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Serum selenium and manganese levels in obstructive sleep apnea patients and their relationship with GPx and SOD enzyme activities

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ABSTRACT

Selenium and manganese are antioxidant elements, are cofactors in the functioning of enzymes. Obstructive sleep apnea (OSA) is the inability to breathe during sleep and may develop due to changes in oxidative stress, antioxidant defense system, and serum trace element levels. Therefore, we aimed to determine the antioxidant enzyme activities glutathione peroxidase (GPx), superoxide dismutase (SOD), as well as Se, Mn levels, in OSA patients (n=38) and healthy controls (n=27). Se and Mn were determined by Graphite Furnace Atomic Absorption Spectrometry (GFAAS), and GPx, SOD enzyme activities were determined by ELISA method in samples taken after polysomnography (PSG). Our results showed that Se, Mn levels in patients were significantly lower than in controls ($p<0.0001$). GPx activity in patients was lower than in controls ($p<0.01$), but serum SOD activity was lower than in healthy individuals but not significant ($p>0.05$). The results showed that the patients' Se, Mn

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levels, as well as GPx, SOD enzyme activities, were lower than the controls. In conclusion, our study showed that low levels of Se and Mn trace elements in OSA patients are associated with decreased antioxidant enzyme activities and increased oxidative stress. These findings suggest that trace elements affect the antioxidant enzyme activities in which they act as cofactors and that their deficiencies should be eliminated with supportive treatments in OSA patients.

Keywords: selenium, manganese, glutathione peroxidase, superoxide dismutase, obstructive sleep apnea

INTRODUCTION

Trace elements, which are essential minerals at the micro and macro levels, have very important functions in the body and play a part in the synthesis and structural stabilization of nucleic acids and proteins[1]. Hence, imbalances in the optimal levels of trace elements may adversely impress biological processes and are associated with many diseases[2].

Selenium (Se) is known as an important trace element for the body; however, its high concentrations have a toxic effect on the body. Low Se concentrations in the blood can lead to heart diseases[3-4]. Epidemiological studies have shown that Se has anti-inflammatory and antioxidant effects that can protect against cardiovascular diseases and reduce cardiovascular mortality and certain types of cancer[5-6]. Se is a microelement and cofactor for many enzymes and is also a component of the glutathione peroxidase (GPx) enzyme structure, which protects the organism from oxidative damage[7]. Se protects cells by the catalytic activity of GPx from the damage caused by free radicals that formed from molecular oxygen and disrupts hydrogen peroxide (H_2O_2), and fatty acid peroxidases formed in the cells. Moreover, Se is present in kidney and liver more than in another tissues[8-9]. Se, manganese (Mn), copper, and zinc are essential trace elements in the activation of antioxidant enzymes, such as GPx and superoxide dismutase (SOD) enzymes[10]. GPx contains a Se atom in its structure. The concentration of Se in the blood is 60–100 μg L^{-1} has been reported[11].

The other microelement we studied, Mn is essential for the activity of many enzymes (hydrazines, kinases, decarboxylases, and transferases) and metalloenzymes (arginase, pyruvate carboxylase, and manganese superoxide dismutase [MnSOD]) in the body involved in normal growth, reproduction, and skeletal development through nutrients, and plays an important role in carbohydrate, amino acid, and cholesterol metabolism. Mn is present in the mitochondrial MnSOD composition, which exhibits antioxidant activity against

oxidative production. Mn has a toxic effect at high doses. It participates in lipid and carbohydrate metabolism, cell function, and the construction of cell membranes[10,12]. In people who are exposed to high levels of this metal, it can accumulate in different parts of the brain, causing neurotoxicity[13]. In an experimental study, brain cortical neurons, which are an important component of obstructive sleep apnea syndrome (OSA), were subjected to chronic intermittent hypoxia. It was determined that the cells produced excessive amounts of reactive oxygen species (ROS), whereas the antioxidant defense system, especially MnSOD, was found to elicit them. These studies demonstrate that Mn acts as a cofactor of the MnSOD enzyme. There is a linear relationship between serum Mn and SOD activity[14-16]. Among the adverse health effects that results from increased Mn absorption are central nervous system effects. Symptoms that have been observed include dyspnea, tachycardia, fever, rigidity, and Parkinsonian muscle weakness. Conversely, Mn deficiency has been suggested to be associated with osteoporosis-like decalcification in bones[17]. Normal ranges of Mn levels in body fluids are 4.0–15.0 μg L^{-1} in blood[18].

