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Myeloperoxidase Levels in Apnea Patients With or Without Metabolic Syndrome: The Role of Smoking [Version 1, Awaiting Peer Review]

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Abstract

Purpose: Obtructive sleep apnea (OSA) is recognized as one of the most important cardiovascular risk factors, because intermittent hypoxia is similar to myocardial ischemia/reperfusion injury. Myeloperoxidase (MPO) is also thought to be involved in increased cardiovascular disease risk because it has been implicated in the oxidation of lipids and the promotion of lipid-rich plaque formation. In this study, we aimed to examine MPO levels in OSA patients with/without metabolic syndrome according to the several parameters.

Methods: This study included 72 apparently healthy subjects with newly diagnosed OSA and 20 control subjects with simple snoring who underwent overnight polysomnography and routine blood tests. MPO levels were determined from the blood samples taken in the morning by competitive Elisa method.

Results: The serum MPO levels in the all apnea patients, patients with and without metabolic syndrome (MetS) were significantly higher than that in control subjects ($p<0.0001$, $p<0.001$ and $p<0.005$, respectively). MPO levels were significantly higher in smoker patients and non-smoker patients than those in their controls ($p<0.005$ and $p<0.01$, respectively). In apnea group, smoker patients had higher MPO levels than those in non-smoker patients ($p<0.02$)

Conclusion: Elevated MPO levels indicate increased systemic inflammation and oxidative stress which might contribute to the higher incidence of cardiovascular diseases (CVD). Higher MPO levels in smoker patients may be due to the pro-inflammatory effects of smoking. MPO, as a parameter which can easily be measured, may be a predictor for future CVD in OSA patients.

Keywords

Myeloperoxidase; Obstructive Sleep Apnea; Smoking; Gender

Introduction

OSA is a disease characterized by repetitive obstructions of upper airway during sleep. In OSA, airway obstruction causes a significant reduction of arterial oxygen saturation followed by rapid reoxygenation called intermittent hypoxia (IH), intermittent periods of oxygen saturation below 90%. Because IH is similar to myocardial ischemia/reperfusion injury, OSA is accepted one of the most important cardiovascular risk factors [1].

The studies suggest that OSA can encourage endothelial dysfunction mediated by systemic inflammation and oxidative stress which have been associated with cardiovascular injury. An inflammatory process in OSA and its contribution to the development of cardiovascular disease are supported by a number of studies [2]. Recent data supports a central role of inflammation in the pathogenesis of atherosclerosis at all stages of atheroma formation. Inflammatory cells adhere to the endothelium and release a number of inflammatory mediators including cytokines such as tumor necrosis factor-α or chemokines such as interleukin-8 [3]. It has been demonstrated that increase in markers of inflammation in OSA markedly decrease after effective treatment with continuous positive airway pressure (CPAP) [4].

MPO, a member of the heme peroxidase superfamily, generates reactive oxygen species [5]. It catalyzes the reaction of hydrogen peroxide with chloride ions and causes the formation of hypochlorous anions. In addition, the reaction of hypochlorous anion with hydrogen peroxide leads to the formation of highly reactive singlet oxygen. Interactions between superoxide radical and hydrogen peroxide which occurred during inflammation may cause the formation of bactericidal hydroxyl radical [6]. By means of these reactive species; MPO has been implicated in the oxidation of lipids and the promotion of lipid-rich plaque formation. Enzyme might also catalytically consume endothelium-derived nitric oxide (NO) and impair its vasodilatory and anti-inflammatory function, leading to vasoconstriction [7]. Moreover, a recent study has shown that plasma concentrations of MPO predict mortality after acute myocardial infarction (AMI) [8].

It is well established that smokers are significantly more susceptible to a variety of diseases, including coronary artery diseases. Besides trace amounts of microbial cell components, cigarette smoke contains several toxins which have immunomodulatory effects [9]. Cigarette smoke is a profound pro-inflammatory stimulus and inflammatory cells express enzymes, including NADPH oxidase, nitric oxide synthase, and MPO. Smokers have increased blood counts of neutrophils and monocytes, which are the main endogenous sources of MPO. Hence, in this study, we primarily aimed to analyze the levels of MPO in OSA patients with/without metabolic syndrome according to the smoking status. We also aimed to investigate the association between MPO and other parameters.

