Received: 1 May 2025 | Revised: 9 June 2025 | Accepted: 20 June 2025

DOI: 10.1002/slp2.70009

RESEARCH ARTICLE

Sleep Research | WILEY

Decreased multidrug resistance protein 1 and increased platelet activation in obstructive sleep apnea syndrome

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Funding information

Istanbul Üniversitesi, Grant/Award Number: 2367/06.07.2010

Abstract

Introduction: Obstructive sleep apnea syndrome (OSAS) is an inflammatory disease characterized by recurrent apnea and hypopnea. Multidrug resistance protein 1 (MRP1) is an anti-inflammatory protein that protects the cell from agents caused by oxidative stress. The aim of this study was to investigate the role of MRP1 in platelet function in OSAS.

Methods: According to the polysomnography results, 14 patients with simple snoring, 16 with mild OSAS, 14 with moderate OSAS, and 15 with severe OSAS were included in the study. Platelet aggregations were evaluated by an aggregometer. MRP1, CD62P (P-selectin), CD41b, and CD42b expressions were measured by a flow cytometer.

Results: Platelet aggregation levels were higher in the severe OSAS group than in the simple, mild, and moderate OSAS groups ($p = 0.041$). On the other hand, CD42b+/MRP1+ expression was lower in the severe OSAS group than in the simple, mild, and moderate OSAS groups ($p = 0.002$). MRP1 and CD42b expressions were consistent with this result ($p = 0.013$, $p = 0.009$, respectively). A positive correlation was found between apnea/hypopnea index and platelet aggregation ($r = 0.289$ $p = 0.028$) and a negative correlation was found between CD42b, CD42b+/MRP1+ ($r = -0.419$ $p = 0.001$, $r = -0.357$ $p = 0.006$, respectively).

Conclusion: Our findings suggest that high platelet activity and low MRP1 expression contribute to inflammation in OSAS and thus may be biomarkers.

KEYWORDS

AHI, apnea, CD42b, MRP1, OSAS, platelet aggregation, sleep

1 | INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a sleep disorder characterized by recurrent upper airway obstructions during sleep as airflow drops to 20% or less of its normal value for at least 20 s. In OSAS, the amount of oxygen in the blood decreases and the amount of carbon dioxide increases. Waking up from sleep can be considered as a defense mechanism developed by the body to end apnea and hypopnea.[1–4] OSAS is seen in approximately 1%–5% of adult males and 1.2%–2.5% of females.[5,6]

Multidrug resistance protein 1 is an ATP-dependent transmembrane protein encoded by the ABCC1 (ATP binding cassette subfamily C member 1) gene. It is a protein with broad substrate specificity in almost all

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cells, transporting oxidative stress products and some agents outside the cell.[7] MRP1 is expressed in most organs and peripheral blood cell types.[8,9] Overexpression of MRP1 has been found to be closely associated with clinical outcomes of various malignancies and inflammatory diseases such as rheumatoid arthritis,[10] atherosclerosis,[11] Crohn's disease, and colitis ulcerosa,[12] but its physiological functions are still not fully defined. In a study with bronchial biopsies, MRP1 levels were found to be higher in chronic obstructive pulmonary disease (COPD) patients than in controls.[13] Chaouat et al. defined the prevalence of COPD as 11% in OSAS.[14] However, the role of MRP1 in OSAS still remains unclear.

Increased platelet activation significantly affects the course of some inflammatory diseases such as asthma, COPD, diabetes mellitus, and atherosclerosis.[15] Platelets are blood cells responsible for coagulation and thrombosis formation. Platelet and leukocyte interactions during thrombosis and inflammation are mediated by P-selectin. P-selectin is found in platelet and endothelial cells and is a molecule responsible for weak and early adhesion. Two other activation markers responsible for platelet activation are CD42b and CD41b. CD42b (glycoprotein Ib = GpIb) ensures platelet adhesion to the endothelium by vWF, and CD41b (glycoprotein IIb = GpIIb) ensures platelet-platelet aggregation.[16–18]

Based on this information, we aimed to investigate the relationship between activated platelets, P-selectin, MRP-1, and increased AHI in patients with OSAS. As a result of our literature search, we could not find a study describing the role of MRP-1 in OSAS and how platelet activity contributes to the pathophysiology of OSAS. In terms of literature, our study will be the first in this field. We believe that our study may contribute to the development of new treatment strategies to prevent possible problems related to cerebrovascular and coronary artery diseases that may develop with changes in platelet functions and MRP-1 expressions in OSAS.

