A New Predictor for Obstructive Sleep Apnea Syndrome: Monocyte to HDL Ratio

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Abstract The aim of this study was to investigate the relation of serum monocyte to serum HDL cholesterol ratio with obstructive sleep apnea syndrome (OSAS). A total of 336 patients who underwent polysomnography (PSG) were included in this study. The individuals with an apnea hypopnea index (AHI) <5/h were included in the study as controls while the patients with an AHI > 5 and excessive daytime sleepiness were included in the study as OSAS patients. OSAS patients were compared with the control group for serum monocyte count, high density lipoprotein (HDL) levels, and monocyte to HDL ratio (MHR). Mild, moderate and severe OSAS subgroups were compared for the same parameters. Additionally, correlations of serum monocyte count, HDL level and MHR with other PSG parameters were analyzed. The mean MHR of control and OSAS groups were 12.90 ± 6.64 and 4.91 ± 6.98 , respectively, and the difference was statistically significant ($p = 0.041$). Mean HDL level of the control group was 47.25 ± 13.61 mg/dL while it was 43.14 ± 13.61 mg/dL in OSAS group ($p < 0.001$). Comparison of OSAS subgroups for MHR and HDL levels revealed statistically significant differences ($p < 0.001$ and $p = 0.020$, respectively). MHR was higher in OSAS patients compared to the controls. MHR may be a new, useful predictor for OSAS.

Keywords High-density lipoprotein · Monocyte · Leukocyte · Neutrophil · Sleep apnea

Introduction

Obstructive sleep apnea syndrome (OSAS) is a clinical syndrome characterized by recurrent partial or total obstructions of the upper airway. The main symptoms are snoring, excessive daytime sleepiness, and witnessed apnea. OSAS is diagnosed using an overnight polysomnography (PSG) test. The diagnostic criteria for OSAS are an apnea hypopnea index (AHI) >5 on PSG and presence of symptoms; or an AHI > 15 in case of an asymptomatic patient [1]. It is a common disorder, its prevalence has been estimated as 4 % in adult men and 2 % in adult women, and it causes significant morbidity and mortality in affected individuals [2].

OSAS has been associated with increased risk for cardiovascular diseases including coronary artery disease (CAD) and cerebrovascular diseases. It is together with an abnormal lipid profile that leads to atherosclerosis and CAD. In association with the severity of OSAS, triglyceride, total cholesterol, and low density lipoprotein (LDL) levels increase while HDL level decreases [3]. Atherosclerosis leading to CAD occurs via an inflammatory process [4]. In CAD, counts of leukocyte and leukocyte subgroups (neutrophil, lymphocyte, monocyte, eosinophil) increase, and this is associated with a poor prognosis [5]. Monocyte is responsible for vascular endothelial damage in pathogenesis of atherosclerosis. Monocytes transform to macrophages by phagocytizing lipids, and secrete metalloproteinases such as elastase and collagenase leading to atherosclerosis [6, 7]. A relation between a low HDL level and a high monocyte count was described previously. It was reported that a high monocyte to HDL ratio (MHR) was a risk factor in cardiovascular diseases [8].

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The aim of this study was to investigate correlation of MHR, which is an easily available and relatively cheap test, with OSAS and severity of OSAS.

Methods

The Study Population

This study was performed in Ankara Numune Education and Research Hospital, Department of Otorhinolaryngology between January 2013 and January 2015. Ankara Numune Education and Research Hospital's local ethics committee approved the study protocol.

A total of 336 patients that underwent overnight PSG due to complaints of witnessed apnea, excessive daytime sleepiness and snoring were included in the study. First, the patients were divided into two groups. The ones with an AHI < 5 was considered as the control group while the patients with an AHI > 5 with OSA symptoms were considered as the OSAS group. Subsequently, the OSAS group was divided into three subgroups according to the severity OSAS: the patients with an AHI of 5–15 were considered as mild OSAS subgroup, the patients with an AHI of 15–30 were considered as moderate OSAS subgroup, and the patients with an AHI > 30 were considered as severe OSAS subgroup. In the morning of PSG, venous blood samples of the patients were obtained after a fasting period of 12 h, and triglyceride, cholesterol, LDL, HDL levels; and leukocyte, neutrophil, lymphocyte, monocyte counts determined with Sysmex WE-2100 America device. MHR was calculated by dividing the monocyte count to HDL level.