Materials and Methods

Subjects

72 OSA patients and 20 healthy controls involved in this study were selected from subjects attended to Sleep Disorders Center in Department of Chest Diseases, Ankara Diskapi Yildirim Beyazit Training and Research Hospital, for suspected sleep apnea. Before admission, all subjects were interviewed for the presence of sleep-related symptoms, snoring, witnessed apnea, and excessive daytime sleepiness. Epworth sleepiness test was used to determine the level of daytime sleepiness. After examination by an otorhinolaringologist, patients having anatomical nasal problems such as septal deviation were excluded from the study.

All participants' rights were protected, and informed consent was obtained according to the Helsinki Declaration. The study protocol was approved by the local Ethic Committee from

the Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey.

Polysomnography

Presence and severity of OSA were determined by standard overnight polysomnography (16 channels, Embla, Flaga). All data obtained from the electroencephalogram (electrodes at positions F3M2, F4M1, C3M2, C4M1, O1M2 and O2M1), electrooculogram, and electromyogram (submental EMG and EMG tibialis), oronasal air flow measurements (cannula), breathing movements of the chest and abdomen, snoring detected by using a tracheal microphone, body position, and pulse oxymetry at the finger tip of the patients were recorded and evaluated by the Somnologica 3.2 version software program. Analysis of sleep stages were performed according to the Criteria of AASM [10].

Apnea was defined as an absence of air flow for at least 10 s, and hypopnea was defined as a 30% reduction in airflow accompanied by a reduction in oxygen saturation by 3% from baseline or arousal. Mean oxygen saturation (mean SaO2) was defined as average of oxygen saturation during the night. Lowest oxygen saturation (lowest SaO2) was defined as the lowest value of oxygen saturation during the night. To assess the severity of hypoxia induced by apnea-hypopnea events, we also measured the duration of an oxygen saturation <90% and <85%. The apnea–hypopnea index (AHI) was defined as the average number of apneic and hypopneic events per sleep hour. The AHI levels greater than 5/h was considered as diagnostic of OSA. Based on the results of polisomnography, Thirty five out of 72 subjects were classified as having severe OSA (AHI≥30) and 37 mild-to-moderate OSA (5≤AHI<30). Control subjects had an AHI less than 5/h. All controls were apparently healthy and without a history of hypertension, diabetes, renal disease and any acute disease.

Metabolic Syndrome Criteria

Subjects were also evaluated for Metabolic Syndrome according to Adult treatment Panel III (ATP III) criteria [11]. The criteria; 1) abdominal obesity: waist circumference (WC) > 102 cm in males and > 88 cm in females, 2) hypertriglyceridemia: >150 mg/dl, 3) low levels of HDL cholesterol: < 40 mg/dl for males and < 50 mg/dl for females, 4) high fasting glucose: >110mg/dl. 5) high blood pressure : >130/85 mmHg; The current use of antihypertensive medication was also considered as an indication of high blood pressure. Based on the results of these criteria, 41 of the 72 patients had more than three criteria of Metabolic Syndrome.

MPO Assay

Peripheral venous blood samples were obtained in the morning after the diagnostic polisomnography was performed. Separated serum samples for MPO measurements were kept frozen at –80ºC until analysis. The MPO levels were detected with a Myeloperoxidase (MPO) Enzyme Immunoassay Test Kit (Biocheck, Inc, CA). All measurements were repeated three times.

Statistical Analysis

Data were expressed as the mean (standard deviation, SD), and statistical analyses were performed by the student's t-test and Mann-Whitney U-test. Chi-Square test was used to determine the relation between categorical variables. Analysis of variance (ANOVA) was used to determine the intergroup differences. Bivariate Pearson correlation test was used to statistically determine the relationships among parameters. Statistical analyses were performed with a IBM SPSS Statistics 22 Package (SPSS Inc., U.S.A.). Power analysis and Sample Size Calculation were performed with the GraphPad StatMate 2.00 Package program (GraphPad Software, Inc., USA).

Results

Table 1: Baseline characteristics, sleep data, and laboratory values of OSA patients with/without MS and healthy controls.