OSA is known for recurrent attacks of the upper airways and is associated with respiratory depression, repetitive sleep-stimulating outcomes, and episodic oxyhemoglobin desaturation. Sleep apnea syndrome is a risk factor for cardiovascular and cerebrovascular morbidity and mortality, as well as daytime sleepiness and loss of cognitive performance[19]. The most common complaint of this syndrome is excessive daytime sleepiness and/or snoring. These attacks, especially with the temporary cessation of breathing during sleep, have been observed to increase oxidative stress and inflammation in OSA patients[20-21]. Oxidative stress can cause lipid peroxidation, including low-density lipoprotein (LDL) oxidation[22]. Major cardiovascular diseases results accompanying OSA are hypertension, coronary artery disease, metabolic syndrome, cardiac arrhythmia, left or right-sided heart failure, pulmonary hypertension, stroke, and sudden death[19,23]. The severity of obstructive sleep apnea is indicated by the apnea–hypopnea index (AHI) and divided into certain segments. The AHI is the sum of apnea and hypopnea in a 1-h sleep and has tensile polysomnography as its gold standard. The severity of the syndrome of the AHI is as follows: AHI < 5, normal; AHI = 5–15, mild; AHI = 15–30, moderate; and AHI > 30, severe OSA[19].

Free radicals that also cause oxidative stress are high-energy, unstable compounds that contain one or more pairs of electrons in their outer atomic orbital. Organic free radicals formed during metabolic events can also be caused by external factors. They are very active and can interact with all cell components.

The organism has defensive systems that will neutralize the harmful effects of free radicals. This defense system protects the organism from the harmful effects of free radicals by keeping the rate of physiological activity neutralized by the formation of free radicals. The oxidant–antioxidant balance is provided to protect the organism from damage. Degradation of this balance leads to oxidative stress[24].

GPx, SOD, glutathione reductase, and catalase enzymes are the principal endogenous enzymatic defensive systems of whole aerobic cells. They work in this system, with some microelements acting as cofactors of these enzymes[25]. SOD enzymes are the first and most important line of antioxidant enzyme defense systems against ROS and particularly superoxide anion radicals[10]. Three distinct isoforms of SOD have been identified in mammals, two of them have copper and zinc as cofactors and are localized in the intracellular compartment. The third SOD has Mn as cofactor and is localized in the mitochondria. SOD enzymes transform superoxide into oxygen and hydrogen peroxide[12]. GPx is a selenoenzyme that converts hydrogen peroxide into the water with the element Se. Additionally, it can transform other ROS into water. The effects of the elements associated with these enzymes and acting as cofactors are shown in Figure 1.

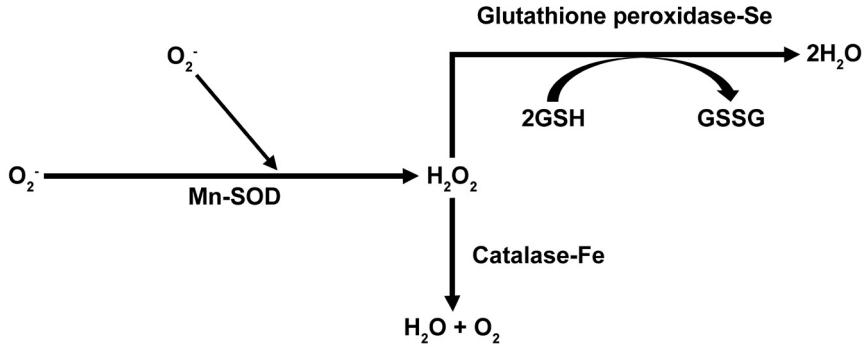

Figure 1. The kinetic mechanism of manganese superoxide dismutase (Mn-SOD) and glutathione peroxidase-Se (GPx-Se) as antioxidants

In this study we want to determine the levels of serum Se and Mn elements in OSA patients and also quantify the amounts of the antioxidant enzymes GPx and SOD, which are related to these elements. All results were detected in OSA patients, and these levels were compared with control groups.

