ORIGINAL ARTICLE

An Investigation of Serum Magnesium and Red Blood Cell Distribution Width Values in Patients with Obstructive Sleep Apnoea Syndrome

K Kilic[1], MS Sakat[1], O Araz[2], MS Gozeler[1]

ABSTRACT

Objective: *Obstructive sleep apnoea syndrome (OSAS) leads to complications in several systems. The purpose of this study was to examine serum magnesium and red cell distribution width (RDW) values in OSAS, a chronic inflammation, and thus to reveal the relations between these two parameters and with other sleep parameters.*

Methods: *A total of 160 patients diagnosed with OSAS and 50 controls were enrolled in this retrospective study. Study and control groups were constituted using the medical records. Age, gender, magnesium and RDW values were obtained from all patients' medical records. Values for apnea–hypopnea index (AHI), SpO_2, mean desaturation level, total sleep time (TST) and total sleep time in which oxygen saturation is below 90% (TST90) were also obtained from the polysomnography records.*

Results: *Red cell distribution width values of the patients in the study group were statistically significantly higher compared to those of the control group ($p < 0.001$). The magnesium levels of the patient group were significantly lower compared to those of the control group ($p < 0.001$). Also, serum RDW and Mg levels were negatively correlated.*

Conclusion: *We determined that serum magnesium levels decreased in the presence of OSAS and that this is related to the severity of OSAS. Similarly, we observed that RDW values increased in patients with OSAS and exhibited a significant correlation with AHI. Also, RDW and Mg levels were found to be negatively correlated. To our knowledge, this is the first study in the literature that demonstrates the association between RDW and Mg levels in the same patient population.*

Keywords: Inflammation, magnesium, obstructive sleep apnoea syndrome, red blood cell distribution width.

INTRODUCTION

Apnoea refers to the interruption of respiration exceeding 10 seconds during sleep. Obstructive sleep apnoea syndrome (OSAS) is a syndrome characterized by apnoea throughout sleep, periods of hypopnea and accompanying decreased blood oxygen saturation, daytime sleepiness, interruptions of sleep and collapse in the upper airways (1). The severity of the disease depends on the hourly number of apnoea/hypopnoea events during sleep. The mean hourly number of apnoea/hypopnoea events is known as the apnea/hypopnea index (AHI). An AHI of 5–15 is defined as mild OSAS, 15–30 as moderate OSAS and higher than 30 as severe OSAS (2). Obstructive sleep apnoea syndrome leads to complications in several systems. Oxidative stress and chronic inflammation are involved in the pathogenesis of these complications. Inflammatory biomarkers such as interleukin 6 (IL-6) and tumour necrosis factor-alpha (TNF-α) have been shown to increase in patients with OSAS (3).

Red blood cell distribution width (RDW) is a numerical value providing information concerning erythrocyte

From: [1]Department of Otorhinolaryngology, Faculty of Medicine, Ataturk University, Erzurum, Turkey and [2]Department of Chest Diseases, Faculty of Medicine, Ataturk University, Erzurum, Turkey.

Correspondence: Dr K Kilic, Department of Otorhinolaryngology, Regional Training and Research Hospital, Erzurum 25240, Turkey. Email: korhankilic@gmail.com

 DOI: 10.7727/wimj.2017.153

dimensions in complete blood counts. This value showing erythrocyte variability in the circulation is generally used to determine types of anaemia (4). However, studies in recent years have shown that RDW values also increase in the event of chronic inflammation, hypoxia and oxidative stress. Özsu *et al* reported an increase in RDW values in OSAS patients compared to the normal population (5).

Magnesium is the second most abundant cation in intracellular fluid and plays an active role in several biochemical and enzymatic reactions in the body. Magnesium deficiency has been shown to be associated with several diseases (6–8). Low levels of magnesium have also been shown in OSAS, a chronic inflammatory disease (9).

The purpose of this study was to examine serum magnesium and RDW values in OSAS, a chronic inflammation, and thus to reveal the relations between these two parameters and with other sleep parameters. To our knowledge, this is the first study in the literature that demonstrates the association between RDW and Mg levels in the same patient population.

SUBJECTS AND METHODS

The study was performed by examining the records of 360 patients undergoing polysomnography between June 2015 and January 2017 at the Sleep Disorders Laboratory. Ethical committee approval was granted from local Ethics Committee with admission number 2017:1-1. Anamnesis is routinely taken from patients presenting to our Sleep Disorders Laboratory, and a detailed physical examination is performed at which they are weighed and measured, and their body mass index (BMI) values calculated. Blood is also collected from all patients before polysomnography, complete blood count and broad biochemical tests, and medical records are established from these.