Key points

- There was a positive correlation between apnea/hypopnea index (AHI) index and platelet aggregation and a negative correlation between CD42b and multidrug resistance protein 1 (MRP1). Platelet activation was high while MRP1 expression was low in severe obstructive sleep apnea syndrome (OSAS) independent of smoking, age, and gender.
- Our findings may suggest that inflammation in OSAS is due to low MRP1 expression.
- Our data suggest that upregulation of MRP1 protein for the prevention of increased oxidative stress and inflammation in OSAS may be effective in controlling the disease.
- We evaluate that close monitoring of increased platelet aggregation and administration of antiaggregant drugs in OSAS may improve the course of the disease. Once the mechanisms are resolved, the modulation of platelet function can be used for new treatments and draw clinicians' attention to the potential efficacy of existing antiplatelet drugs.

2 | METHODS

2.1 | Patient choice

Fifty-nine individuals who complained of shortness of breath during sleep and met the study case selection criteria were included in our study. Patients were divided into 4 groups as simple snoring (14), mild OSAS (16), moderate OSAS (14), and severe OSAS (15) according to the polysomnography (PSG) results. Patients signed consent forms. This study was approved by the Istanbul University Cerrahpasa Faculty of Medicine Ethics Committee (project number: 2367/06.07.2010). Patients with a previous diagnosis of asthma or COPD or those with symptoms suggestive of asthma or COPD, such as chronic cough, shortness of breath, wheezing attacks, or exertional dyspnea, were excluded from the study. Patients using anticoagulant medication and cholesterol medication were excluded. This approach was adopted to ensure a homogeneous population of study and to minimize confounding factors related to chronic respiratory diseases. Among the study participants, 18 patients were diagnosed with hypertension. These patients were not using any medication that could affect platelet function. No other medication known in the literature to affect MRP1 activity was permitted during the study period. A detailed anamnesis was taken from the patients who underwent PSG for the detection of additional diseases. Patients who could change the course of the study by looking at the pulmonary function test with a ZAN 100 handy 2 computerized spirometer device, arterial blood gas (ABG), lung film, and hemogram values with the Radiometer Copenhagen ABL800flex branded blood gas device were excluded from the study.

2.2 | Sleep study

Measurements of patients were recorded for 5–8 h during their sleep using the Somnoscreen PSG

serial:0369 device at 10 PM. PSG recordings were taken in 30-s intervals for sleep, respiration, and oxygenation according to the common criteria. Cessation of respiratory airflow for 10 s and more was referred to apnea. Fifty percent decrease in respiration amplitude compared to the basal level and at least 3% decrease in oxygen saturation or arousal is accepted as hypopnea.[19] Obstructive apnea was referred to chest movement existence while there was no airflow. AHI was determined by PSG. Patients were separated into four groups including simple snoring (AHI < 5), mild OSAS (AHI: 5–15), moderate OSAS (AHI: 15–30), and severe OSAS (AHI > 30) through AHI values.[20]

2.3 | Platelet aggregation

Blood samples were taken to the tubes with heparin and citrate (3.8% citrate) in the morning from PSG patients who were not under any treatment with continuous positive airway pressure. Platelet rich plasma (PRP) on the upper phase was collected by centrifugation at 300 g for 15 min for platelet aggregation. Five hundred microlitre PRP was added into the aggregometer tube. Then, 1 μM adenosine diphosphate (ADP) was added into the tube. The platelet aggregation curve was calculated and measured separately as % amplitude and slope.[21]

2.4 | Platelet activation parameters

CD62P monoclonal antibody (MoAb) levels for P-selectin, a platelet surface antigen, CD41b for GpIIb, and CD42b for GpIb were measured by flow cytometry.[22] For this measurement, heparinized blood samples were centrifuged at 300Xg for 15 min to obtain PRP samples. Then, a platelet pellet was obtained from PRP samples. Phosphate buffered saline containing EDTA was added to the pellet to obtain a platelet suspension. Hundred microlitre platelet suspension was stained with CD62P, CD41b, CD42b, MRP1 MoAbs, and isotypes of these antibodies. Data on proteins labeled on the platelet surface were recorded with a flow cytometry device (BD, FACSCalibur™, Becton Dickinson Immunocytometry Systems, USA). Platelets were plotted by platelet gates on SSC/FCS log/log dot plots and at least 10,000 cells were counted in each gate. Data were analyzed with CellQUEST software (BD Biosciences, USA). The platelet population was evaluated separately as single (histogram) and double (dot plot).[23]