METHODOLOGY

Study population and data collection

The present study was approved by the Marmara University, Institute of Health Sciences, Ethics Committee of Clinical Research. Blood samples were collected from OSA (n=38) patients and AHI index>5 patients who applied to the Somnus Sleep Disorders Center, Istanbul for routine examination. And healthy volunteers (n=27) were taken as controls with an AHI < 5. All people who want to take part in the study gave written inform consent to participate in the study. Subjects participating in the study underwent a polysomnography (PSG) test19-20. Overnight PSG (Somnologica, Flaga, Iceland) was performed between 11 PM and 7 AM. PSG consisted of simultaneous recordings of two channels EEG (C3 A2 and C4 A1), left and right electro-oculography, and chin electromyography from surface leads for sleep staging. In addition, air flow from a nasal cannula, thoracic and abdominal strain gauges for respiratory effort, tracheal microphone for snoring, pulse oximetry for oxyhemoglobin level, and sensor for body position during sleep were used. Respiratory data including AHI, minimum and mean oxyhemoglobin desaturations, were produced automatically by a computer program (Somnologica version 2.0.1, Flaga, Iceland). In the first hour, the blood samples were centrifuged at 3500 rpm for 10 min to separate the serum. They were aliquoted into Eppendorf tubes and stored at –80°C until analysis.

Exclusion criteria

People with Diabetes Mellitus, any kind of neurodegenerative diseases, endocrinological diseases, cancer and acute or chronic infection were excluded from the study groups.

Measurement of trace elements

To measure these concentrations of Se and Mn were measured in a graphite furnace atomic absorption spectrometer (Shimadzu, AA-6800, Japan) with an autosampler (Shimadzu, ASC-6100, Japan) and refrigerated circulator (EYELA CA1115A-1). Pyrolytic graphite platforms and furnaces were used. A background corrector (Zeeman) was used to prevent interference. Argon (99.996%) was applied as a protective gas. All reagents and standards were the analytical grades, and 0.5% (v/v) HNO_3 was used in the dilutions of standard solutions and blank.

For sample preparation, 70% nitric acid (99.999% trace metals basis) (Merck) and Triton X-100 (Merck) were used. Because of the low sample sizes and high

protein structure, the samples were studied using a palladium matrix modifier Pd $(NO_3)_2$ (10.0 g L^{-1}) in HNO_3 0.1% and TritonX-100 0.1%). Triton acts as a detergent to eliminate carbonaceous residues formed inside the graphite tube and helps in the cleaning of the autosampler capillary between sampling[25]. Standard solutions were prepared the 1000 mg L^{-1} selenium titrisol (SeO_2 in 6.3% HNO_3) and manganese titrisol standard ($MnCl_2$ in H_2O). The calibration curves were plotted at Se 196.0 nm and Mn 279.5 nm with a graphite furnace atomic absorption spectrophotometer (GFAAS) using an autosampler. GFAAS and furnace conditions are given in Table 1 and Table 2.

