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SLEEP

The Frequency of Monocyte Chemoattractant Protein-1 Gene Polymorphism in Obstructive Sleep Apnea Syndrome

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Abstract

Purpose In obstructive sleep apnea syndrome (OSAS) many proinflammatory cytokines are released from activated endothelial cells due to repeated decreases in arterial oxygen saturation. Some of these proinflammatory cytokines are involved in the etiology of coronary artery disease (CAD). Although the association between OSAS and CAD is known, risk factors for CAD have not been determined in this patient group. Monocyte chemoattractant protein-1 (MCP-1) is a proinflammatory cytokine that plays a key role in the development of atherosclerosis. In this study, we compared the frequency of *MCP1* rs1024610-rs1024611 single-nucleotide polymorphisms (SNPs) in OSAS patients with no comorbidity, OSAS patients with no comorbidity except CAD, and healthy individuals.

Material and Methods The study included 301 subjects. Two hundred one patients with OSAS (OSAS only and OSAS + CAD groups) and 100 healthy control subjects underwent polysomnography. MCP1 rs1024610 and rs1024611 mutation frequencies were determined.

Results Body mass index, apnea–hypopnea index, triglyceride levels, and mean oxygen desaturation were significantly higher in the OSAS patients than in the healthy population ($p < 0.05$). In *MCP1* rs1024611 SNP analysis, homozygous mutation was significantly more common in the OSAS + CAD group than in the OSAS and control groups ($p < 0.001$). *MCP1* rs1024610 SNP analysis showed no significant differences among the study groups.

Conclusion OSAS patients with homozygous *MCP1* rs1024611 SNP are at higher risk for CAD. The *MCP1* rs1024610 SNP was not associated with incidence of CAD. Patients with OSAS and *MCP1* rs1024611 homozygous mutation are more susceptible to CAD and early detection and treatment may significantly reduce mortality and morbidity.

Keywords Atherosclerosis · Coronary arterial diseases · Monocyte chemoattractant protein-1 · Obstructive sleep apnea syndrome

Introduction

Obstructive sleep apnea syndrome (OSAS) is a condition characterized by recurrent episodes of apnea/hypopnea and subsequent oxygen desaturation during sleep due to upper airway obstruction [1]. Various inflammatory chemokines are released due to the oxidative stress resulting from recurrent apnea/hypopnea episodes in patients with OSAS. Chemokines are important markers of inflammation and belong to a large family of polypeptides believed to be associated with infection, tissue damage, allergies, malignant tumor pathophysiology, cardiovascular diseases, and diabetes [2].

One of the most important of these chemokines is the protein MCP-1. MCP-1 is encoded by the *MCP1* (also known as *CCL2*) gene and plays an important role in mononuclear

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cell activation and migration to sites of infection. In studies investigating associations of *MCP1* rs1024610 and rs1024611 single-nucleotide polymorphisms (SNPs) with atherosclerosis and diabetes, statistically significant results were obtained in both patient populations [3, 4]. A biallelic A/G polymorphism in the MCP-1 distal gene regulatory region at position 2518 has been found that affects the level of MCP-1 expression in response to an inflammatory stimulus. Monocytes from individuals carrying a G allele at 2518 produce more MCP-1 after treatment with IL-1b than monocytes from A/A homozygous subjects. Also, previous data suggest that MCP-1 promoter 2518 polymorphism is involved in the pathogenesis of coronary artery diseases [5, 6].

Early-increased arterial intima-media thickness is a significant risk factor for progression to atherosclerosis in patients with OSAS. MCP-1 is a key chemokine in cell migration during inflammation and is involved in the development of atherogenic events in OSAS. It is secreted from cytokine-activated endothelial cells and vascular smooth muscle cells to attract circulating monocytes to sites of inflammation. A greater predisposition toward coronary artery disease (CAD) has been observed in individuals with the *MCP1* rs1024610 and rs1024611 SNPs compared to control groups; however, studies in OSAS patients on their association with CAD, which is an important cause of mortality in this patient group, are insufficient [7].

