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Assesment of Red Cell Distribution Width (RDW) in Patients With Obstructive Sleep Apnea Syndrome

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Abstract
Objective: Obstructive sleep apnea syndrome (OSAS) is associated with increased cardiovascular morbidity and mortality. Red cell distribution width (RDW), a measure of the variability in size of circulating erytrocytes, has been reported to be a risk marker of morbidity and mortality for cardiovascular disease. Therefore, we have investigated the possible association between OSAS and RDW.
Material and Methods: We selected 30 mild, 32 moderate and 31 severe OSAS patients and 31 healthy control subjects matched for age, sex, and body mass index. RDW was measured by using an automated blood cell counter.
Results: The RDW values were significantly higher in patients with severe OSAS than in the control group (14.6±2.1 vs.13.2±2.4 %; p=0,03). There were no significant differences between controls and patients with mild and moderate OSAS (13.2±2.4 vs. 13.4±0.6 %; p=0,98; 13.2±2.4 vs. 14.0±2.4 %; p = 0.43) and between patients with mild, moderate and severe OSAS (13.4±0.6 vs. 14.0±2.4 vs. 14.6±2.1 %; p=0,67 for comparison of mild and moderate OSAS, p=0.08 for comparison of mild and severe OSAS, p=0.56 for comparison of moderate and severe OSAS) in respect to RDW. Additionally, significant correlation of RDW with parameters of sleep was noted. RDW was correlated with apnea-hypopnea index (r=0,264, p=0.01) and minimal oxygen saturation (r=-0,284, p=0.006).
Conclusions: RDW is a widely available diagnostic marker, routinely performed hemogram. In our study, we found that RDW was higher in the patients with OSAS compared with the control group. These results show that RDW is an important marker in terms of identifying the risk of atherosclerosis in patients with OSAS at an early stage.
Key Words: Complete Blood Count; Obstructive Sleep Apnea Syndrome; Red Cell Distribution Width.

Obstrüktif Uyku Apne Sendromlu Hastalarda Eritrosit Dağılım Genişliğinin Değerlendirilmesi

Özet
Amaç: Obstrüktif uyku apne sendromu (OUAS) kardiyovasküler morbidite ve mortalitede artış ile ilişkilidir. Dolaşımdaki eritrosit boyutlarındaki değişikliğin göstergesi olan eritrosit dağılım genişliği (EDG)'nin kardiyovasküler hastalıklardaki morbidite ve mortalite için bağımsız bir risk faktörü olduğu bildirilmiştir. Çalışmamızda OUAS ile EDG arasındaki olası ilişkiyi araştırdık.
Gereç ve Yöntemler: Çalışmaya yaş, cinsiyet ve vücut kitle indeksi yönünden benzer 30 hafif, 32 orta ve 31 ciddi dereceli OUAS hastası ile 31 sağlıklı birey alındı. EDG otomatik kan sayım cihazı kullanılarak ölçüldü.
Bulgular: Ciddi dereceli OUAS hastalarında EDG, kontrol grubuna kıyasla anlamlı derecede yüksekti (14.6±2.1 vs.13.2±2.4%;p=0,03). Kontrol grubu ile hafif ve orta dereceli OUAS hastaları arasında (13.2±2.4 vs. 13.4±0.6 %; p=0,98; 13.2±2.4 vs. 14.0 ±2.4 %; p = 0.43) ve hafif, orta, ciddi dereceli OUAS hastalarının kendi arasında (13.4±0.6 vs. 14.0±2.4 vs. 14.6±2.1 %; p=0,67 hafif ve orta dereceli OUAS hastaları karşılaştırıldığında, p=0.08 hafif ve ciddi dereceli OUAS hastaları karşılaştırıldığında, p=0.56 orta ve ciddi dereceli OUAS hastaları karşılaştırıldığında) EDG değerleri açısından fark yoktu. İlave olarak EDG ile uyku parametreleri arasında anlamlı korelasyon saptandı. EDG, apne hipopne indeksi (r=0.264 , p=0.01) ve en düşük oksijen satürasyonu (r=-0,284, p=0.006) ile korele idi.
Sonuç: EDG, hemogram içerisinde rutin olarak bakılan bir tanı aracıdır. Çalışmamız OUAS'lu hastalarda kontrol grubuna kıyasla EDG'nin daha yüksek olduğunu bulduk. Bu sonuçlar, EDG'nin OUAS'lu hastalardaki ateroskleroz riskinin erken evrede saptanması için önemli bir tanı aracı olduğunu göstermektedir.
Anahtar Kelimeler: Total Kan Sayımı; Obstrüktif Uyku Apne Sendromu; Kırmızı Hücre Dağılım Genişliği.