Table 1. Graphite furnace atomic absorption spectrophotometer instrumental parameters for Mn and Se analysis in serum samples

Parameters	Mn (II)	Se (IV)
Wavelength	279.5 nm	196.0 nm
Slit	0.2 nm	1.0 nm
Lamp current	10.0 mA	23.0 mA
Calibration mode	Absorbance, peak high	Absorbance, peak high
Background correction	Zeeman effect	Zeeman effect
Light Mode	BGC-D2	BGC-D2
Injection volume	20.0 µL	20.0 µL

Table 2. Graphite furnace atomic absorption spectrophotometer furnace conditions for Mn and Se determination in OSA patients and healthy control groups

Step	Temp°C Mn	Temp°C Se	Ramp (s)	Hold (s)	Flow (mL min^{-1})
1	150	120	5	20	1.0
2	250	250	5	10	1.0
3	600	600	5	10	1.0
4	600	600	2	3	0
5	2300	2200	1	3	0

The slope values and R values of the curves were calculated as for Se: R = 0.9990; for Mn: R = 0.9948.

Recovery and accuracy studies of trace element measurement

A recovery study was performed for these metals to better evaluate the accuracy and reliability of the results of the Se and Mn concentrations obtained from the analysis. In the absence of a reliable comparison method, recovery studies should be important[26]. Reference serum material Seronorm Serum level 1 (lot JL 4409) used for the accuracy of the developed analytical method was used. To determine the accuracy of the method for GFAAS, Se, and Mn were evaluated in a serum sample using a spike recovery test. According to the accuracy studies, it was determined whether the results met the AOAC (2002) criteria[27].

Biochemical analysis

Total lipid, total cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, and high-density lipoprotein (HDL) cholesterol levels were determined by Abbott Architect ci8200 auto-analyzer (Abbott Park, IL, USA). GPx and SOD enzyme activities were evaluated by using enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (Cayman Chemical, Ann Arbor, USA).

Statistical analysis

Statistical analysis was carried out using GraphPad InStat Software Inc. All data are expressed as the means ± SD. The student's t-test was used to evaluate the group's results; comparisons of more than two independent groups were undertaken by analysis of variance with Tukey's post hoc test. Values of $p<0.05$ were regarded as significant.

RESULTS and DISCUSSION

OSA has been increasing in the middle-aged population in recent years and is associated with obesity and heart diseases. It is known as a recurrent upper respiratory tract barrier and is a disease often accompanied by oxygen desaturations during sleep[28].

In our study we included 65 patients and 38 of them were OSA (AHI ≥ 5) whereas 27 were in the control group (AHI < 5). The age distribution was found to be in a similar range between the OSA group (41.8 ± 9.1 years) and the control group (41.0 ± 8.9 years). The AHI of OSA patients was 15.0 ± 8.0 while the oxygen desaturation index was 79.5 ± 21.2%. Patients with these findings are classified as mild to moderate OSA group. Because the healthy control group has an AHI level of 3.0 ± 2.0 and an oxygen saturation index 95.4 ± 11.2%, which were significantly different to the OSA group. The general anthropometric, PSG and biochemical results of the OSA and healthy control group are

shown in Table 3.

Table 3. Anthropometric, polysomnographic, and biochemical results in OSA and healthy control subjects

Anthropometric results	OSA group (n=38)	Control group (n=27)	P value
Age (years)	41.8 ± 9.0	41.0 ± 8.9	0.7210
Weight (kg)	91.4 ± 13.3	79.7 ± 16.6	0.0030
Size (m)	1.75 ± 7.0	1.71 ± 10.0	0.0659
BMI (kg m^{-2})	30.1 ± 4.3	27.3 ± 4.3	0.0137
Polysomnographic results			
AHI	15.0 ± 8.0	3.0 ± 2.0	<0.0001
Oxygen saturation (%)	79.5 ± 21.2	95.4 ± 11.2	<0.0001
Biochemical results			
Total lipid (mg dL^{-1})	570.2 ± 207.6	534.3 ± 126.9	0.4143
Triglycerides (mg dL^{-1})	219.3 ± 177.3	141.6 ± 74.3	0.0304
Total cholesterol (mg dL^{-1})	217.7 ± 41.8	210.0 ± 45.8	0.4765
LDL cholesterol (mg dL^{-1})	97.4 ± 23.2	137.3 ± 41.9	<0.0001
HDL cholesterol (mg dL^{-1})	35.8 ± 5.5	44.6 ± 11.0	<0.0001

