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Title: Evaluation of oxidative stress and thiol/ disulfide parameters according to BMI in adult individuals

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

Materials and Methods: 165 adult patients were grouped as normal weight (BMI 18.5 to <25; n=39), pre-obese or overweight (BMI 25 to <30; n=47), obese (BMI 30 to <35; n=44) and severely obese (BMI 35<; n=35). Besides thiol/ disulfide homeostasis parameters, 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 overweight, obese ve severely obese groups compared to normal weight group ($p<0.001$). Disulfide levels were elevated in overweight group compared to normal weight group ($p<0.01$). While TOS and OSI levels of normal weight group were elevated compared to overweight ($p<0.001$) and obese, severely obese groups ($p<0.05$), albumin levels of normal weight group were reduced compared to other groups ($p<0.001$). IMA levels of the overweight group were elevated compared to 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 normal weight and overweight groups ($p<0.001$ and $p<0.01$, respectively).

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

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

Introduction

Obesity is caused by excessive lipid accumulation in adipose tissue due to 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 with high calories and large portions, and sedentary lifestyle. Increased body fat is risk factor which 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). Body mass index (BMI) is a simple classification criteria to assess the medical risks of obesity for adults. It is defined as the body weight in kilograms divided by the square of the height in metres (kg/m^2). Adults are classified according to BMI as underweight (<18.50), normal weight (18.50 to <25), overweight or preobese (25 to <30), obese class I (30 to <35), obese class II (35 to <40), and obese class III ($\geq$ 40).

Increased body weight is reported to be associated with oxidative stres and cellular damage in numerous studies (3-4). Reactive oxidative stress (ROS) members like superoxide anion ($O_2^{\cdot-}$), 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 sulphur 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 for formation of other ROS types (3-4). For example, obesity causes insulin resistance, hyper glycemia and elevated free fatty acid levels. The increase in intracellular glucose levels stimulates over expression of NADH and $FADH_2$, electron losses in mitochondrial inner membrane and subsequent superoxide formation. Free fatty acids also distrupt adenine translocation which leads up to superoxide production in 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 cellular antioxidant defense system in neutralizing increased ROS production (6-7). To prevent cellular damage that results from ROS, an array of mechanisms have 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, vitamin 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/disulfide ratio appeared as a novel biomarker in patients with diabetes, cardiovascular diseases, cancer several other diseases (8-10). Thiol is a sulfidryl (-SH) group containing organic compound which can bind C atoms. Plasma thiol pool is composed of albumin and other protein thiols, cysteinylglycine, cysteine, homocysteine, glutathione and γ-glutamylcysteine (11).

In this study, status of 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 formed according to their BMI's.

Materials and Methods

The study was conducted on patients who attended to polyclinic of internal medicine of Istanbul Bağcılar Training and Research Hospital, Health Sciences University. This cross-sectional study included 165 patients (104 females and 61 males) of 18-60 age group without any history of heart and kidney deficiency, stroke, cerebrovascular diseases and pregnancy. Patients' (selected with simple random sampling method) body kilograms 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: 18.50 to <25; n=39), pre-obese or overweight (BMI: 25 to <30; n=47), obese (BMI: 30 to <35; n=44) and severely obese (BMI: ≥35; n=35). Serums were collected from blood samples taken from volunteers and kept at -80^{0}C. Serum samples were then transported in cold chain (-20^{0}C) to Biochemistry Department of Ankara Yıldırım Beyazıt University Faculty of Medicine where analyses were performed. The study was conducted after approval was received from the clinical research ethical committee of Istanbul Bilim University (29.11.2016/55-41).

Thiol-disulfide pair tests in serum were determined according to the method of 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 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 commercially kits (Rel Assay Diagnostics, Gaziantep, Turkey) (12-13). Dark blue-green colored 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) radical is reduced to colorless reduced-ABTS form with antioxidants. The change of absorbance at 660nm is related with 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 530nm is related with TOS of the sample. 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 (470nm) of color production due to the reaction of albumin-cobalt with dithiothreitol. The reaction was performed by adding 50µL 0.1% cobalt (II) chloride ($CoCl_2$,$6H_2O$), 50µL 1.5 mg/mL dithiothreitol and 1µL 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 level (g/L) were measured by clinical biochemistry autoanalyzer (Roche, cobas 501, Mannheim, Germany).

Statistical analysis

Statistical analyses were performed using SPSS 22.0 program (SPSS, Inc., Chicago, IL, USA). To data that show compliance with the normal distribution, ANOVA test using the post-hoc Tukey test was applied, while to data that normal distribution does not fit, the Kruskal– Wallis ANOVA with the post-hoc Dunn's multiple comparison test was applied. Results were expressed as mean±SD and median (minimum-maximum), $p<0.05$ was considered significant.

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Results

Demographic Information

Gender distribution of experimental groups consisted of normal weight group 20 female, 19 male (n=39) pre-obese or overweight obese 20 female, 27 male (n=47) obese 18 female, 26 male (n=44) and severely obese 18 female, 19 male (n=35). Median (interquartile range) levels of ages of study groups are 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 normal weight group while there was also a significant increase in **Disulfide** (µmol/L) levels of overweight group than normal weight (P<0.01) and obese (P<0.05) groups. 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. Overweight group also had significantly elevated **Disulfide/total thiol** (%) levels and decreased **Native thiol/total thiol** (%) levels than the obese group (p<0.01 for both).