Parameters	Healthy Controls (n=20)	Patients with MS (n=41)	Patients without MS (n=31)	p
Demographics				
Age, year (SD)*	42.5 (8.1)	51.3 (9.6)	49.1 (13.3)	0.012
Gender				
Male (%)	11 (55.0)	19 (46.3)	23 (74.2)	
Female (%)	9 (45.0)	22 (53.7)	8 (25.8)	
Body Mass Index, kg/m^2 (SD)	27.7 (3.9)	33.4 (4.3)	32.6 (7.3)	0.001
Neck thickness, cm (SD)				
Male	39.2 (2.2)	42.3 (3.0)	40.9 (3.7)	0.045
Female	35.0 (2.0)	37.3 (2.3)	38.6 (4.0)	0.023
Diabetes Mellitus (Yes/No)	0/20	8/33	0/31	
Hypertension (Yes/No)	0/20	15/26	4/27	
Total Time Asleep, min (SD)	369.2 (48.4)	371.9 (51.9)	363.3 (51.6)	0.776
Epworth Scala, mean (SD)	8.4 (5.4)	10.5 (5.8)	9.5 (5.6)	0.389
Metabolic Syndrome Criteria				
Waist circumference, cm (SD)				
Male	93.7 (7.3)	112.8 (10.4)	104.7 (13.6)	0.000
Female	92.9 (10.3)	109.1 (8.9)	117.6 (13.6)	0.000
Diastolic Blood pressure, mmHg (SD)	76.0 (10.5)	80.4 (12.2)	75.8 (12.0)	0.184
Systolic Blood pressure, mmHg (SD)	116.0 (13.5)	126.6 (18.0)	115.8 (15.7)	0.010
Fasting Blood Glucose (mg/dL)	85.0 (10.6)	106.3 (29.7)	87.1 (11.8)	0.000
Triglyceride(mg/dL)	108.1 (41.8)	230.9 (168.4)	117.2 (46.8)	0.000
HDL- Cholesterol				
Male	39.2 (6.8)	37.0 (10.1)	45.1 (8.8)	0.021
Female	51.9 (14.3)	42.9 (9.5)	47.7 (4.3)	0.095
Diagnostic Sleep Data				
AHI (events/h)	3.2 (1.5)	37.3 (27.9)	38.3 (27.6)	0.000
SaO_2I (events/h)	35.4 (20.1)	284.6 (188.3)	284.9 (175.5)	0.000
Percentage of time <90%O_2 saturation, min (SD)	0.3 (0.8)	63.9 (95.8)	99.0 (122.3)	0.003
Percentage of time <85%O_2 saturation, min (SD)	0,02 (0,1)	21.9 (65.0)	53.5 (98.6)	0.035
Mean SaO_2 (%)	79.7 (27.5)	77.6 (8.5)	71.3 (18.6)	0.186
Lowest SaO_2 (%)	94.4 (2.5)	90.4 (4.9)	88.4 (6.6)	0.001
Inflammation markers				
MPO, µmol/L	2.62 (1.75)	5.02 (3.75)	4.83 (3.11)	0.019
C-Reactive Protein (CRP), mg/L	4.12 (2.18)	7.63 (5.02)	8.64 (8.07)	0.026
Fibrinogen, mg/dl	318.1 (30.5)	367.4 (43.3)	377.03 (79.34)	0.001

*Standard Deviation

The study participants were further divided into two groups according to metabolic syndrome (MS) status. Baseline characteristics and polysomnographic results of OSA patients with/without MS and controls are given in Table 1. Age, BMI, and neck thickness were much higher in the apnea patients with/without MetS than in the controls (Table 1). As might be

expected, all the criteria for metabolic syndrome, except for diastolic blood pressure, were much different in the apnea patients with MetS than those in the apnea patients without MetS and/or controls (Table 1). Similarly, all sleep data, except Mean SaO2 (%), were significantly different in the both apnea patient groups than those in the control (Table 1).

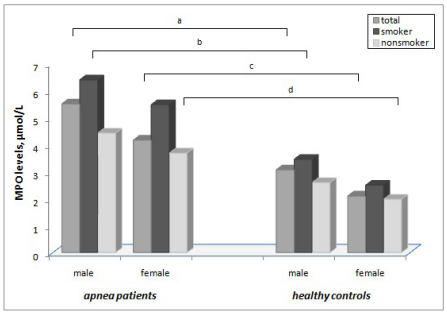
The serum MPO levels were higher in all apnea patients, patients with MetS, and patients without MetS compared to the healthy controls ($p<0.0001$ $p<0.001$ and $p<0.002$, respectively) (Table 2). In addition, patients in the severe and mild/moderate apnea groups had higher MPO levels than those in controls ($p<0.005$ and $p<0.001$), respectively) (Table 2). In the patient group, there were no any statistically significant differences in MPO levels according to the severity of disease or the status of having metabolic syndrome.