INTRODUCTION

Obstructive sleep apnea (OSAS) is characterized by repetitive apnea or hypopnea due to narrowing of the upper airways during sleep. It is a common disorder of middle-aged adults, affecting 4% of men and 2% of women (1). OSAS is an independent risk factor for cardiac mortality and morbidity. In patients without underlying cardiovascular disease, hypertension, coronary artery disease, stroke, and heart failure are shown to be associated with OSAS. These conditions are independent risk factors for cardiovascular morbidity and mortality and OSAS participates in the genesis of these conditions (2,3). Recent studies have indicated that OSAS is associated with multiple causal factors of endothelial damage and atherosclerosis. Systemic inflammation, oxidative stress, increased levels of

soluble adhesion molecules and coagulation factors seem to be responsible for this relationship. Furthermore, all of these factors have been reported to significantly decrease after treatment with continuous positive airway pressure (4,5).

MATERIAL AND METHODS

Red cell distribution width (RDW), which measures the variability in the size of circulating erythrocytes, is easily measured during routine complete blood counts (6). Recently, a strong independent association between RDW and prognosis of patients with cardiopulmonary diseases, including acute myocardial infarction, acute and chronic heart failure, coronary artery disease, peripheral vascular disease, pulmonary embolism and also in the general population have been reported (7-13). The association of RDW with negative clinical outcomes in cardiovascular diseases has not been fully elucidated. Inflammation may induce changes in red blood cell maturation by disturbing the red cell membrane, leading to increased RDW (14). Recently, a strong correlation of RDW with inflammatory markers, C-reactive protein (CRP) and sedimentation rate is demonsrated (15). Increased RDW may arise from an underlying inflammatory state that is associated with negative clinical outcomes (16). The aim of this study was to investigate the RDW levels in OSAS patients without hypertension, smoking, diabetes, hyperlipidemia and any cardiovascular disease and to assess whether there is any correlation between RDW and severity of disease.

Patients between ages 30 and 60 years with OSAS diagnosis who were examined in the department of Chest Diseases outpatient clinic between dates March 2009 and October 2010 were included in this study after conducting polysomnographies at the sleep laboratory. According to the severity which was determined by the AHI (apnea-hypopnea index), patients were examined in three groups; 30 patients in mild OSAS (AHI=5-15), 32 patients in moderate (AHI=16-30) OSAS and 31 patients in severe (AHI>30) OSAS group. As a control group, we chose 31 asymptomatic healthy individuals aging between 30 and 60 years without cardiovascular diseases who visited department of Cardiology outpatient clinic for cardiovascular check-up. The healthy group in the study included patients suitable for the study from the perspective of cardiac anatomy and functions, those with no night snoring or day-time sleepiness, who scored less than 10 in the Epworth sleepiness scale, and had low risk of OSAS in the Berlin questionnaire form evaluation (17-19). The study was approved by the local Ethics Committee. Informed consents which have been taken from every individual included in the study. All patients underwent a detailed examination of the cardiovascular system.