BMI: Body mass index; AHI: apnea–hypopnea index; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

According to the biochemical results in Table 3, when the cholesterol levels of the samples were examined, it was found that weight, total lipid, triglycerides, and total cholesterol levels were higher in OSA patients compared to the control group. LDL and high-density lipoprotein (HDL) cholesterol were found to be significantly lower than the control groups. According to the polysomnographic results, the AHI index was found to be significantly higher than the results obtained in patients with OSA, and the oxygen saturation (%) was lower compared to the control group. Abnormalities in lipid metabolism are very commonly observed in patients who are obese. As shown on Table 3 BMI and weight of the OSA patients are significantly higher than the control group, which confirms the data. A reduction in LDL-cholesterol level and a higher HDL-cholesterol level in OSA patients with respect to the control group show

that these patients use medications against hypercholesterolemia[19].

The serum Se concentration in OSA patients were 35.06 ± 10.12 μg L^{-1} and in control subjects 59.73 ± 8.98 μg L^{-1}, $p<0.0001$. Additionally, the Mn levels in serum samples of OSA patients were 7.09 ± 2.33 μg L^{-1} and 19.85 ± 9.14 μg L^{-1} in control, $p<0.0001$ (Figure 2).

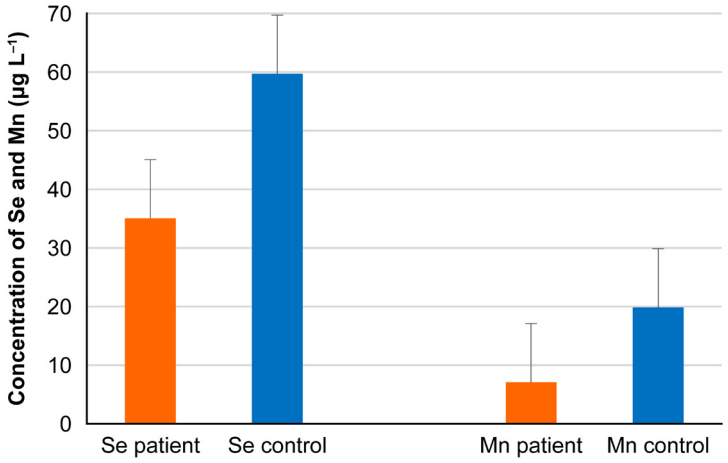

Figure 2. Serum Se and Mn values in OSA and control groups. The significance between OSA patients and control groups were $p<0.0001$ for both parameters.

The recovery results obtained in the serum sample for 13.00 mg L^{-1} Se, 24.00 mg L^{-1} Se, 1.00 mg L^{-1} Mn, and 2.00 mg L^{-1} Mn were 91.30%, 98.10%, 95.38%, and 101.5%, respectively. According to the accuracy studies, the results were found to be appropriate because recoveries were within the range proposed by AOAC (2002) (70%–125%) upon the concentration series studied[27]. These findings demonstrate that the Se and Mn levels measured in our study are accurate and valid.

The major antioxidant enzymes -GPx and SOD- found in mammalian cells are thought to be essential for life in all cells that metabolize oxygen. As shown in Table 4 the GPx activity in OSA patients and healthy control groups were 27.30 ± 11.70 U mL^{-1} vs. 34.90 ± 13.70 U mL^{-1}, respectively. The minimum and maximum levels were 5.09 U mL^{-1} and 71.30 U mL^{-1} in OSA patients and 15.28 U mL^{-1} and 81.49 U mL^{-1} in control subjects. There was a significant change between the groups ($p<0.01$). The mean serum SOD activity in patients with OSA were found to be 2.62 ± 1.83 U mL^{-1} and 3.03 ± 1.71 U mL^{-1} in the control group. The minimum and maximum levels were changed between 0.30 U mL^{-1} and 9.00 U mL^{-1} in OSA patients and 1.00 U mL^{-1} and 7.60 U mL^{-1} in control

subjects. The meaningfulness between the groups was not significant (p>0.10)