Table 2: Mean (SD) levels of MPO according to the smoking in patients and healthy controls.

	Total		Non-smoker		Smoker	
Demographics	**N**	**MPO levels**	**N**	**MPO levels**	**N**	**MPO levels**
Controls	20	2.62 (1.75)	12	2.23 (1.65)	8	3.21 (1.84)
Total Apnea	72	4.94 (3.47)[a]	41	4.02 (2.72)[b,c]	31	6.15 (3.99)[d]
Apnea with MS	41	5.02 (3.75)[e]	24	3.92 (2.60)[f]	17	6.58 (4.60)
Apnea without MS	31	4.83 (3.11)[g]	17	4.18 (2.97)	14	5.62 (3.20)

(a) $p<0.001$ compared with total controls; (b) $p=0.008$ compared with non-smoker controls; (c) $p=0.014$ compared with smoker patients; (d) $p=0.005$ compared with smoker controls; (e) $p=0.001$ compared with total controls; f) $p=0.041$ compared with smoker patients with MS ; (g) $p=0.002$ compared with total controls

MPO levels were increased by smoking in both control and all apnea groups. MPO levels of smoker patients were much higher than in smoker controls ($p=005$) (Table 2). In the total patients and apnea patients with MS, MPO levels of smokers were significantly higher than those in non-smokers ($p=014$ and $p=0.041$, respectively) (Table 2). According to the severity of apnea, although smoker patients had higher MPO levels than those in non-smoker patients in all groups, there was only statistically significant difference in severe apnea group ($p=0.026$). In addition, non-smoker patients had higher MPO levels than those in non-smoker controls ($p=0.008$) (Table 2).



(a) P=0.007 compared with male controls
(b) P=0.023 compared with male smoker controls
(c) P=0.004 compared with female controls
(d) P=0.017 compared with female nonsmoker controls

Figure 1: The changes in serum myeloperoxidase levels according to the gender and smoking status of the patients and controls.

As seen in (Figure 1), in both control and patient groups, serum MPO levels of males were slightly, but not statistically significant, higher than those of females in total, smoker, and nonsmoker subjects ($p>0.05$) (Figure 1). In both male and female groups, total patients had higher MPO levels than those of same gender groups in the controls ($p<0.05$) (Figure 1). However, smoker male and nonsmoker female patients had higher levels compared to same groups in the controls ($p<0.05$) (Figure 1).

MPO was only positively correlated with AHI in the severe apnea patients ($R=0.468$, $p=0.005$). MPO was not definitely associated with any other sleep data in the apnea patients. We found negative correlation between MPO and HDL in both total patients ($R=-0.403$, $p=0.001$) and patients with MS ($R=-0.451$, $p=0.002$). When evaluated according to smoking status, correlations between MPO and HDL observed in total patients ($R=-0.390$, $p=0.037$) and patients with MS ($R=-0.489$, $p=0.046$). Any correlation between MPO and HDL was not observed in the control group, but there was a weak correlation among them in nonsmoker patients ($R=-0.309$, $p=0.063$).

Discussion

OSA is an important public health issue, and one of every five people has apnea at different degrees [12]. It is suggested that OSA is a most likely risk factor for morbidity and mortality due to atherosclerotic disease [13]. However, the underlying mechanisms between OSA and cardiovascular diseases have not been completely understood and may be multifactorial in origin. Chronic inflammation is one of the pathophysiological pathways suggested for the development of cardiovascular disease in OSA [14], because inflammation is accepted as critical in the pathogenesis of atherosclerosis at every stage of atheroma formation [15]. In previous clinical studies, elevated levels of inflammatory markers, such as C-reactive protein (CRP), interleukin-6 (IL-6), ESR, etc., have been shown in patients with OSA [16,17].

Myeloperoxidase (MPO) is linked to both inflammation and oxidative stress by its location in neutrophils and its role in producing reactive species for bactericidal effect [7]. In the initiation of atheroma formation, MPO has been implicated in oxidation of LDL-cholesterol and dysfunction of HDL-cholesterol. Increases in MPO release might be a potential initiating mechanism of atherogenesis in OSA [18]. We found few studies on MPO levels in the OSA. In one of these, Svensson et al studied several inflammation markers in women with sleep-disordered breathing [19]. Although they found significantly higher levels of CRP, IL-6 and lysozyme in subjects with AHI ≥15 compared with women with lower AHI, they did not find a difference in MPO levels in subjects according to the severity of the apnea. On the other hand, Hanikoğlu et al showed increased MPO levels in severe apnea patients than those in controls. In our study, we found higher MPO levels in total patients compared with healthy controls [20]. In a recent study, Arısoy et al. did not find any differences in MPO levels between control and OSA groups

[21]. According to MS status, we observed similar MPO levels in patients with and without MS, slightly higher in MS group, but MPO levels were significantly higher in patients in both groups than those in controls. We also observed higher levels in other inflammation markers, such as CRP and ESR. However, in contrast to CRP and ESR, MPO levels tended to be higher in males than those in females in both control and patient groups.