Exclusion criteria were as follows: (1) impaired cardiopulmonary function, defined as the occurrence of respiratory failure, pulmonary infection or congestive heart failure; (2) coronary artery disease, defined as having a typical angina pectoris, history of a prior myocardial infarction, presence of a positive stress test or positive coronary angiographic findings; (3) valvular disease, atrial fibrillation or congenital heart disease; (4) hypertension (Hypertension was considered to be present if the systolic pressure was > 140 mmHg and/or diastolic pressure was > 90 mmHg after averaging three separate blood pressure measurements determined at 10 min intervals, as well as patients receiving antihypertensive treatment were accepted as hypertensive), diabetes mellitus (Diabetes mellitus was defined as a fasting blood glucose level > 126 mg/dl or current use of a diet or medication to lower blood glucose and/or HbA_{1c}>6,5%), dyslipidemia (low-density lipoprotein (LDL) cholesterol >160 mg/dl, Total cholesterol >240 mg/dl, Triglyceride >250 mg/dl), using antihypertensives, antidiabetics and lipid-lowering treatment; (5) chronic alcoholism and smoking; (6) malignancy, hyperthyroidism and hypothyroidism; (7) history of prolonged use of non-steroid anti-inflammatory drugs or anticoagulants; (8) renal and liver insufficiency; (9) known hematologic disease such as leukemia or myelodysplastic syndrome; (10) a history of recent blood transfusion (<1 month).

There are two tools that have been used to determine if a patient may be suffering from sleep apnea. The Epworth Sleepiness Scale and the Berlin Questionnaire are simple questionnaires focused on the risk factors (like high blood pressure) and chronic behaviors (like excessive loud snoring) that are indicative of the presence of a sleep disorder such as sleep apnea in a patient. In Berlin questionnaire, there are 10-question for its accuracy in predicting the presence of sleep apnea in patients. The questionnaire consists of 3 categories related to the risk of having sleep apnea. Patients can be classified into high risk or low risk based on their responses to the individual items and their overall scores in the symptom categories. The Epworth Sleepiness Scale is an 8-question questionnaire which is used to determine the level of a person's daytime sleepiness (17-19).

Polysomnography was performed with 16 channels Embla (Medcare Inc, Iceland) with a continuous sleep technician monitoring. The system consists of 4 channels of EEG, 2 channels of EOG, submental EMG, oronasal air flow, thoracic and abdominal movements, pulse oximeter oxygen saturation, tibial EMG, body position detector, electrocardiogram and tracheal sound. Apnea was defined as complete stopping of airflow lasting more than 10 seconds. Hypopnea was defined as 30% or more reduction in respiratory airflow lasting more than 10 seconds and it is accompanied with a decrease of ≥4% in oxygen saturation. The average number of episodes of apnea and hypopnea per hour of sleep were defined as apnea hypopnea index (AHI). According to the severity, included patients were classified as mild OSAS (AHI=5-15), moderate OSAS (AHI=16-30) and severe OSAS (AHI>30). Sleep stages were scored following standard criteria with 30-s epochs and were reviewed and verified by a certified sleep physician (20).

Biochemical parameters were obtained from venous blood samples drawn after a 12 hour fasting period.

RDW was measured in a blood sample collected in dipotassium EDTA tubes. An automatic blood counter was used for whole blood counts.

All data were analyzed with "MedCalc 11.0.4" and "SPSS 15.0 for Windows" software. Numerical variables were defined as mean ± standart deviation, categorical variables were defined as frequencies and percentiles. In comparison of three or more groups, if the variables fit the normal distribution, the one way ANOVA test; if not, the Kruskal Wallis test was used. In comparison of the categorical variables multiple comparison Chi Square test was used. In post-hoc analysis Tukey test was used after one way ANOVA test. The Mann–Whitney U test with Bonferroni correction was used for post hoc analysis after performing the Kruskal–Wallis test. The alpha critical value for the Mann-Whitney U test in Bonferroni correction was accepted as 0.03 because the Mann-Whitney U test loses its value below 0.03. Kolmogorov-Smirnov test was used in testing for normality of the distribution. Spearman correlation analysis performed for the determination of correlation. All hypotheses were established as two-way, and alpha critical value was accepted as 0.05.