The patients with cardiovascular diseases, chronic lung disease, chronic liver disease, acute infection, malignancies, and on medicines that could impair lipid profile (e.g. lipid-lowering medicines, steroids) were excluded from the study. The patients in OSAS and control groups were compared for triglyceride, cholesterol, LDL, HDL levels; leukocyte, neutrophil, lymphocyte, monocyte counts, and MHR. Furthermore, mild, moderate, and severe OSAS subgroups were compared with the control group for the same parameters. Triglyceride, cholesterol, LDL, HDL levels; leukocyte, neutrophil, lymphocyte, monocyte counts, and MHR were separately compared with AHI, REM AHI, non-REM AHI, minimum oxygen saturation, the time of sleep under 90 % oxygen saturation in OSAS patients.

Polysomnography

All patients underwent a full-night PSG study during their spontaneous sleep in Ankara Numune Education and

Research Hospital's Sleep Center. All PSGs were performed using Alice 5 PSG device, in a single room, under the supervision of a sleep technician. Video and audio recordings were obtained for entire PSG. PSG channels included four electroencephalogram (EEG), submental and left and right tibialis electromyogram (EMG), two electrooculogram (EOG; right and left), and two electrocardiography (ECG) channels. Body position, respiratory monitoring with nasal airflow were also recorded. Oxygen saturation was obtained with a pulse oximeter, and respiratory effort was recorded with chest and abdomen belts.

Statistical Analysis

Statistical analysis was carried out using SPSS program, version 21.0 (SPSS Inc., Chicago, IL, USA). Continuous data were presented as mean $\pm$ standard deviation (SD). Categorical variables were presented as percentages. Continuous variables with a normal distribution was analyzed with Student *t* test while Mann–Whitney *U* test was used for normally distributed variables. Pearson's method was used for correlation analysis. Kruskal–Wallis test was used to compare the differences between the groups. A *p* values <0.05 was considered as statistically significant.

Results

The PSG results of 336 patients showed that 58 individuals did not have OSAS (control group), and 278 patients had OSAS (OSAS group). The control group with normal AHI consisted of 32 males (55.1 %) and 26 females (44.9 %). OSAS group consisted of 198 (71.2 %) males, and 80 females (28.8 %). The mean age of control group was 46.47 ± 9.23 years while it was 48.67 ± 9.48 years in the OSAS group. Body mass index (BMI) in control and OSAS groups were calculated as 27.74 ± 4.08 and 30.55 ± 4.22 kg/m², respectively (Table 1).

The triglyceride levels were significantly different between control and OSAS groups (*p* < 0.001). Although total cholesterol and LDL levels were different between OSAS and control groups, those differences did not reach statistical significance (*p* = 0.617 and *p* = 0.786, respectively). There was a significant difference between OSAS and control groups for HDL levels, and the mean HDL levels were 43.14 ± 13.61 mg/dL and 47.25 ± 13.61 mg/dL in those groups, respectively. OSAS and control groups showed significant differences for mean leukocyte (*p* = 0.007) and lymphocyte (*p* = 0.026) counts. The neutrophil counts were also different in OSAS and control groups, but the difference was not statistically significant (*p* = 0.083). The mean monocyte count was 598.04 ± 189.16 10³/μL in OSAS group, and

Table 1 The characteristics of obstructive sleep apnea patients and controls

	AHI < 5 (normal) mean $\pm$ SD	AHI > 5 (OSAS) mean $\pm$ SD	<i>p</i> value
Gender			
Male	32	198	0.017
Female	26	80	
Age	46.47 $\pm$ 9.23	48.67 $\pm$ 9.48	0.106
BMI (kg/m ²)	27.74 $\pm$ 4.08	30.55 $\pm$ 4.22	<0.001

AHI apnea hypopnea index, BMI body mass index

Bold values are statistically significant ($p < 0.05$)

556.03 $\pm$ 196.60 10³/μL in the control group, without any significant difference in between ($p = 0.140$). MHR of control group was 12.90 $\pm$ 6.64 while it was 14.91 $\pm$ 6.98 in OSAS group, and the difference between the groups was statistically significant ($p = 0.041$; Table 2).

The comparison of the controls with mild, moderate and severe OSAS groups showed significant differences for triglyceride, cholesterol, LDL, HDL levels; leukocyte, lymphocyte, monocyte counts and MHR, however the difference for neutrophil count was not significant (Table 3). There was a significant difference between the controls and severe OSAS subgroup, and between mild and severe OSAS subgroups for HDL ($p = 0.004$ and 0.031 , respectively). There were significant differences for monocyte counts between controls and moderate OSAS subgroup, controls and severe OSAS subgroup, mild and severe OSAS subgroups ($p = 0.018$, $p = 0.046$, $p < 0.001$, respectively). MHR showed significant differences between controls and moderate OSAS subgroup, between controls and severe OSAS subgroup, between mild and moderate OSAS subgroups, and between mild and severe OSAS subgroups ($p = 0.024$, $p = 0.008$, $p = 0.008$, and $p = 0.001$, respectively; Table 4). The monocyte count significantly increased as AHI and non-REM AHI increased ($p = 0.012$ and $p = 0.010$, respectively). High AHI, high REM AHI, and high non-REM