In the light of existing evidence that *MCP1* rs1024610 and rs1024611 gene polymorphisms play an important role in endothelial damage and atherosclerotic plaque formation, in the present study we aimed to compare OSAS patients with and without CAD and a normal population to determine whether these mutations are associated with a higher prevalence of CAD.

Materials and Methods

Study Population

Individuals aged 20 years or older who presented to the Atatürk University Department of Pulmonary Diseases Sleep Laboratory with one or more relevant complaints (snoring, witnessed apnea, and/or excessive daytime sleepiness) were included in the study. A total of 210 patients were initially included. Exclusion criteria were the presence of chronic or clinically significant infectious or inflammatory conditions within the last month, asthma, chronic obstructive pulmonary disease, malignancy, active smoking habit or history of smoking, invasive surgical intervention within the last month, uncontrolled hypertension, diabetes, cerebrovascular disease, or kidney disease. Patients with coronary artery disease diagnosed by cardiology clinic were identified. Based on these criteria, 3 patients were excluded due to a history of upper airway disease within the last month, 4 patients due to uncontrolled hypertension, and 2 patients due to high-fasting blood glucose level. As a result, a total of 201 patients were included in the study. In addition, 100 individuals aged 20 years or older who had an apnea–hypopnea index (AHI) lower than 5 based on polysomnographic evaluation, met none of the exclusion criteria, and did not have coronary artery disease were included as a healthy control group.

Study Groups

Three hundred one individuals aged 18–70 years whose polysomnographic evaluations were manually scored and who did not meet any exclusion criteria were included in the study based on their AHI values. Group 1 was comprised of patients with AHI < 5/h ($n = 100$), Group 2 included OSAS patients without CAD ($n = 110$), and Group 3 consisted of OSAS patients with CAD ($n = 91$) (Table 1).

Polysomnography

Full polysomnography monitoring was performed using the Compumedics E-series Sleep System (Compumedics Sleep, Melbourne, Australia). Recordings included simultaneous electroencephalography (EEG), electrooculography, electromyography, and electrocardiography. Surface electrodes were used to record EEG channels, right and left electrooculographies, and submental electromyography. Ventilatory flow was measured as airflow through the nose or the nose and mouth. Body position and respiratory movements of the chest and abdomen were monitored using inductive plethysmography bands. Arterial oxygen saturation was measured transcutaneously with a finger oximeter.

Apnea was defined as continuous cessation of airflow for ≥ 10 s, while hypopnea was defined as at least 50% reduction in airflow for ≥ 10 s together with oxygen desaturation of ≥ 3% or an arousal from sleep on EEG. Apneas were classified as obstructive, central, or mixed according to the standard American Academy of Sleep Medicine criteria [8].