RESULTS

There were no difference among groups in terms of demographic data; age, sex, body mass index, systolic and diastolic blood pressures, and in laboratory parameters; fasting blood glucose, HbA1c, seurm lipid parameters, hemoglobin, hematocrite and platelet count (Table 1). The mean AHI in mild OSAS patient group was 10.3±3.0, in moderate OSAS patient group it was 21.5±3.5, and in severe OSAS patient group it was 59.4±15.9. The difference in AHI among groups was statistically significant. Minimal oxygen saturation (min-SaO2) and the percentage of recording time spent at a SaO2 less than 90% (SaO2 < %90 (TST%)) were different among groups with statistical significance (Table 1). The RDW values were significantly higher in patients with severe OSAS than in the control group (14.6±2.1 vs.13.2±2.4%; p=0.03) (Figure 1). There were no significant differences between controls and patients with mild and moderate OSAS (13.2±2.4 vs. 13.4±0.6%; p=0.98; 13.2±2.4 vs. 14.0±2.4%; p=0.43) and between patients with mild, moderate and severe OSAS (13.4±0.6 vs. 14.0±2.4 vs. 14.6±2.1%; p=0.67 for comparison of mild and moderate OSAS, p=0.08 for comparison of mild and severe OSAS, p=0.56 for comparison of moderate and severe OSAS) in respect to RDW (Figure 1). Additionally, significant correlation of RDW with parameters of sleep were noted. RDW correlated positively with AHI (r=0.264, p=0.01) and correlated negatively with minimal oxygen saturation (min-SaO2) (r=-0.284, p=0.006) (Figure 2).

Table 1. Baseline characteristcs in control group and OSAS subgroups

	Control group (mean±sd) (n= 31)	Mild OSAS (mean±sd) (n=30)	Moderate OSAS (mean ± sd) (n=32)	Severe OSAS (mean±sd) (n=31)	P Value
Age (years)	46.7±8.4	46.1±8.2	48.3±7.6	47.3±7.7	0.71
Female (n, %)	6 (19.3%)	5 (16.6%)	6 (18.7%)	6 (19.3%)	0.99
BMI (kg/m^2)	28.9±2.9	28.4±3.1	28.7±2.7	29.2±2.9	0.77
SBP (mmHg)	119.8±8.8	119.1±6.7	121.7±6.7	121.6±8.9	0.49
DBP (mmHg)	73.7±6.0	73.8±5.0	74.7±5.0	75.8±5.0	0.77
Fasting blood glucose (mg/dl)	89.4±8.2	89.8±8.6	91.7±10.5	92.5±9.4	0.49
HbA1c (%)	5.5±0.4	5.6±0.2	5.6±0.4	5.6±0.4	0.78
Total cholesterol (mg/dl)	191.3±23.8	188.7±33.1	190.5±43.1	195.6±26.4	0.86
LDL cholesterol (mg/dl)	117.5±23.5	113±33.9	119.7±35.9	119.8±30.6	0.81
HDL cholesterol (mg/dl)	46.8±10.8	44.9±13.6	44.2±10.0	45.2±10.4	0.83
Triglyceride (mg/dl)	146±67.9	144.6±57.9	148.4±81.7	149.5±50.8	0.99
Hemoglobin (g/dl)	14.5±1.1	14.2±1.1	14.1±0.9	13.3±1.3	0.41
Hematocrit(%)	42.4±3.2	41.6±3.3	41.3±2.6	40.6±3.6	0.50
Mean corpuscular volume (fl)	85.2±5.2	85.0±3.5	83.3±6.4	83.2±6.7	0.49
Red cell distribution width (%)	13.2±2.4	13.4±0.6	14.0 ± 2.4	14.6±2.1[*]	0.028
AHI		10.3±3.0	21.5±3.5	59.4±15.9	<0.0001
SaO2 min		87.3±3.6	83.2±4.8	71.4±10	<0.0001
SaO2<90% (TST%)		0.22±0.34	3.9±8.2	20.5±17.3	<0.0001