Table 4. Statistical evaluation of serum GPx and SOD activities in OSA patients and healthy control subjects

Statistical data	GPx Activity		SOD Activity	
	OSA group (n=38)	Control group (n=27)	OSA group (n=38)	Control group (n=27)
Mean (U mL^{-1})	27.30	34.90	2.62	3.03
Standard deviation (SD)	± 11.70	± 13.70	± 1.83	± 1.71
Standard error the mean (SEM)	1.90	2.50	0.30	0.32
Minimum (U mL^{-1})	5.09	15.28	0.30	1.00
Medium (U mL^{-1})	25.47	30.59	2.35	2.30
Maximum (U mL^{-1})	71.30	81.49	9.00	7.60
P value	p<0.01		p>0.10	

Se is one of the most important elements of our study and the GPx enzyme is an important part of our body and shows an antioxidant property. The low level of Se paralleled with decreased activity of GPx enzyme. In a study of moderate and severe OSA patients, GPx and SOD activities were found to be in parallel with our study. In this study serum zinc and erythrocyte Se levels were low, and serum Cu and Fe levels were high determined in OSA patients[29]. These studies strengthen our hypothesis and demonstrate that serum or erythrocyte trace element levels can alter antioxidant enzyme activities[29-30].

Studies have reported that Se detoxifies heavy metal ions such as mercury and Mn in the human body and protects the nervous system by reducing ROS production. OSA causes sleep hypoxia and low GPx and SOD activities in humans. The apnea/apnea index of OSA is negatively correlated with the amount of Se in red blood cells, suggesting that low Se levels increase OSA severity[29]. Se has different roles in different diseases[6,8-9]. Studies show that evaluation of Se levels in humans, low levels of Se can significantly trigger the disease, and the addition of Se to daily diet helps prevent and to treat the disease[31].

Compared with the literature, the results were found to be compatible. According to the data obtained from our experimental studies GPx and SOD enzyme activities were also found to be decreased in the OSA patients, related to the low levels of Se and Mn levels,

which act as cofactors in enzyme systems in the participants. This can be considered one of the reasons for the emergence of OSA. Here in, it can be said that the possibility of low activities of enzymes is expected due to low Se and Mn amounts. In a study with cell culture and transgenic mice, overexpression of MnSOD was shown to reduce chronic intermittent hypoxia (CIH)-mediated cortical neuronal apoptosis. Together, data from in-vitro and in-vivo experiments have shown that CIH-mediated mitochondrial oxidative stress can play an important role in neuronal cell loss and neurocognitive dysfunction in OSA. Therefore, therapeutic strategies aimed at reducing ROS from mitochondria may increase neurobehavioral morbidity in OSA[14].

Research has revealed the role of trace elements, particularly Se and Mn, and the antioxidant defense system in combating OSA. Se and Mn trace elements have a fundamental importance for human life[1]. Recent studies show that essential elements may be associated with various diseases and immune system diseases[2].

Acute decompensated heart failure is a common cause of acute respiratory failure. When the studies conducted were examined, it was found in the articles that there was a relationship between acute decompensated heart failure and antioxidant enzyme levels. It has been observed that oxidative stress increases heart failure and is closely related to mortality[32]. Studies conducted to elucidate the effects of Se, and the antioxidant system have reported that Se decreases ROS production and increases the level and activity of antioxidant enzymes, such as GPx and thioredoxin reductase[30]. GPx, which contains four Se atoms in its structure, and is responsible for the removal of hydroperoxides formed in cells, is known as a selenoenzyme that protects cells against damage. Se deficiency causes a decrease in GPx activity[6]. The inverse correlation between serum Se and C-reactive protein (CRP) suggests that low amounts of Se may be associated with oxidative stress leading to lipid peroxidation. The existing literature has a few studies investigating the pathophysiological role of Se and selenoenzymes in OSA. The inverse correlation between serum Se and CRP suggests that low amounts of Se may be associated with oxidative stress leading to lipid peroxidation[33]. It has been demonstrated that serum GPx concentrations are lower in individuals with OSA and are inversely correlated with average oxygen saturation and directly correlated with AHI[20,22,34]. A study by Chen and colleagues with OSA patients showed lower levels of antioxidant enzyme activity and lower erythrocyte Se concentrations in erythrocyte GPx levels compared with OSA patients and control groups. Erythrocyte Se levels showed a large reverse correlation with the AHI ratio. In other words, when the AHI is high, the Se concentration was found to be low[29].