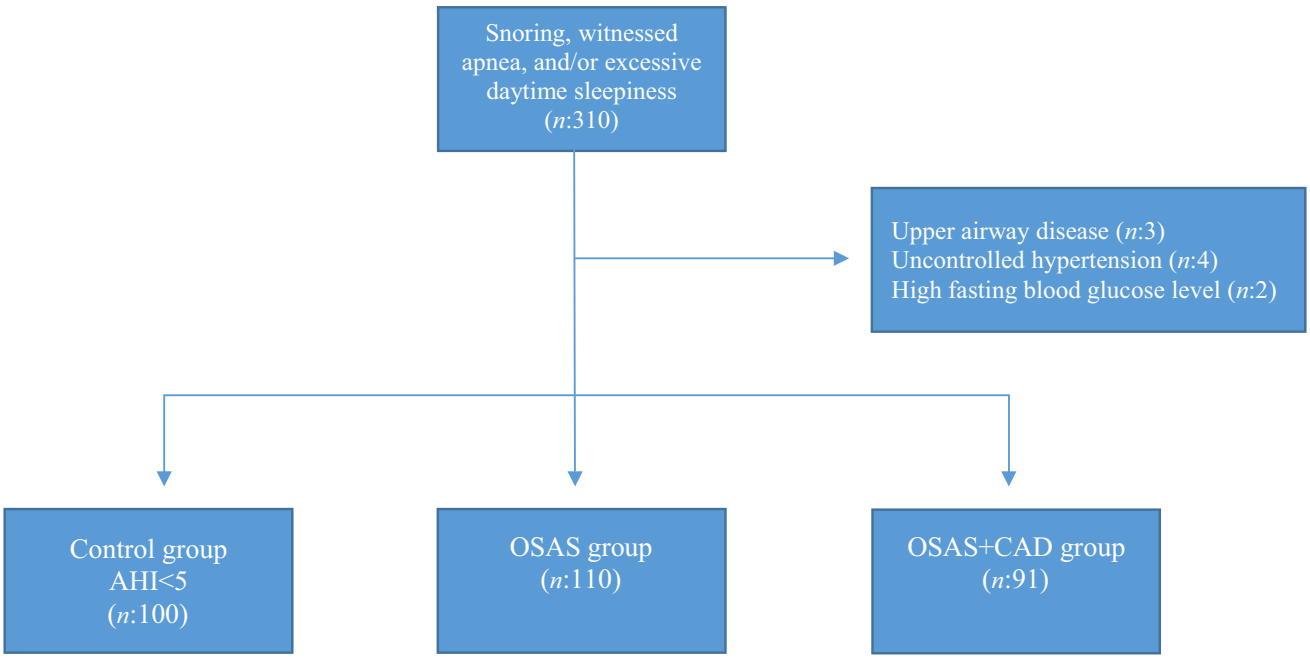
All patients were informed about the study and provided written informed consent prior to their participation. The study was designed and conducted in accordance with the ethical guidelines set forth in the Declaration of Helsinki, and the study protocol was approved by the local ethics committee.

Molecular Analysis

DNA Isolation Protocol

Blood samples were collected into EDTA tubes. DNA of the patients was extracted by QIAGEN®, EZ1® Advanced XL

Table 1 Patient selection



(Veltek Associates, Inc.) system. The PCR reactions were performed in 50 µl reaction mixture containing 18.5 µl PCR master mix (Qiagen GmbH, Hilden Germany), 2 µl of each primer, 0.5 µl Taq DNA polymerase, 17 µl H2O, and 10 µl mtDNA in a thermal cycler (SensoQuest Labcycler, GmbH, Hilden, Germany) under the following conditions: 95 °C for 15 min (initial denaturation) followed by 32 cycles at 94 °C for 1 min (denaturation), 56 °C for 1 min (annealing), 72 °C for 80 s (extension), and a final extension at 72 °C for 15 min.

Analysis of rs1024610 and rs1024611 Single-Nucleotide Polymorphisms

The primer/probe mix was designed and validated under the name snpsig™ Real-Time PCR Genotyping Kit, rs1024610 (PrimerDesign). A single 0.2-ml PCR tube was labeled for each individual. Polymerase chain reactions were prepared to a total volume of 20 µl (9 µl Master mix, 1 µl primer/probe mix, 8 µl RNase-free water, 2 µl DNA sample). Wild and mutant control DNA were synthesized for this study. The primers and wild/mutant controls were diluted with 500 µl of RNase-free water before use. The primer/probe mix was diluted with 65 µl of RNase-free water. It was incubated for 5 min and vortexed. Wild/mutant controls were diluted at a ratio of 1/10 before use. Real-time PCR was performed in a LightCycler 480 system (Roche Diagnostics GmbH, Mannheim, Germany). Melting curve analysis was conducted using LightCycler analysis software as per the manufacturer's instructions (Roche Diagnostics Applied Science).

Statistical Analysis

Statistical analysis was performed using the SPSS package (version 20.0; SPSS for Windows, Chicago, IL, USA). Pearson's chi-square test was used to compare parameter values between groups. Differences between the groups were evaluated with one-way ANOVA for *MCP1* rs1024610 and rs1024611 SNP frequencies and Kruskal–Wallis test for non-parametric data. P value < 0.05 was considered statistically significant. Binary logistic regression analysis was done using CAD as the dependent variable.