Abbreviations: OSAS: Obstructive sleep apnea syndrome, mean ± sd: mean±standart deviation, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, AHI: Apnea-hypopnea index, SaO2 min: Minimal oxygen saturation, TST: Total sleep time, SaO2<90% (TST%): Percentage of recording time spent at a SaO2<90%. [*]p=0.028 (patients with severe OSAS versus control group)
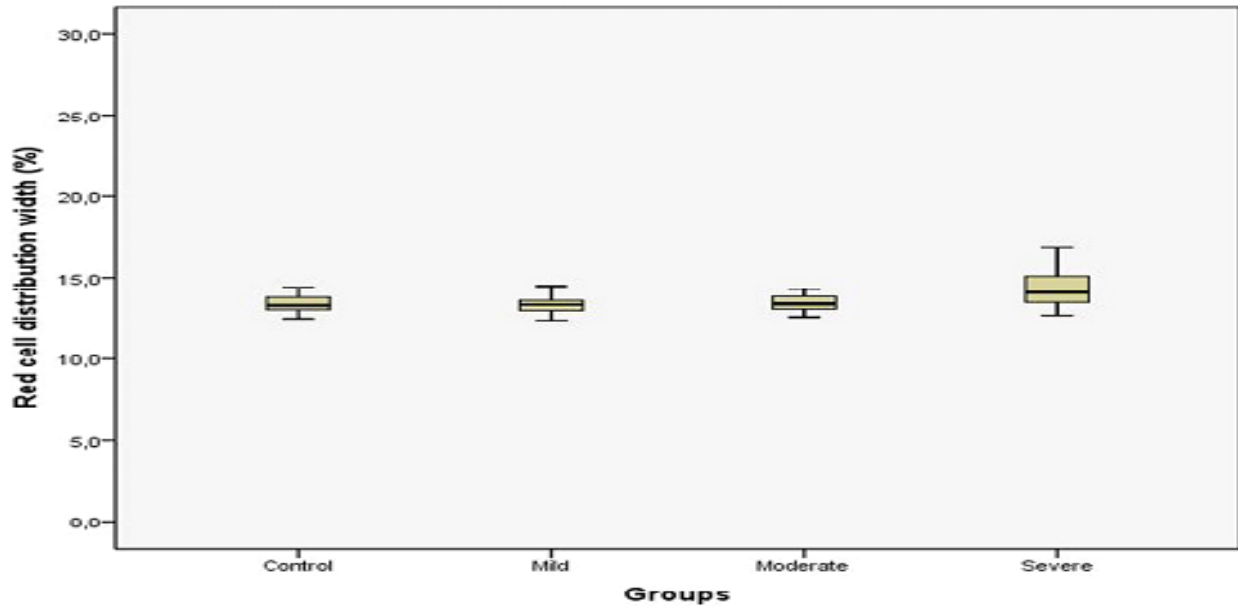
Figure 1. Comparison of patients with obstructive sleep apnea and control values for red cell distribution width.
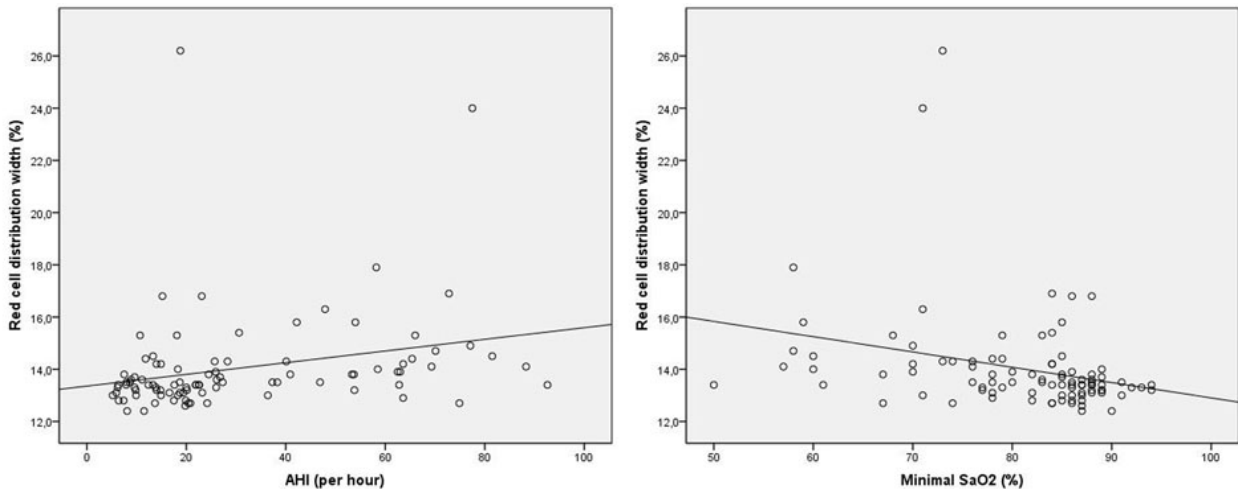