2.5 | Statistical analysis

In the study, the Shapiro–Wilk test was used for the conformity of the data to the normal distribution. One-way analysis of variance (ANOVA) was used for group comparisons of data conforming to the normal distribution, and Kruskal–Wallis ANOVA was used for comparisons of data not conforming to the normal distribution. The tests used are indicated under the tables. When groups were determined to be significantly different, the Tukey multiple comparison test was performed to understand which group or groups cause the difference. The chi-squared/Fisher's exact test was used to compare OSAS patients with nominal data. The relationship between AHI measurements (%) and parameters was determined by the Pearson correlation coefficient. The SPSS 11.5 program was performed in analyzing data.

3 | RESULTS

In this study, platelet aggregation test results in four groups determined as simple, mild, moderate, and severe OSAS according to AHI values were evaluated together with other clinical findings according to the presence (+) and absence (−) of CD62P, CD41b, CD42b, and MRP1 proteins. The slope, which is an indicator of platelet aggregation, was significantly higher in patients in the severe OSAS group than in the simple and mild OSAS group (simple-severe $p = 0.020$; mild-severe $p = 0.011$), but there was no difference between the other groups (Table 1). CD41b −/CD62P+ values were significantly different in OSAS groups ($p < 0.05$). According to multiple comparison tests

A. The CD41b−/CD62P+ of the patients in the severe OSAS group was higher than the patients in the mild OSAS group (mild-severe $p = 0.018$), but there was no difference between the other groups (Table 1),
B. CD42b values were different between OSAS groups ($p < 0.01$). The CD42b values of the patients in the simple and mild OSAS group were lower than the patients in the severe OSAS group (simple-severe $p = 0.015$; mild-severe $p = 0.033$). There was no difference between the other groups (Table 1).
C. CD42b+/MRP1+ values were different between OSAS groups ($p < 0.01$). In other words, the CD42b+/MRP1+ levels of the patients in the severe OSAS group were lower than the patients in the simple, mild, and moderate OSAS groups (simple-severe $p = 0.002$; mild-severe $p = 0.022$; moderate-severe $p = 0.004$), but there was no difference between the other groups (Table 1).
D. MRP1 values were different between OSAS groups ($p < 0.05$). The MRP1 medians of patients with severe OSAS were found to be significantly lower than the simple, mild, and moderate groups (simple-severe $p = 0.028$; mild-severe $p = 0.014$; moderate-

TABLE 1 Comparison of platelet parameters of patients based on OSAS stages.