Results

The study included a total of 301 subjects consisting of 110 OSAS patients, 91 OSAS + CAD patients, and 100 control subjects. The mean age of the OSAS group ($n = 110$) was 47.7 ± 11.9 years, and the gender distribution was 60% male ($n = 66$) and 40% female ($n = 44$). In the OSAS + CAD group ($n = 91$), the mean age was 58.02 ± 10.43 years; 59.3% ($n = 54$) of the patients were male and 40.7% ($n = 37$) were female. The mean age of the control group ($n = 100$) was 54.6 ± 11.7 years, and the male-to-female ratio was 1:1.

Comparison of the OSAS and OSAS + CAD groups showed that age, BMI, AHI, low-density lipoprotein (LDL) cholesterol, and mean oxygen desaturation values were

significantly higher in the OSAS + CAD group ($p < 0.05$). Comparison of the OSAS and control groups revealed significantly higher mean age in the control group, while BMI, AHI, triglyceride level, and mean desaturation values were significantly higher in the OSAS group ($p < 0.05$). The OSAS + CAD group had significantly higher mean age, BMI, triglyceride, LDL cholesterol, and total cholesterol levels compared to the control group ($p < 0.05$). In binary logistic regression analysis to determine factors associated with CAD in OSAS, the overall accurate prediction rate of the model including the variables of age, AHI, BMI, triglyceride, cholesterol, LDL cholesterol, HDL cholesterol, and mean desaturation was 74.1%. Mean desaturation and age emerged as significant factors. According to the model, each 1 unit increment in age increases CAD by 1.071-fold and mean desaturation by 1.262-fold (Tables 2, 3).

In the rs1024611 SNP evaluation, each group was classified as AA wild type (negative control), AG heterozygous, or GG homozygous (positive control). The OSAS group was found to comprise 17.3% wild type, 34.5% heterozygous, and 48.2% positive control. The OSAS + CAD group was 3.3% wild type, 26.4% heterozygous, and 70.3% positive control. The control group was 12% wild type, 37% heterozygous, and 51% homozygous (Table 4).

In analysis of the rs1024610 SNP, AA was regarded as wild type (negative control), AT as heterozygous, and TT as

Table 2 Analysis of OSAS, OSAS + CAD, control groups according to demographic characteristics and laboratory values

	n	Mean	Standard deviation ±	*p**	*p***	*p****
Age						
OSAS	110	47.70	11.896	< 0.001	< 0.001	0.036
OSAS + CAD	91	58.02	10.435			
Control	100	54.62	11.741			
BMI						
OSAS	110	31.5309	8.07329	< 0.001	0.006	< 0.001
OSAS + CAD	91	37.7066	8.51614			
Control	100	28.9260	5.17460			
AHI						
OSAS	110	30.43	25.355	< 0.001	< 0.001	< 0.001
OSAS + CAD	91	50.20	28.959			
Control	100	2.50	1.049			
Triglyceride						
OSAS	110	191.35	107.107	0.914	< 0.001	< 0.001
OSAS + CAD	91	192.99	104.763			
Control	100	127.43	65.652			
HDL cholesterol						
OSAS	110	45.05	19.544	0.475	0.200	0.332
OSAS + CAD	91	43.51	6.803			
Control	100	42.17	11.378			
LDL cholesterol						
OSAS	110	131.84	32.112	0.037	0.080	< 0.001
OSAS + CAD	91	140.90	28.462			
Control	100	124.04	32.036			
Cholesterol						
OSAS	110	195.00	42.401	0.055	0.051	< 0.001
OSAS + CAD	91	206.44	41.267			
Control	100	183.49	42.545			
Average desaturation						
OSAS	110	5.60	2.323	< 0.001	< 0.001	< 0.001
OSAS + CAD	91	8.29	3.917			
Control	100	2.53	0.915			