Figure 2. Correlation between red cell distribution width and apnea-hypopnea index (AHI), minimal oxygen saturation (minimal SaO$_2$)

DISCUSSION

Red cell distribution width shows variability in the size of circulating erythrocytes and is routinely measured by automated hematology analyzers as part of a complete blood count (6). In the present study, we demonsrated increased RDW levels in OSAS patients compared to controls.

OSAS is a systemic disorder and leads to cardiovascular complications (21). Recent studies showed that OSAS is not a simple respiratory abnormality during sleep, with the systemic inflammatory response it seems to be associated with cardiovascular diseases and increased atherosclerotic process. OSAS is associated with the hypertension, diabetes mellitus and hyperlipidemia

which increase the risk of atherosclerosis. In OSAS, hypoxia and intermittant reoxygenation episodes result with the oxidative stress which leads to endothelial dysfunction and increased symphatetic tone (21,22).

Atherosclerosis is a progressive inflammatory process which results with fatal vascular events (23). Endothelial injury is the initial mechanism that triggers the atherosclerotic process. OSAS is more prevalent in patients with hypertension, diabetes mellitus, obesity, coronary artery disease, stroke and heart failure, in which the endothelial dysfunction plays a key role (22). Recent studies have shown the presence of the endothelial dysfunction in OSAS. It has been shown that various proinflammatory and prothrombotic factors in OSAS (21,22). Serum CRP, fibrinogen, interleukin-6 (IL-6) levels and insulin resistance were shown to be increased

in OSAS patients. Nasal CPAP (continous positive airway pressure) therapy have shown to decrease CRP, IL-6 levels and insulin resistance (5).

