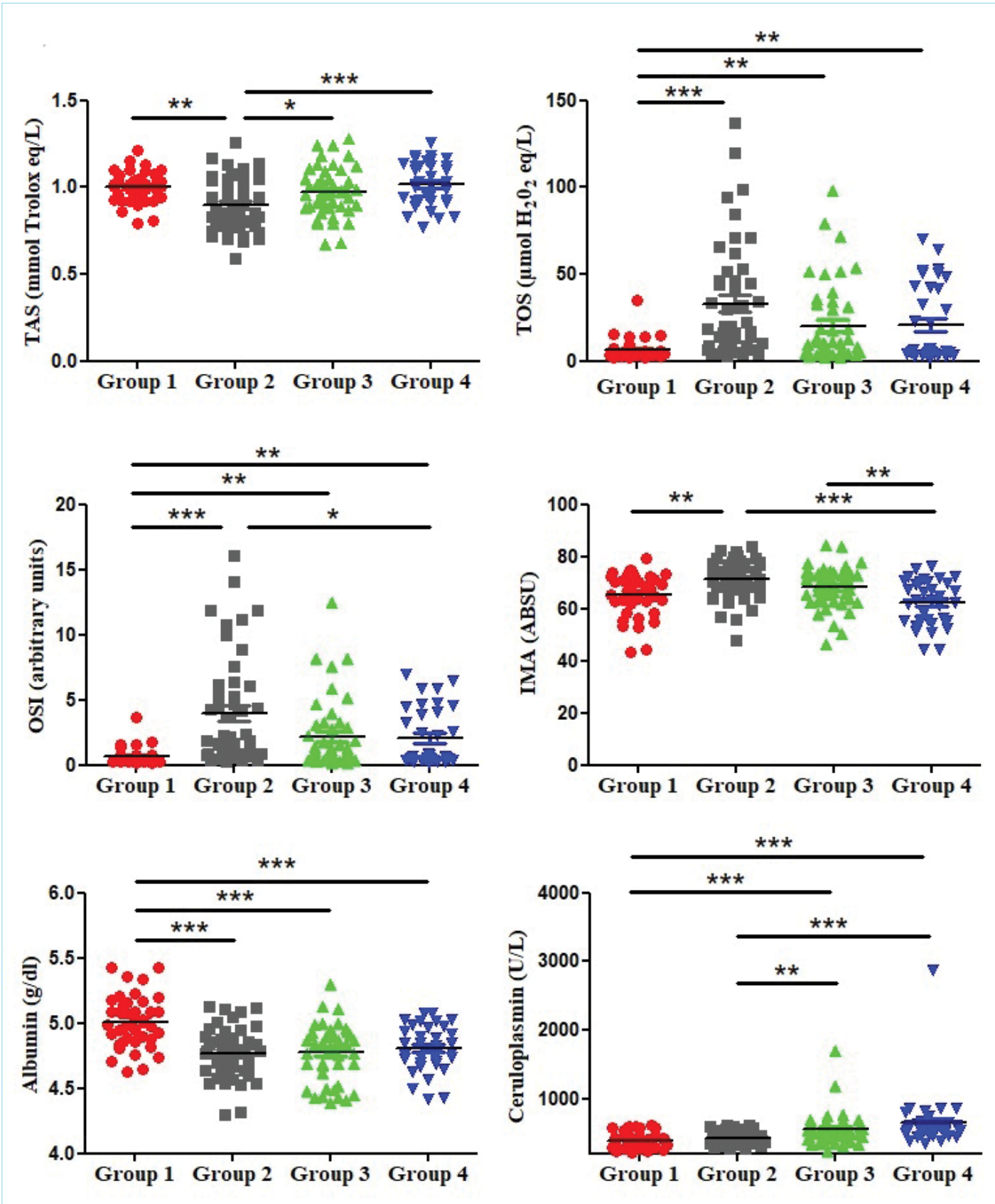

Figure 2. Oxidant and antioxidant variables. Group 1 (normal weight; BMI: 18.5 to 24.9); Group 2 (overweight; BMI: 25 to 29.9); Group 3 (obese; BMI: 30 to 34.9); and Group 4 (severely obese; BMI: >35). TAS: total antioxidant status; TOS: total oxidant status; OSI: oxidative stress index; IMA: ischemia-modified albumin
* p<0.05, ** p<0.01, ***p<0.001

CONCLUSION

Oxidative stress was observed to increase in groups with above-normal BMI (>25) in our study. This increase was also shown by thiol–disulfide homeostasis, total oxidant, and total antioxidant parameters that have recently been used as markers for several disorders. In addition, we think that increased oxidative stress levels in the overweight group compared to obese (>30) groups is caused by the initial reaction of body to disruption of the oxidant–antioxidant equilibrium stability.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of of Istanbul Bilim University (29.11.2016/55-41).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Conceived and designed the experiments or case: IS, UGD. Performed the experiments or case: ASA, ESG, PGA, OE. Analyzed the data: ASA, IS. Wrote the paper: IS, UGD. All authors have read and approved the final manuscript.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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