BMI body mass index, *AHI* Apnea–hypopnea index, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

*p** Comparison of OSAS—OSAS + CAD; *p*** Comparison of OSAS—Control; *p**** Comparison of OSAS + CAD—Control

Table 3 Regression analysis between OSAS and OSAS + CAD groups

	B (SE)	Wald	*p* value	Exp (B)	%95 Exp (B) lower	%95 Exp (B) upper
AGE	0.069 (0,17)	16.43	0.001	1.071	1.036	1.107
BMI	− 0.103 (1.16)	0.784	0.37	0.902	0.719	1.133
AHI	− 0.004 (0.08)	0.231	0.63	0.996	0.981	1.012
Triglyceride	− 0.001 (0.02)	0.146	0.7	0.999	0.995	1.003
LDL cholesterol	0.006 (0.14)	0.102	0.7	1.006	0.971	1.042
HDL cholesterol	− 0.005 (0.21)	0.05	0.82	0.995	0.954	1.038
Cholesterol	0.005 (0.14)	0.114	0.73	1.005	0.978	1.032
Average desaturation	0.233 (0.7)	11.02	0.001	1.262	1.1	1.449

Table 4 rs1024611 SNP analysis between groups

Groups	rs1024611		
	Polymorphism	*n*	%
OSAS	AA[a,b]	19	17.3
	AG[d,e]	38	34.5
	GG[g,h]	53	48.2
Total		110	100
OSAS + CAD	AA[a,c]	3	3.3
	AG[d,f]	24	26.4
	GG[g,i]	64	70.3
Total		91	100
Control	AA[b,c]	12	12.0
	AG[e,f]	37	37.0
	GG[h,i]	51	51.0
Total		100	100

A adenine, *G* guanine, *OSAS* obstructive sleep apnea syndrome, *CAD* coroner artery disease

[a]Comparison with OSAS + CAD group (*p*: < 0.001)

[b]Comparison with control group (*p*: 0.189)

[c]Comparison with control group (*p*: 0.008)

[d]Comparison with OSAS + CAD group (*p*: 0.137)

[e]Comparison with control group (*p*: 0.410)

[f]Comparison with control group (*p*: 0.078)

[g]Comparison with OSAS + CAD group (*p*: 0.001)

[h]Comparison with control group (*p*: 0.394)

[i]Comparison with control group (*p*: 0.005)

Table 5 rs1024610 SNP analysis between groups

Groups	rs1024610		
	Polymorphism	*n*	%
OSAS	AA[a,b]	2	1.8
	AT[d,e]	33	30.0
	TT[g,h]	75	68.2
Total		110	100
OSAS + CAD	AA[a,c]	0	0
	AT[d,f]	31	34.1
	TT[g,i]	60	65.9
Total		91	100
Control	AA[b,c]	5	5.0
	AT[e,f]	27	27.0
	TT[h,i]	68	68.0
Total		100	100

A adenine, *T* thymine, *OSAS* obstructive sleep apnea syndrome, *CAD* coroner artery disease

[a]Comparison with OSAS + CAD group (*p*: 0.298)

[b]Comparison with control group (*p*: 0.185)

[c]Comparison with control group (*p*: 0.037)

[d]Comparison with OSAS + CAD group (*p*: 0.321)

[e]Comparison with control group (*p*: 0.372)

[f]Comparison with control group (*p*: 0.037)

[g]Comparison with OSAS + CAD group (*p*: 0.425)

[h]Comparison with control group (*p*: 0.547)

[i]Comparison with control group (*p*: 0.440)

homozygous (positive control). The OSAS group was determined to be 1.8% wild type, 30% heterozygous, and 68.2% homozygous. The distribution was 34.1% heterozygous and 65.9% homozygous in the OSAS + CAD group, with no wild type. The control group was 5% wild type, 27% heterozygous, and 68% homozygous (Table 5).