Platelet parameters	OSAS stages	Mean ± SD	Median (min–max)	p[a]
Platelet count cell/μL	Simple OSAS	251,357.14 ± 70,878.67	229,000 (174,000–369,000)	0.245
	Mild OSAS	238,187.50 ± 47,121.43	239,500 (166,000–366,000)	
	Moderate OSAS	241,357.14 ± 78,994.27	267,000 (198,000–495,000)	
	Severe OSAS	253,542.37 ± 68,209.44	240,000 (151,000–495,000)	
Platelet aggregation test slope Ohm (Ω)	Simple OSAS	85.80 ± 42.41	70.62 (53.75–183.75)	0.041
	Mild OSAS	77.25 ± 28.56	71.25 (33.75–140)	
	Moderate OSAS	99.80 ± 48.66	81.12 (52.50–240)	
	Severe OSAS	115.98 ± 46.56	101.25 (50–197)	
Platelet aggregation test amplitude %	Simple OSAS	84.64 ± 13.22	85.62 (58.75–111.25)	0.404
	Mild OSAS	77.23 ± 20.34	81.25 (46.25–110)	
	Moderate OSAS	87.70 ± 8.23	88.25 (73.75–101.25)	
	Severe OSAS	85.48 ± 17.22	87.75 (33.75–105)	
CD41b+/CD62P− mean fluorescence intensity	Simple OSAS	27.58 ± 7.18	26.07 (17.51–45.13)	0.600
	Mild OSAS	31.43 ± 17.79	28.18 (12.45–71.98)	
	Moderate OSAS	25.19 ± 12.36	21.73 (13.64–56.66)	
	Severe OSAS	27.67 ± 11.03	23.88 (13.60–48.59)	
CD41b+/CD62P+ mean fluorescence intensity	Simple OSAS	65.35 ± 8.02	68.39 (50.52–76.65)	0.273
	Mild OSAS	56.56 ± 22.05	61.68 (13.34–83.37)	
	Moderate OSAS	58.69 ± 18.12	62.80 (19.18–81.44)	
	Severe OSAS	55.42 ± 11.07	55.03 (36.36–72.98)	
CD41b−/62P+ mean fluorescence intensity	Simple OSAS	4.25 ± 4.19	2.39 (0.34–13.51)	0.048
	Mild OSAS	5.84 ± 10.07	1.15 (0.07–38.38)	
	Moderate OSAS	8.06 ± 7.66	3.99 (0.31–22.87)	
	Severe OSAS	8.96 ± 9.18	4.24 (1.47–29.61)	
CD41b+ mean fluorescence intensity	Simple OSAS	92.92 ± 5.95	95.70 (82.12–99.44)	0.069
	Mild OSAS	87.99 ± 13.28	94.05 (53.25–99.24)	
	Moderate OSAS	83.88 ± 11.94	86.11 (63,50–97.37)	
	Severe OSAS	83.09 ± 13.77	86.81 (52.70–96.92)	
CD62P+ mean fluorescence intensity	Simple OSAS	69.60 ± 7.50	70.53 (54.06–78.39)	0.328
	Mild OSAS	62.40 ± 21.97	68.81 (15.25–85.44)	
	Moderate OSAS	66.76 ± 18.56	72.18 (21.75–83.15)	
	Severe OSAS	64.38 ± 10.05	65.08 (45.75–83.96)	
CD42b+ mean fluorescence intensity	Simple OSAS	81.12 ± 25.22	87.38 (0.03–98.08)	0.009
	Mild OSAS	72.12 ± 38.04	91.04 (0.01–99.01)	
	Moderate OSAS	81.70 ± 11.07	80.02 (59.90–97.05)	
	Severe OSAS	46.80 ± 36.79	64.02 (0,04–93.38)	
CD42b+/MRP1+ mean fluorescence intensity	Simple OSAS	8.18 ± 6.05	6.76 (0.07–20.95)	0.002
	Mild OSAS	5.12 ± 3.84	5.40 (0.0–10.90)	
	Moderate OSAS	6.43 ± 5.25	4.92 (0.62–21.72)	
	Severe OSAS	2.01 ± 2.32	1.73 (0.01–8.47)	

TABLE 1 (Continued)

Platelet parameters	OSAS stages	Mean ± SD	Median (min–max)	p[a]
CD42b–/MRP1+ mean fluorescence intensity	Simple OSAS	0.70 ± 1.07	0.17 (0.03–3.48)	0.082
	Mild OSAS	2.89 ± 4.86	0.14 (0.01–13.14)	
	Moderate OSAS	1.75 ± 1.58	1.87 (0.0–5.20)	
	Severe OSAS	2.22 ± 2.03	2.0 (0.12–7.56)	
MRP1+ mean fluorescence intensity	Simple OSAS	8.87 ± 6.11	7.18 (0.20–21.35)	0.013
	Mild OSAS	8.01 ± 4.95	6.99 (2.35–18.79)	
	Moderate OSAS	8.17 ± 5.25	6.81 (0.62–21.98)	
	Severe OSAS	4.23 ± 4.06	3.72 (0.24–16.03)	

Note: Simple OSAS $n = 14$, Mild OSAS = 16, Moderate OSAS = 14, Severe OSAS = 15.

Abbreviations: CD42b, cluster of differentiation 42b (platelet glycoprotein Ib alpha chain); CD62P, cluster of differentiation 62P (P selectin); max, maximum; min, minimum; MRP, multi-drug resistance-related protein; OSAS, obstructive sleep apnea syndrome; SD, standard deviation.

[a]Kruskal–Wallis variance analyze.

TABLE 2 Correlations with AHI % index.

	AHI %	
	r[a]	p
BMI	0.559	0.000
PO_2	–0.297	0.022
SO_2	–0.398	0.002
HCO_3	0.469	0.000
Platelet count	0.364	0.005
Slope	0.289	0.028
CD42b	–0.419	0.001
CD42b+/MRP1+	–0.357	0.006
MRP1	–0.281	0.032

Abbreviations: AHI, apnea/hypopnea index; BMI, body mass index; CD42b, cluster of differentiation 42b (platelet glycoprotein Ib alpha chain).

[a]Pearson correlation coefficient.

severe $p = 0.046$), but there was no difference between the other groups (Table 1).