Although smoking is regarded as a risk factor for cardiovascular disease, the precise mechanism is still not known exactly. Coronary endothelial dysfunction and increased inflammatory responses has been suggested as some of the mechanisms [18]. In a previous study, smoking was found to be associated with epicardial coronary endothelial dysfunction and increased levels of inflammatory biomarkers, including MPO [22]. Moreover, another study has shown that plasma MPO levels predict mortality after acute myocardial infarction [23]. Although smoking is not an established risk factor for OSA, significant associations between cigarette smoking and sleep apnea were shown in several epidemiological surveys [24] . A dose-dependent relationship was found between smoking and the severity of apnea [25]. Besides trace amounts of microbial cell components, cigarette smoke contains more than 4500 different chemical compounds and some of these are toxins which have immunomodulatory effects [26]. Smokers are known having a higher concentration of blood leukocytes than those in non-smokers. Leukocytes and platelets in the blood circulation are the major sources of inflammatory cytokines and adhesion molecules. Inflammatory cells also express enzymes, including NADPH oxidase, nitric oxide synthase, and MPO, that generate reactive oxygen species in situ and contribute to inflammation and tissue damage [27]. There are few studies showing relationship between smoking and MPO in OSA. In two studies, Svensson et al demonstrated higher MPO levels in smoker women with sleep-disordered breathing [19], but Hanikoğlu et al did not find any correlation between MPO and smoking in OSA patients [20]. In our study, we investigated MPO levels in different apnea groups according to the smoking habits and we observed increased MPO levels in smokers in all patient groups, even in the control group. However, significant increases in the MPO levels were observed in smoker compared to non-smoker in total apnea, apnea with MS and severe apnea groups. According to the gender, males had higher MPO levels, but not statistically significant, in all smoking groups.

In our previous study [17], we demonstrated higher CRP and fibrinogen levels, as other markers of inflammation, in females than in males in both patient and control groups, as in this study (data not given). However, in contrast to them, MPO levels were slightly higher in the males compared to the females in both patient and control groups. According to the smoking status, differences in the levels of MPO did not change in both gender groups. As far as we know, there was no any clear study evaluating the MPO levels in OSA according to the gender. Recently, Hanikoglu and coworkers declared that there was no any correlation among plasma MPO and gender [20].

An interesting finding of this study was correlation between MPO and High-Density Lipoprotein (HDL)-cholesterol in OSA patients. As far as we know, this is the first study showing correlation between MPO and HDL in sleep apnea. We observed inverse correlations among MPO and HDL in apnea patients, and correlations were found especially in smoker patients. HDL postpones atherosclerosis by promoting cholesterol efflux from macrophages by ATP-binding cassette transporter A1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1) pathways [28]. In addition, Apolipoprotein A-1 (apoA-1), the major protein fraction of HDL, has anti-inflammatory property. When specific residues on apoA-I are oxidized and nitrosylated by MPO, cholesterol efflux by ABCA1 is impaired and inflammatory pathways are activated. During chronic systemic and vascular inflammation, HDL has been suggested to convert to a dysfunctional form and to lose its atheroprotective functions and become even proinflammatory [29]. Yunoki et al showed a significant inverse correlation between MPO and paraoxonase-1 bound to HDL in patients with stable and unstable angina pectoris. After the discovery of the relationship between HDL and MPO, studies on MPO inhibitors to prevent the formation of atherosclerosis started [30].

In conclusion, higher MPO levels in smoker patients may be due to the pro-inflammatory effects of smoking. Because smokers have increased blood counts of neutrophils, which are the main endogenous sources of MPO, smoking cessation may be beneficial to reduce the risk of cardiovascular disease associated with chronic inflammation in apnea patients. The presence or absence of smoking seems to have more effect on the MPO levels than the severity of OSA. MPO, as a parameter which can easily be measured, may be a predictor for future CVD in OSA patients.

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