No significant difference was observed between the OSAS group and the control group in distributions of wild-type, heterozygous, and homozygous mutations in the rs1024611 SNP. Comparison of the OSAS and OSAS + CAD patient groups revealed significantly higher prevalence of the wild-type genotype in the OSAS group ($p < 0.001$) and of homozygous mutation in the OSAS + CAD group ($p < 0.001$). However, no statistically significant differences were observed in the frequency of heterozygous mutation. Between the OSAS + CAD group and the control group, there was no significant difference in terms of heterozygous mutation, but wild-type and homozygous mutation frequencies differed significantly ($p = 0.008$ and $p = 0.005$) (Table 4). There were no statistically significant differences between age, weight, height, BMI, AHI, triglyceride, LDL cholesterol, HDL cholesterol, cholesterol, mean desaturation

values, and rs 1,024,611 SNP (wild-type, heterozygous, and homozygous mutations) ($p > 0.05$ for all). The calculated Chi-Square value obtained was 1.62 which is lower than the tabulated value of 3.84 at 5% level of significance at 1 degree of freedom. Therefore, the studied population was in accordance with Hardy Weinberg equilibrium with respect to rs1024611 [9].

For the rs1024610 SNP, our analysis of wild-type and heterozygous and homozygous mutation frequencies revealed no statistical differences among the study groups ($p > 0.05$) (Table 5).

The groups were divided based on AHI values into mild (AHI 5–15), moderate (AHI 15–30), and severe (AHI 30 or above) OSAS subgroups. OSAS was mild in 31.8%, moderate in 31.8%, and severe in 36.4% of the patients in the OSAS group. In the OSAS + CAD group, these proportions were 3.3%, 30.8%, and 65.9%, respectively. There was significant difference in AHI between the patient groups (OSAS, OSAS + CAD) ($p < 0.001$) (Table 6). There was no significant difference in AHI correlation between genders in the patient groups (Table 7).

Discussion

The current study was conducted to evaluate whether OSAS patient groups show significant genotypic variation in *MCP1*, which has been identified as an important factor for CAD, and we found that the rs4611 homozygous mutation was significantly more common among OSAS patients with CAD compared to the other groups.

OSAS is a clinical condition characterized by recurrent upper airway obstruction during sleep, increased respiratory effort in response to this airway blockage, and frequent sleep interruption [10]. Successive apnea episodes lead to increased sympathetic nervous system activity, oxidative stress, intrathoracic pressure fluctuations, sudden spikes in systemic blood pressure, hypoxia, and, as a result of these, endothelial dysfunction [8, 11, 12].

Endothelial dysfunction in OSAS causes the release of numerous proinflammatory and chemoattractant cytokines. Continuous positive airway pressure (CPAP) therapy has been found to significantly reduce levels of several cytokines, such as TNF-alpha, IL-2, IL-4, IL-6, MCP-1, and PDGF, by eliminating oxidative stress [13, 14]. Genetic and epigenetic factors play an important role in the development of OSAS. Polymorphism studies on proinflammatory cytokines have shown that SNPs in the TNF-alpha and IL-6 genes increase the risk of OSAS in both the pediatric and adult age groups [15, 16].

MPC-1 is among the key chemoattractant proteins in the migration of monocytes, macrophages, T lymphocytes, and natural killer cells due to endothelial dysfunction. MCP-1 is a dual-acting protein with proinflammatory and anti-inflammatory properties. SNP studies on the dual action of MCP-1 have suggested that due to its proinflammatory action it may play a role in conditions involving endothelial damage, such as insulin resistance, inflammatory bowel diseases, retinopathy secondary to oxidative stress, tumor neovascularization, and especially atherosclerosis [17].

OSAS commonly coexists with diseases in which endothelial dysfunction is an important pathophysiologic factor, including hypertension, diabetes, obesity, CAD, stroke, and heart failure [18, 19]. CAD is among the leading causes of morbidity and mortality in OSAS. In addition to increased sympathetic nervous system activity induced by hypoxia, the resulting endothelial dysfunction and arteriosclerosis are known to be the main cause of CAD.