Correlation of % AHI with other parameters examined is given in Table 2.

As mentioned in the Methods section, some clinical values of patients classified according to OSAS stages by measuring AHI values are given in Table 3. Although there was no significant difference in the age, body mass index (BMI), Fev1/forced vital capacity (FVC), Fev1, FVC, Mef2575, pH, PCO_2, PO_2, and SO_2 measurements of the patients in the OSAS stages ($p > 0.05$), on the contrary, there was a significant difference in the HCO2 measurements ($p < 0.05$). The mean HCO_2 of patients in the simple OSAS stage was significantly lower than the patients in the severe OSAS stage (Tukey's multiple comparison test $p = 0.029$). There was no statistically significant difference between the other groups (Table 3). There was no significant difference in terms of gender distribution, smoking rate, incidence of diabetes, and hypertension in patients with different stages of OSAS ($p > 0.05$) (Table 4). Hypercholesterolemia was not observed in any patient. The parametric test was used in Table 3 and effect sizes were added to the table. Nonparametric test (Kruskal–Wallis variance analysis) was used in the comparisons in Table 1. Since effect sizes for nonparametric tests cannot be calculated in the SPSS program, effect sizes could not be given in the comparisons in Table 1.

4 | DISCUSSION

In this study, we examined whether there is a difference in platelet function and MRP1 expression in patients with simple snoring due to AHI detected during sleep and mild, moderate, and severe OSAS, regardless of factors such as age, gender, and tobacco use. MRP1 is a transmembrane protein that transports leukotriene C4 (LTC4) from platelets and leukocytes out of the cell. LTC4 is a critical mediator that functions in the chemotaxis of leukocytes and platelets to the site of inflammation by causing vasoconstriction, bronchospasm, and increased vascular permeability.[24,25] According to a study by Lorico et al. (1997), the decrease in LTC4 levels caused an inadequate inflammatory response in the MRP1 (–/–) transgenic rat model.[26,27] Yoshioka et al. (2009) also conducted a study with the MRP1 (–/–) transgenic rat model and showed that MRP1 plays a role in the regulation of IgE-mediated cysteinyl leukotriene (CysLT), which is secreted from mast cells and leads to the development of allergic airway inflammation.[28] In recent years, it has become clear that MRP1 is not only involved in excretion of xenobiotics but also transports lipid mediators such as

TABLE 3 Comparison of clinical and personal measurements in patients in OSAS stages.

	Simple OSAS Mean ± SD $n = 14$	Mild OSAS Mean ± SD $n = 16$	Moderate OSAS Mean ± SD $n = 14$	Severe OSAS Mean ± SD $n = 15$	p[a]	Partial eta squared (η^2)
Age	43.36 ± 12.85	44.25 ± 12.94	49.54 ± 13.88	52.33 ± 12.60	0.201	0.080
BMI	27.85 ± 4.97	30.07 ± 6.93	30.42 ± 6.32	35.71 ± 11.05	0.051	0.130
Fev1/fvc	77.93 ± 5.95	80.25 ± 7.07	76.87 ± 5.45	77.67 ± 5.52	0.454	0.046
Fev1	91.64 ± 11.95	97.06 ± 14.24	94.36 ± 14.22	94.67 ± 14.49	0.764	0.021
FVC	98.14 ± 13.70	101.19 ± 14.29	101.00 ± 15.37	98.27 ± 15.30	0.902	0.010
Mef2575	65.71 ± 18.67	80.50 ± 32.29	69.29 ± 25.16	68.67 ± 21.92	0.392	0.053
pH	740.29 ± 1.98	740.62 ± 2.19	741.29 ± 1.64	740.87 ± 2.42	0.635	0.030
PCO_2	38.07 ± 2.92	38.31 ± 4.19	37.86 ± 3.25	38.60 ± 3.74	0.951	0.006
PO_2	85.07 ± 9.27	87.31 ± 6.35	82.29 ± 8.13	82.20 ± 12.47	0.372	0.055
SO_2	96.42 ± 0.65	96.75 ± 0.68	96.21 ± 1.05	96.13 ± 1.77	0.440	0.047
HCO_2	23.79 ± 1.30	29.40 ± 1.02	24.37 ± 1.15	26.25 ± 1.85	0.047	0.134

Abbreviations: BMI, body mass index; Fev1/fvc, volume of air exhaled in the first second of forced expiration/forced vital capacity; FVC, forced vital capacity; Mef2575, maximal expiratory flow 25–75; OSAS, obstructive sleep apnea syndrome; SD, standard deviation.