AHI as well as reduced minimum oxygen saturation were significantly correlated with low HDL ($p = 0.001$, $p < 0.001$, $p = 0.001$, and $p = 0.003$, respectively). REM AHI, non-REM AHI, and the time under 90 % oxygen saturation and reduced minimum oxygen concentration correlated significantly with a high MHR ($p = 0.004$, $p = 0.004$, $p = 0.010$, and $p = 0.024$, respectively; Table 5).

Discussion

Repetitive episodes of nocturnal apnea in OSAS patients cause sympathetic system activation, increased oxidative stress, sudden increase in systemic hypertension, hypoxia, and hypercapnia [9]. Hypertension, diabetes, CAD, and congestive heart failure are frequently associated with OSAS, all of which also implicated in the pathophysiology of endothelial dysfunction [10].

Endothelial dysfunction along with increased sympathetic system activation due to hypoxia contributes to vascular complications [4]. High LDL and low HDL concentrations are strong risk factors for CAD [11]. The association between OSAS and dyslipidemia is defined by chronic intermittent hypoxia corresponding the generation of stearoyl-coenzyme A desaturase-1 and reactive oxygen species,

Table 2 Laboratory test results of obstructive sleep apnea patients and controls, and statistical analysis

	Control group	OSAS group	<i>p</i> value
Triglyceride (mg/dL)	149.43 $\pm$ 64.94	201.12 $\pm$ 129.94	<0.001
Cholesterol (mg/dL)	207.84 $\pm$ 35.56	210.50 $\pm$ 41.92	0.617
LDL (mg/dL)	130.71 $\pm$ 32.13	129.42 $\pm$ 34.61	0.786
HDL (mg/dL)	47.25 $\pm$ 13.61	43.14 $\pm$ 13.61	0.035
Leukocyte (/μL)	7291.55 $\pm$ 1346.74	7881.58 $\pm$ 2044.67	0.007
Neutrophil (/μL)	4227.93 $\pm$ 1073.65	4521.27 $\pm$ 1507.59	0.083
Lymphocyte (/μL)	2315.34 $\pm$ 562.87	2509.06 $\pm$ 723.52	0.026
Monocyte (103/μL)	556.03 $\pm$ 196.60	598.04 $\pm$ 189.16	0.140
Monocyte/HDL	12.90 $\pm$ 6.64	14.91 $\pm$ 6.98	0.041

LDL low-density lipoprotein, HDL high-density lipoprotein

Bold values are statistically significant ($p < 0.05$)

Table 3 Comparison of controls and obstructive sleep apnea subgroups for laboratory parameters, and statistical analysis

	Controls	Mild OSAS	Moderate OSAS	Severe OSAS	<i>p</i> value
Triglyceride (mg/dL)	149.43 ± 64.94	205.24 ± 134.15	198.87 ± 136.94	200.10 ± 123.86	0.036
Cholesterol (mg/dL)	207.84 ± 35.56	213.91 ± 42.47	218.97 ± 40.32	203.26 ± 41.65	0.013
LDL (mg/dL)	130.71 ± 32.13	127.64 ± 37.63	137.76 ± 29.85	125.32 ± 34.88	0.016
HDL (mg/dL)	47.25 ± 13.61	45.30 ± 13.53	43.97 ± 11.35	41.35 ± 9.85	0.020
Leukocyte (/μL)	7291 ± 1346	7339 ± 1827	7993 ± 2290	8130 ± 1958	0.004
Neutrophil (/μL)	4227 ± 1073	4251 ± 1420	4602 ± 1649	4628 ± 1456	0.107
Lymphocyte (/μL)	2315 ± 562	2353 ± 675	2519 ± 778	2593 ± 705	0.042
Monocyte (10 ³ /μL)	556 ± 196	520 ± 160	638 ± 204	617 ± 182	<0.001
Monocyte/HDL	12.90 ± 6.64	12.62 ± 6.27	15.74 ± 7.87	15.74 ± 6.52	<0.001

LDL low-density lipoprotein, HDL high-density lipoprotein

Bold values are statistically significant (*p* < 0.05)

Table 4 Statistical comparisons of obstructive sleep apnea subgroups and the control group