MCP-1 contributes to the stabilization and progression of atherosclerotic plaques by promoting monocyte proliferation in areas where atherosclerotic plaques form [7]. In studies on MCP-1 and its receptor CCR2, a significant reduction in arterial lipid accumulation and atherosclerotic plaque formation was observed in the absence of CCR2.

Table 6 OSAS weight degree analysis between groups

Groups	Mild OSAS	Moderate OSAS	Severe OSAS	Total	*p**
OSAS *n* (%)	35 (31.8%)	35 (31.8%)	40 (36.4%)	110 (100%)	< 0.001
OSAS + CAD *n* (%)	3 (3.3%)	28 (30.8%)	60 (65.9%)	91 (100%)	

OSAS obstructive sleep apnea syndrome, *CAD* coroner artery disease

**p* Comparison of OSAS-OSAS + CAD group with mild OSAS and severe OSAS

Table 7 Statistical analysis of the severity Comparison to gender in the OSAS and OSAS + CAD groups

	Mild OSAS	Mild OSAS + CAD	Moderate OSAS	Moderate OSAS + CAD	Severe OSAS	Severe OSAS + CAD
Male *n* (%)	1 (1.5%)	3 (5.6%)	22 (29.5%)	18 (33.3%)	43 (65.2%)	33 (61.1%)
Female *n* (%)	2 (4.5%)	0 (0%)	13 (31.8%)	10 (27%)	29 (65.9%)	27 (73%)

Studies on *MCP1* rs4610 and rs4611 have demonstrated increased risk for early CAD in groups with these SNPs compared to the healthy population. The A/G SNP at position 2518 in the distal gene regulatory region of *MCP1* was found to cause MCP-1 expression and positively correlate with CAD due to increased MCP-1 level [6].

In OSAS patients, AHI and mean oxygen desaturation are also important factors in the development of CAD [20]. Data from the present study show that these values were significantly higher in patients with OSAS and CAD compared to those with OSAS only. While our comparison of the *MCP1* rs4611 SNP revealed no significant difference in the frequency of homozygous (GG) mutation between the OSAS group and the control group, there was a significant difference between the OSAS + CAD group and the control and OSAS groups. This shows that unlike proinflammatory cytokines, which increase with the presence and duration of hypoxic stress, the *MCP1* rs4611 mutation may be an independent marker of CAD development in patients with OSAS.

Hypoxia plays an important role in MCP-1 expression [21]. According to our data, there were no significant differences in laboratory parameters, demographic characteristics, or polysomnography data between the rs4611 wild-type (AA), heterozygous mutation (AG), and homozygous mutation (GG) groups ($p > 0.05$ for all). Increases in CAD risk factors triglyceride, cholesterol, and LDL cholesterol, decreases in HDL cholesterol, and lack of a significant difference between OSAS groups in mean desaturation level, which is important in endothelial dysfunction and CAD development, show that rs4611 SNP can be used reliably as a marker for CAD development in patients with OSAS.

In our comparison of *MCP1* rs4610 SNP, no significant difference homozygous (TT) mutation frequency was observed between the three study groups. Unlike other studies, our findings suggest that the rs4610 homozygous mutation is not a risk factor for CAD. In addition, the absence of a statistically significant difference between the groups in our study may be interpreted as evidence that MCP-1 is not affected by hypoxic stress and its duration as proinflammatory cytokines are. One of the limitations of our study is that our findings do not definitively demonstrate CAD risk for both sexes due to the non-homogeneous gender distribution in our OSAS patient groups.

Our study indicates that the *MCP1* rs4611 homozygous SNP can increase the risk of CAD in patients with OSAS. Obtaining peripheral blood samples from patients with OSAS before comorbid diseases develop will allow patients with the rs4611 homozygous mutation to be monitored closely for CAD.

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Compliance with Ethical Standards

Conflict of interest The authors received no financial support for the research and/or authorship of this article. The authors declare that they have no conflicts of interest to the publication of this article.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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

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