Vitamins A, C, and E and minerals are essential microelements that act as antioxidants to protect lipids, proteins, nucleic acids, and other important biomolecules against oxidative stress damage[24]. Their antioxidant properties

are related to their ability to donate electrons. Se is present as selenoproteins, which are important in many reactions, such as the formation of thyroid hormones and antioxidant defense[8]. In particular, the slow metabolism in the elderly slows the transition to blood in essential elements such as vitamins and minerals[2]. Additionally, respiratory events are slowing due to various diseases, such as heart diseases, lung diseases, and deformation in the upper respiratory tract. This prevents the passage of oxygen from the lungs to the blood, thereby reducing the enzymes and activities involved in the blood composition. As seen from the studies done, air, water, nutrient support, and balanced nutrition are needed for human metabolism to work properly and healthy[35]. Mineral entry into the human body should be achieved through the regular and balanced feeding of the people. Furthermore, activities such as sports and hiking, which are necessary for regular metabolism, are diminished in elderly individuals. Moreover, with the development of technology, people are constantly being in a still position for a long time[35]. Consequently, various illnesses arise at early ages with various side effects. Considering that OSA is not treated and followed correctly for human life, it is very important, and its treatment is necessary. Therefore, although the roles of Se and Mn in different diseases are still different, low levels of these elements significantly induce disease and may help prevent and treat disease when supplemented. Considering that OSA is not treated and followed correctly for human life, it should be considered that it is very important, and its treatment should be done. Although ventilators are provided in hospitals, it should be considered that the application of supportive treatment containing Se and Mn under the control of a doctor may contribute to recovery. It has been suggested that an increase in the intake of antioxidant-rich foods and supplements may lead to less exposure to free radicals, thereby minimizing health problems[35].

In conclusion, we found that Se and Mn levels in OSA patients decreased in parallel with GPx and SOD activities compared to the control group, the antioxidant defense systems of the patients were weakened, and oxidative stress became clear. These results show that patients with OSA have a weakened antioxidant defense system due to increased oxidative stress due to decreased SOD and GPx enzyme activities synthesized due to Se and Mn. Se and Mn, which are essential elements, play an important role in the synthesis of ROS by binding to the structures of SOD and GPx, which act as antioxidant enzymes in our body. Since ROS are harmful species that should not be produced in our body, in the management of patients with OSA, Se and Mn containing antioxidant food or antioxidant food supplements can be used as complementary treatments to prevent complications and other serious diseases. There have not been illuminating

studies on the roles of Se and Mn in the progression of OSA and various related cardiovascular comorbidities, and more research is needed on this subject.

STATEMENT OF ETHICS

This study was approved by the Marmara University, Institute of Health Sciences, Ethics Committee of Clinical Research (Project No:16.11.2012-16).

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept – G.E., S.K.; Design – G.E., S.K., M.Y.; Supervision – G.E., M.Y.; Resources G.E., S.K., M.Y.; Materials – G.E., M.Y., O.U.D., Z.P., H.K.O.; Data Collection and/or Processing – S.K., G.E., M.Y.; Analysis and/or Interpretation – G.E., S.K., M.Y.; Literature Search – S.K.; Technical or Financial Support– Marmara University BAPKO; Writing – S.K.; Critical Reviews and Supervisions – G.E., M.Y.

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