RDW was shown to be associated with an increased risk of coronary heart disease events, possibly because it reflects the bone marrow's response to systemic ongoing inflammation (24). Increased RDW levels are observed with nutritional defiencies including iron, folate and vitamin B_{12}, suggesting that these conditions may be associated with inflammation (25). Inflammation may influence erythropoesis, erythrocyte circulatory half-life and erythrocyte deformability, promoting anisocytosis and thus increasing RDW levels (26). Recently, it was demonstrated that greater RDW levels were independently associated with greater high-sensivity CRP levels, a well-established marker of inflammation and cardiovascular disease (15,27). In a study of healthy individuals, increase in RDW was found as an independent risk for future cardiovascular disease (24). Increased RDW was found to be independently and strongly associated with mortality in patients with chronic and acute congestive heart failure, prior stroke, prior myocardial infarctions without symptomatic heart failure, acute myocardial infarction and in men referred for coronary angiography (7-10,28-30). The underlying mechanism explaining RDW's association with cardiovascular events is not clear. Possible mechanisms may include oxidative stres, inflammatory and neurohormonal activation (27,31). Oxidative stress has been shown to be associated with RDW. Antioxidants, including serum selenium, total carotenoids were shown to be significantly associated with a decrease in RDW. IL-6 was found to be an attenuating factor for this association (32). Both inflammation and oxidative stress play major roles in the pathogenesis of OSAS (4). An elevated RDW may reflect underlying inflammation and oxidative stress in OSAS and may be proposed as a simple diagnostic marker for monitoring patients with OSAS. Furthermore, neurohumoral activation may influence erythropoiesis. The sympathetic system and renin-angiotensin system may accalarate erythropoiesis by stimulating the release of erythropoietin (33). Increased sympathetic stres and enhanced activity of the renin-angiotensin system was shown in patients with OSAS (34).

The literature contains only 2 studies which describe relationship between OSAS and RDW (35,36). In the study by Ozsu et el. similar to our findings, RDW has been found significantly higher in patients with OSAS versus patients in control group, and a significant correlation between RDW and AHI, CRP has been observed (35). Sökücü et al has also reported that RDW increased significantly with increased severity of OSAS and was positively correlated with AHI (36). These studies have not excluded coronary artery disease, diabetes mellitus, hypertension which could lead to elevation of RDW (10,35,37,38). In our study, conditions increasing RDW, like cardiovascular disease, hypertension, diabetes mellitus have been excluded.

The exact mechanism of a high level of RDW in patients with OSAS is not clear. Three main pathways may be implicated. First is the augmented sympathetic activity with increased concentrations of epinephrine and norepinephrine as a result of hypoxemia and repetitive arousals from sleep (39,40). Secondly, increased RDW may be caused by acute and chronic intermittent hypoxia (35). A third mechanism is chronic inflammation. This is known that chronic inflammation occurs in OSAS and lead to increased secretion of IL-6 and other pro-inflammatory cytokines (5,41).

Our study has some limitations. First is the small sample size. Second is that in our study, we did not investigate the causes of elevated RDW, such as iron defiency, vitamin B12 and folate defiency. Third, although we speculate that sympathetic system and renin-angiotensin system may cause increase in RDW, we did not assess laboratory markers including norepinephrine and angiotensin II. Fourth, erythropoietin, reticulocyte count, inflammatory markers such as IL-6, CRP, sedimentation rate, TNF-a were not evaluated. Fifth, might be using the method of Epworth and the Berlin scale rather than the AHI in the selection of control individuals. However, in daily clinical practice, we use these methods for the selection of appropriate patients for the polysomnography test. In addition, previous reports have demonstrated the correlation of the Epworth Sleepiness Scale with the AHI (42). Sixth, since this design is cross sectional, it is not possible to investigate any causal relationship between RDW and OSAS. Seventh, RDW was assesed on a single occasion instead of serial measurements, therefore biologic variabilities and measurement errors could not be evaluated.

We have found that serum RDW values of patients with severe OSAS were significantly higher than those of the control group and RDW was correlated with AHI. In conclusion, we suggest that we could demonstrate the future risk of atherosclerosis by keeping track of the RDW values of patients diagnosed with OSAS. Therefore, our study suggests that RDW value is an important marker in terms of identifying the risk of atherosclerosis in patients with OSAS at an early stage. We demonstrated that even a simple full blood count could determine the risk. Risk of atherosclerosis can be proposed through the review of the RDW value with no need for a supplemental blood test or radiology examination. We think that, these significant findings of our analysis can guide for further clinical practice. However these findings must be supported clinically with prospective cohort studies with larger number of patients.

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