[a]One-way analysis of variance (ANOVA).

TABLE 4 Comparison of nominal parameters (discrete variables) of patients based on OSAS stages.

	Simple OSAS		Mild OSAS		Moderate OSAS		Severe OSAS		
	n	%	n	%	n	%	n	%	p[a]
Gender									
Female	4	28.6	7	43.8	5	35.7	7	46.7	0.747
Male	10	71.4	9	56.2	9	64.3	8	53.3	
Smoking									
Nonsmokers	10	71.4	15	93.8	11	78.6	13	86.7	0.372
Smokers	4	28.6	1	6.2	3	21.4	2	13.3	
Diabetes									
No	13	92.9	15	93.8	12	85.7	13	86.7	0.843
Yes	1	7.1	1	6.2	2	14.3	2	13.3	
Hypertension									
No	13	92.9	13	81.2	8	57.1	10	66.7	0.127
Yes	1	7.1	3	18.8	6	42.9	8	33.3	

Abbreviation: OSAS, obstructive sleep apnea syndrome.

[a]Chi-squared test/Fisher's exact test.

leukotrienes or prostaglandins.[29,30] Thus, MRP1 has become a good target molecule in the explanation and control of inflammation, as it plays a role in the transport of leukotrienes and prostaglandins, which are mediators of the inflammatory response. A genetic study in which MRP1 was knocked out revealed a decrease in CysLT levels in Bronco alveolar lavage (BAL) fluid, thus revealing the important role of MRP1 in the inflammatory response of the allergic airway.[28,31] Furthermore, a decrease in CysLT levels in the BAL fluid occurs due to the lack of MRP1.[28] In addition, although studies on the MRP1 protein in various inflammatory diseases such as rheumatoid arthritis,[10] atherosclerosis,[11] Crohn's disease, and ulcerative colitis[12] correlate the MRP1 protein with inflammatory diseases, no MRP1 study associated with OSAS could be detected. Since MRP1 is an important protein in oxidative stress and inflammation, we predicted that oxidative stress and

inflammation can be controlled by MRP1 in COPD and OSAS diseases. Accordingly, we determined the MRP1 protein levels based on platelets in OSAS using the flow cytometry method. We found MRP1 protein levels to be lower in patients with severe OSAS compared to simple, mild, and moderate groups (simple-severe $p = 0.028$; mild-severe $p = 0.014$; moderate-severe $p = 0.046$). In severe OSAS groups, this low expression level, negative correlation between AHI % index, and MRP1 protein levels (Table 2) may explain inflammation and oxidative stress. In conclusion, MRP1 protein modulation may be a hope in the treatment process for patients with OSAS. The observed correlation between MRP1 and AHI, while statistically significant, is of moderate strength. Several factors may account for this, including the relatively limited sample size and the presence of comorbidities such as diabetes ($n = 6$) and hypertension ($n = 18$) among participants. These conditions may have introduced additional variability, potentially attenuating the correlation. Future studies with larger, more homogeneous cohorts are warranted to clarify the relationship between MRP1 expression and OSAS severity. MRP1 is a high-affinity transporter responsible for exporting nascent LTC4. Reduced MRP1 function may lead to increased local concentrations of LTC4 in the pericellular environment, particularly around platelets. This sustained exposure can prolong the activation of the CysLT2R receptor on platelets, thereby enhancing platelet activation and the release of prothrombotic mediators.[32,33] MRP1 is also critical for exporting oxidized glutathione (GSSG), thus maintaining a cellular redox balance. Downregulation of MRP1 results in intracellular GSSG accumulation and elevated oxidative stress, which in turn promotes platelet hyperreactivity through the activation of glycoprotein IIb/IIIa and other ROS-mediated signaling pathways.[34,35] These mechanisms are interrelated; dysregulated leukotriene metabolism can further exacerbate oxidative stress, creating a feedback loop that amplifies platelet activation and fosters a prothrombotic state.[11] MRP1 has been implicated in a range of thrombotic and inflammatory conditions. In atherosclerosis, MRP1-mediated efflux of proinflammatory mediators such as LTC4 contributes to disease progression, and MRP1 inhibition has shown promise in reducing atherosclerotic plaque formation in preclinical models. In COPD, MRP1 activity is associated with the severity of airway inflammation, whereas in ulcerative colitis, its expression is dynamically regulated during inflammatory episodes and can be modulated by therapeutic agents.[11,13] In the literature, nocturnal hypoxia, hemodynamic changes, increased sympathetic activity due to falling asleep, and consequently increased epinephrine levels have been reported among the important consequences of OSAS. It has been suggested that increased sympathetic activity causes platelet activation during sleep.[36,37] OSAS is a common disease with serious cardiovascular consequences. Mechanisms that may explain the relationship between OSAS and cardiovascular diseases have been identified as increased sympathetic activity ranges and hypoxemia, oxidative stress, inflammation, endothelial dysfunction, advanced coagulation, and platelet activation.[38] Bokinsky et al. 1995 was the first known study to measure platelet aggregation, P-selectin, and platelet function in OSAS. In this study, platelet activation was detected in the OSAS group compared to the control group, but apnea index and correlation findings were not included. In another study conducted by Geiser et al. in 2002, CD62P-positive platelets were evaluated and it was reported that nocturnal platelet activation was increased in patients with OSAS compared to the control group, but it was not correlated with AHI values.[39]