Study and control groups were constituted using these medical records in this study. Age, gender, magnesium and RDW values were obtained from all patients' medical records. Values for AHI, SpO_2, mean desaturation level, total sleep time (TST) and total sleep time in which oxygen saturation is below 90% (TST90) were also obtained from the polysomnography records. Based on the polysomnography results, patients with AHI < 5 were enrolled as the control group and those with AHI > 5 as the study group. The medical records of both groups were examined, and subjects with any known haematological disease, diabetes mellitus or kidney disease, rheumatologic and allergic diseases, periodontal diseases, with a history of alcohol use of, with infection findings, with a history of drug intakes such as antihypertensives, inhibitors of proton pump and corticosteroids were excluded.

Polysomnography

Full polysomnography was carried out with the Compumedics E-series Sleep System (Compumedics Sleep, Melbourne, VIC, Australia). Electroencephalography (EEG), electrooculography, electromyography and electrocardiography were performed concurrently. Surface electrodes were attached for the recording of EEG channels, right and left electro-oculographies and submental electromyography. Respiratory flow through one or both nostrils and the mouth was measured using airflow. Inductive plethysmography bands were employed to observe thoracic and abdominal breathing movements, in addition to body position. In terms of pulse oximetry, arterial oxygen saturation was determined from the subject's fingertip. Apnoea was defined as uninterrupted cessation of airflow exceeding 10 seconds in duration, and hypopnea as a 30% or greater decrease in airflow exceeding 10 seconds in duration accompanied by an oxygen desaturation of ≥ 3% or a decrease in thoracic wall movement. AHI was calculated as the total number of apnea and hypopnea events per hour of sleep.

Blood samples

Ten cubic centimetre blood specimens were collected from all patients. These were divided into two parts and placed into blood count and biochemistry tubes. After being kept at +4°C for 1 hour, they were centrifuged at 3000 rpm for 10 minutes. Red cell distribution width levels were studied from the plasma obtained using an autoanalyzer (Sysmex XN 9000, Kobe, Japan) and magnesium tests were performed from the serum using an autoanalyzer (Beckman Coulter AU 5800, Brea, California, USA).

Statistical analysis

Statistical analysis was performed on SPSS 17.0 software. The Mann–Whitney *U* test was used for comparisons between the groups. Spearman's correlation test was used for correlation calculations $p < 0.05$ was regarded as significant for all calculations.

RESULTS

Out of 360 patients, 150 patients, whose medical records were examined, were excluded for meeting exclusion

criteria. One hundred sixty patients (99 male, 61 female) aged between 22 and 69 (51.1 ± 12) and a 50-member control group (34 male, 16 female) aged between 37 and 68 (49.9 ± 4.8) were included in the study. There was no significant difference between the groups in terms of gender or age ($p > 0.05$). Also, there was no statistically significant difference in haemoglobin values between the control and study group ($p = 0.54$).

Red cell distribution width values of the patients in the study group were statistically significantly higher compared to those of the control group ($p < 0.001$). The magnesium levels of the patient group were significantly lower compared to those of the control group ($p < 0.001$) (Figure).

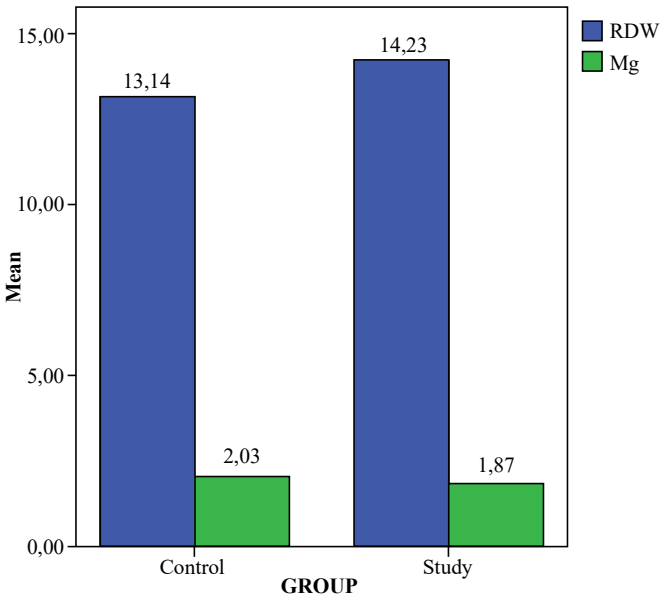

Figure: Mg and RDW values of groups. RDW = red cell distribution width.