Oxidant and antioxidant variables (Table 2, Figure 2)

Total antioxidant status (TAS; mmol Trolox eq/L) levels of the overweight group showed a significant reduction when compared to the severely obese group, normal weight group and obese group (P<0.001, P<0.01 and P<0.05, respectively) while **Total oxidant status** (TOS; µmol H_2O_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 **Oxidative stress index** (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 **Ischemia-modified albumin** (IMA, ABSU) levels when compared to the severely obese and normal weight groups (P<0.001 and P<0.01, respectively) while

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the obese group had significantly elevated IMA levels than the severely obese group (P<0.01). The normal weight group showed a significant increase in **Albumin** (g/L) 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 has an important role in development of cellular damage. Fat accumulation rate is positively correlated with oxidative stress intensity. It is also known that oxidative stress is elevated with increased body mass index (BMI) (16). In our study, TOS and OSI levels were observed to be increased in groups with above normal BMI (25<). Parallel to our results, 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 anti-oxidant statuses of children with obesity and metabolic syndrome, TAS, TOS and OSI levels were shown to be elevated with BMI increase (18).

In addition to these, levels of ceruloplasmin which is an acute phase reactant were also observed to be elevated which is paralleled with BMI increase. This increase in ceruloplasmin levels with weight gain was found to be related to 'OH radical which is generated through 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 play a key role in transportation of antioxidants, and TAS were decreased especially in overweight group. Kinoshita et al. also reported that increased oxidative stress is associated with decreased albumin levels (21). Hydroxyl radicals released from Fenton

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reactions is directed to the targets important for protein conservation, due to high affinity of albumin to metal ions. High levels of albumin in plasma forms the biggest thiol pool in circulation. These sulfidrile groups (–SH) act as antioxidants against 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. IMA levels increase due to modification of albumin N-terminal part by ROS and free radicals. IMA is also considered as an oxidative stress, inflamation and ischemia marker (24). Our result showed that IMA levels were increased in overweight and obese groups compared to controls. Parallel to our results a a previous study also revealed that IMA levels were increased in overweight and obese groups and proposed IMA indicating IMA as an oxidative stress marker (23).

Oxidative stress occurs when antioxidant levels were lower than ROS levels in organisms. ROS levels are attempted to balance by enzimatic and non-enzymatic antioxidants by the organism. Among the most important non-enzymatic antioxidants are thiols containing –SH groups (25). Serum thiol levels are indirect indicators of antioxidant levels. Thiols can make disulfide bonds and then reduced to thiols reversibly. This dynamic thiol/disulfide homeostasis has important roles in antioxidant ability, detoxification and apoptosis. Disruption of this homeostasis is an indicator various disorders such as cardiovascular diseases, cancer, diabetes and Alzheimer (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 overweight group was observed to be higher than 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 equilibirium 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 the our results (27).

Adipose tissue formation in obese individuals were found to be associated with increased inflammation and oxidative stress levels, and decreased anti-oxidant levels (28). We also hypothesized that in gruops with above normal BMI (25≤) inflammation and oxidaitve damage is 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 oxidative stress levels in overweight group were higher compared to obese (30≤) group. Organisms tend exist in a stable equilibrium state. When this equilibrium is distrupted, organism attempts to re-balance it (29). Therefore a possible explanation for our result is that weight gain triggers oxidative stress and overweight group is more susceptible due to distruption in oxidant/antioxidant balance, than obese and severely obese groups in which this distruption in oxidant/antioxidant balance were attempted to be reverted by organism.

In 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 which are recently used as markers for several disorders. In additon to this, we think that increased oxidative stress levels in overweight group compared to obese (30≤) groups is caused by initial reaction of body to distruption of oxidant- antioxidant equilibirium stability.

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Table 1: Thiol / disulfide homeostasis variables

Groups → / Variables ↓	Group 1 (Normal weight; BMI: 18.50 to <25)	Group 2 (Overweight; BMI: 25 to <30)	Group 3 (Obese; BMI: 30 to <35)	Group 4 (Severely obese; BMI: ≥35)	Test p values	Post hoc p values
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****

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						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 mean±SD, median (minimum-maximum), BMI: Body mass index, SD: Standart deviation

(* p<0.05, ** p<0.01, *** p<0.001)

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Table 2: Oxidant and antioxidant variables

Groups → Variables ↓	Group 1 (Normal weight; BMI: 18.50 to <25)	Group 2 (Overweight; BMI: 25 to <30)	Group 3 (Obese; BMI: 30 to <35)	Group 4 (Severely obese; BMI: ≥35)	Test p values	Post hoc p values
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_2O_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**

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						3-4 p=0.008**
Albumin (g/L)	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 mean±SD, median (minimum-maximum), BMI: Body mass index, SD: Standart deviation

(* p<0.05, ** p<0.01, *** p<0.001)

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Figure 1: Thiol / disulfide homeostasis variables. Group 1 (normal weight; BMI: 18.50 to <25), Group 2 (overweight; BMI: 25 to <30), Group 3 (obese; BMI: 30 to <35) 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: 18.50 to <25), Group 2 (overweight; BMI: 25 to <30), Group 3 (obese; BMI: 30 to <35) 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

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