P-selectin, which is thought to play a role in atherogenesis in the literature and is considered a circulatory marker in terms of cardiovascular conditions, is located on the surface of platelets.[40] When P-selectin is at rest, it rises to the surface because of platelet activation and secretion of α granules. Thus, activated platelets can be examined by flow cytometry using a P-selectin-specific monoclonal antibody. In our study, P-selectin did not differ between groups. There is some research showing that P-selectin can be shed from the cell surface during the experiment.[41] In our experiment, we may not have found a difference between the groups since P-selectin was shed from the cell surface, but if we could detect the levels of free P-selectin that was shed, perhaps we could have obtained a clearer result.

Eisensehr et al. found a significant correlation between P-selectin levels and AHI values in the severe OSAS group (2011) and reported that P-Selectin, active GpIIb/IIIa, and GpIb receptor levels were evaluated in blood samples taken in the morning after sleep. They reported that there was no significant difference in GpIIb/IIIa in patients with saturation less than 90% for more than 1 min/h compared to patients with a saturation of less than 1 min/h, whereas GpIIb/IIIa was significantly reduced in patients with a desaturation greater than 1 min/h. Activated platelet surface GpIIb (CD41b) receptor and GpIb (CD42b) receptor levels, which are markers of platelet activation in OSAS, were assessed by flow cytometry with the use of monoclonal antibody in our study. 42b levels were found to be statistically lower in severe OSAS patients than in simple and mild OSAS groups (simple-severe $p = 0.015$; mild-severe $p = 0.033$) (Table 1). CD42b+/MRP1+ values were found to be significantly lower in

severe OSAS group than other groups which were in line with 42b values (simple-severe $p = 0.002$; mild-severe $p = 0.022$; moderate-severe $p = 0.004$). Besides, the negative correlation was detected between AHI% levels and CD42b, and CD42b+/MRP1+ (Table 2). These findings are exclusively parallel with the work of Rahangdale et al.[42] The main task of the GpIb receptor is primary hemostasis and arterial thrombosis and is suppressed by platelet activation.[32,43–45]

Michelson et al. have shown that the surface GpI receptor enters platelets with platelet activation.[45] Neutrophil cathepsin G has also been shown to be irreversibly proteolyzed by the tumor necrosis factor-α-converting enzyme and other proteases both due to platelet activation and due to the α chain of the GpIb receptor in various studies.[46,47] Monoclonal antibodies, which were used for the GpIb receptor, binds to distal part of the α chain which was proteolyzed. This shows that, because of our study, GpIb levels were found to be lower in the severe OSAS group and further studies are needed in this area. According to the study of Michelson et al., the platelet surface GpIb level changes with platelet activation and it keeps the alteration for longer periods more than other platelet activation markers. For this reason, the resulting stimulus at night is a suitable marker for daytime scoring.[48]