	Normal-mild OSAS <i>p</i> value	Normal-moderate OSAS <i>p</i> value	Normal-severe OSAS <i>p</i> value	Mild-moderate OSAS <i>p</i> value	Mild-severe OSAS <i>p</i> value	Moderate-severe OSAS <i>p</i> value
Triglyceride (mg/dL)	0.002	0.006	<0.001	0.772	0.783	0.949
Cholesterol (mg/dL)	0.374	0.091	0.444	0.452	0.087	0.008
LDL (mg/dL)	0.614	0.195	0.306	0.069	0.666	0.007
HDL (mg/dL)	0.415	0.140	0.004	0.514	0.031	0.095
Leukocyte (/μL)	0.863	0.027	0.001	0.053	0.005	0.661
Neutrophil (/μL)	0.915	0.112	0.039	0.163	0.076	0.908
Lymphocyte (/μL)	0.728	0.078	0.005	0.162	0.019	0.494
Monocyte (10 ³ /μL)	0.270	0.018	0.046	0.559	<0.001	0.459
Monocyte/HDL	0.807	0.024	0.008	0.008	0.001	0.995

Bold values are statistically significant (*p* < 0.05)

Table 5 Correlations of polysomnographic parameters and monocyte, HDL, monocyte/HDL

<i>p</i> value	Monocyte	HDL	Monocyte/ HDL
AHI	0.012	0.001	0.004
REM AHI	0.116	<0.001	0.004
Non- REM AHI	0.010	0.001	0.004
Minimum oxygen saturation	0.054	0.003	0.010
Time <90 % oxygen saturation	0.071	0.057	0.024

Bold values are statistically significant (*p* < 0.05)

peroxidation of lipids, and sympathetic system activation [12]. In a recent study, Ozol et al. showed a lower dyslipidemic profile in moderate OSAS patients when compared to the control group. The study concluded this higher dyslipidemic profile in the control group was associated with increased insulin resistance. Furthermore, they demonstrated that mild and severe OSAS patients had worse dyslipidemic profiles [13]. In our study, LDL levels showed statistically

significant differences among all groups, however there was no relationship between LDL level and severity of OSAS. HDL levels showed significant differences among all groups, and remarkably decreased in accordance with severity of OSAS. It is evident that CPAP treatment has beneficial effects on dyslipidemia, atherosclerosis and cardiovascular diseases in OSAS patients [14].

CAD is one of the most frequently seen cardiovascular diseases induced by atherosclerosis [15]. Inflammation has an important role in CAD formation. Inflammatory cells like monocytes, lymphocytes, eosinophils, and neutrophils increase in CAD [16]. Prentice et al. [17] showed that the patients with CAD had higher monocyte, neutrophil and eosinophil counts when compared to the ones without CAD, and they correlated this findings with a high risk status. Similarly, inflammation has a critical role in the etiopathogenesis of OSAS. Intermittent hypoxia initiates the inflammatory process, and inflammation activates proinflammatory cytokines and adhesion molecules in OSAS. Oxidizing radicals and

proteolytic enzymes accumulate leukocytes and thrombocytes on blood vessel walls, leading to endothelial dysfunction that comprises atherosclerosis [18]. In a recent study, Tamaki et al. [19] demonstrated that monocyte counts were higher in OSAS patients compared to the control group. In our study, we found that moderate and severe OSAS patients had significantly higher monocyte counts compared to the control group. Monocyte count increases as the severity of OSAS increases, and it may be considered as a marker for predicting OSAS severity.

HDL and its major component apolipoprotein A-1 that inhibits the activation of CD11b, which has an anti-inflammatory effect on human monocytes [20]. The reduced HDL levels promote monocyte activation, and consequently increase the risk for atherosclerosis. MHR, which is an easily available and relatively cheap test, can be used as a new predictor for OSAS. Kanbay et al. [21] showed that high MHR was associated with adverse cardiovascular outcomes, and it may be useful for following up cardiovascular disease. In the present study, MHR was found significantly higher in moderate and severe OSAS subgroups when compared to the control group, however mild OSAS subgroup resembles the control group for this parameter. Moreover, MHR significantly increased as AHI, REM-AHI, non-REM AHI, and time under 90 % saturation increased, and minimum oxygen concentration decreased. In OSAS patients, MHR increased as the severity of disease increased.

To conclude, MHR was significantly higher in moderate and severe OSAS patients. We found that MHR increased as OSAS severity, which is defined by PSG, increased. MHR can be used as a new predictor for OSAS. Further longitudinal studies on larger patient populations are needed to determine whether alterations in MHR could be predictive for OSAS severity.

Compliance with Ethical Standards

Conflict of interest No conflict of interest was declared by the authors.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Ethics Committee Approval Ethics committee approval was received for this study from the Ethics Committee of Ankara Numune Education and Research Hospital.

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