Detection of secretion and aggregation following the induction of platelets with ADP is a guiding method for determining platelet function.[49] We found a relationship between increased OSAS severity associated with AHI and platelet aggregation. There was an increase in the platelet aggregation slope in the severe OSAS group compared to the other groups. We found a positive correlation between AHI % values and slope (Table 2). This demonstrated once again that platelet aggregation is increased in OSAS patients. This finding, which shows an increase in platelet activity, is also consistent with the examples above. On the other hand, Sanner et al.[50] did not find a significant change in platelet aggregation between OSAS ($n = 17$) and control groups ($n = 15$), and this result is not satisfactory enough since they did not evaluate the OSAS status using PSG in the control group. In our study, all groups were evaluated with PSG. Platelet aggregation was found to be higher in the severe OSAS group with an AHI value of less than 30 compared to the other 2 groups with an AHI value of less than 15. These findings clearly show that platelet aggregation is higher in the severe OSAS group than in the other groups. Although a positive correlation was found between the AHI % index and platelet count, we did not find any difference in platelet counts. The study conducted by Atan et al. also supports our findings.[51]

There was a significant difference in 4 groups of OSAS regarding BMI in our study, which shows that obesity is a considerable parameter in OSAS. Nir Peled and coworkers (2007) investigated the vascular endothelial growth factor[52] and found that there was a significant relationship between BMI and OSAS severity. In this study, there was no significant relationship between smoking and OSAS groups. This result suggests that our results are independent of smoking. Moreover, the relationship between pulmonary function tests and artery blood gas measurements in OSAS was evaluated. The fact that no significant difference was detected between the groups suggests that the findings did not show any relationship with ABG and pulmonary function test results.

5 | CONCLUSIONS

This is the first report in which a negative correlation between AHI% index and MRP1 was detected in severe OSAS. High platelet aggregation and low MRP1 expression, which we found to be correlated with AHI values that determine disease severity, may be biomarkers for OSAS. Resulting data suggest that upregulation of MRP1 protein to prevent increased oxidative stress and inflammation in OSAS may be effective in controlling the disease. We agree that the potential use of antiplatelet agents, particularly in severe OSAS cases, is an intriguing prospect. However, there is currently a lack of interventional data supporting this approach in OSAS populations. Therefore, we emphasize the necessity for well-designed prospective clinical trials to evaluate the efficacy and safety of antiplatelet therapy in reducing the risk of future cardiac or cerebral thrombotic events in these patients. There are no previous data evaluating MRP1 function in OSAS, and more detailed studies are needed to understand platelet function in OSAS. Once the mechanisms are unraveled, the modulation of platelet function may attract clinicians' attention for new treatments. Given its multifaceted roles, MRP1 represents a promising therapeutic target. Future research should focus on elucidating the precise kinetics of LTC4 in the pericellular space following MRP1 downregulation, investigating cell-specific contributions of MRP1, particularly within platelets, developing selective pharmacological modulators of MRP1, employing systems biology approaches to understand the interplay between MRP1, other ABC transporters, and cellular signaling pathways, and conducting rigorous clinical studies to translate preclinical findings into effective therapies for thrombotic and inflammatory diseases.

AUTHOR CONTRIBUTIONS

Cigdem Bayram Gurel and Engin Korkmaz had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data

analysis. Concept and design: Cigdem Bayram Gurel, Engin Korkmaz, Bulent Tutluoglu, Turgut Ulutin. Collection, analysis or interpretation of data: All authors. Draft created by: Engin Korkmaz, Cigdem Bayram Gurel, Suzan Adin Cinar. Critical revision of the article for important intellectual content: All authors. Statistical analysis: Engin Korkmaz, Suzan Adin Cinar, Cigdem Bayram Gurel. Administrative, technical or material support: Turgut Ulutin, Gunnur Deniz, Gonul Kanigur, Bulent Tutluoglu, Cigdem Bayram Gurel. Supervision: Cigdem Bayram Gurel, Turgut Ulutin.

ACKNOWLEDGMENTS

The authors acknowledge that they have read and approved the entire article. The study was conducted with the approval of Istanbul University Cerrahpaşa Faculty of Medicine Ethics Committee. This study was supported by the Istanbul University Scientific Research Fund. Some data belonging to this study, which cannot represent the entire study, were included in the oral presentation number C0125 within the scope of "24th Biennial International Congress on Thrombosis – EMLTD Congress 2016 4–7 May 2016, Istanbul, Turkey EMLTD Abstracts/Thrombosis Research 141S1 (2016) S1–S92" presented in the declaration.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the Istanbul University Cerrahpasa Faculty of Medicine Ethics Committee (project number: 2367/06.07.2010).

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How to cite this article: Gurel CB, Korkmaz E, Cinar SA, et al. Decreased multidrug resistance protein 1 and increased platelet activation in obstructive sleep apnea syndrome. *Sleep Research*. 2025;1-11. https://doi.org/10.1002/slp2.70009