In terms of study and control group polysomnography data, AHI was 41.6 ± 29.7 in the study group and 2.5 ± 1.2 in the control group. Desaturation rates and TST90 values were significantly higher in patients with OSAS compared to the control group, while TST and SpO_2 were significantly lower ($p < 0.001$). Demographic data, laboratory and polysomnographic parameters for the two groups are shown in Table 1.

Table 1: Comparison of parameters of OSAS and control groups

	Control (n = 50)	Study (n = 160)	*p*
Age	52 ± 5	51.1 ± 12	= 0.89
Gender (M/F)	34/16	99/61	> 0.05
BMI	27.4 ± 2.3	28.2 ± 2.7	= 0.06
RDW (%)	13.1 ± 0.8	14.2 ± 1.5	< 0.001*
Hgb (g/dL)	13.5 ± 0.9	13.7 ± 1.1	= 0.54
Mg (mg/dL)	2 ± 0,1	1.8 ± 0.1	< 0.001*
AHI	2.5 ± 1.2	41.6 ± 29.7	< 0.001*
SpO_2	93.3 ± 1.5	85.9 ± 8.3	< 0.001*
TST (minute)	341.8 ± 60.9	311.9 ± 76.5	= 0.01*
Desaturation ratio	3.4 ± 0.9	6.9 ± 3.1	< 0.001*
TST90 (minute)	5.2 ± 18.7	139.1 ± 108.6	< 0.001*

*: Statistically significant.
AHI = apnea–hypopnea index; BMI = body mass index; RDW = red cell distribution width; TST = total sleep time; TST90 = total sleep time in which oxygen saturation is below 90%.

The results of Spearman correlation analysis performed to identify correlations between variables are summarized in Table 2. Positive correlation was observed between RDW and AHI ($r = 0.349$, $p < 0.001$), BMI ($r = 0.434$, $p < 0.001$), desaturation rate ($r = 0.378$, $p < 0.001$) and TST90 ($r = 0.334$, $p < 0.001$), while negative correlation was observed between RDW and SpO_2 ($r = -0.425$, $p < 0.001$) and total sleep time ($r = -0.142$, $p < 0.05$). Magnesium was negatively correlated with AHI ($r = -0.285$, $p < 0.001$), BMI ($r = -0.282$, $p < 0.001$), desaturation rate ($r = -0.233$, $p < 0.001$) and TST90 ($r = -0.230$, $p < 0.001$), and positively correlated with SpO_2 ($r = 0.234$, $p < 0.001$) and total sleep time ($r = 0.170$, $p < 0.05$). In addition, negative correlation was determined between RDW and magnesium ($r = -0.266$, $p < 0.001$).

DISCUSSION

Our study findings showed that magnesium levels were significantly lower in patients with OSAS compared to the control group, while RDW values were significantly higher compared to the control group. The RDW and Mg levels were found to be related to the severity of OSAS. Also, we have found a negative correlation

Table 2: Spearman correlation test between serum Mg level, BMI, RDW and polysomnographic parameters

		AHI	SpO2	BMI	TST	Desaturation ratio	TST90	Mg
RDW	*r*	0.349**	−0.425**	0.434**	−0.142*	0.378**	0.334**	−0.266**
Mg	*r*	−0.285**	0.234**	−0.282**	0.170*	−0.233**	−0.230**	

**: Correlations significant at 0.01 level.
*: Correlations significant at 0.05 level.
AHI = apnea–hypopnea index; BMI = body mass index; RDW = red cell distribution width; TST = total sleep time; TST90 = total sleep time in which oxygen saturation is below 90%.

between serum RDW and Mg levels. To our knowledge, this is the first study in the literature that demonstrates the association between RDW and Mg levels in the same patient population.

Obstructive sleep apnoea syndrome is a syndrome characterized by obstruction of the upper airway that causes complete interruption of airflow in the mouth and nose during sleep (apnoea) or a decrease (hypopnoea). The episodes of apnoea/hypopnoea are generally accompanied by loud snoring and a reduction in blood oxygen saturation. These episodes typically conclude with sleep interruptions and short arousals, leading to a decrease in REM sleep (10). Patients with OSAS are generally unaware of these sleep interruptions, and this condition is the main cause of daytime sleepiness. Obstructive sleep apnoea syndrome affects 4% of males and 2% of females in the adult population (11). It is significantly associated with morbidity and mortality. Excessive daytime sleepiness may lead to impairments in cognition and social performance and a serious lowering of quality of life. It may even lead to an increase in traffic accidents.

The inflammatory process leading to endothelial dysfunction plays an important role in the pathogenesis of OSAS. In addition, while sympathetic stimulation, oxidative stress, increased coagulation and metabolic impairment have been implicated in the pathogenesis, considering the complex nature of OSAS, the pathogenesis is probably multifactorial. The hypoxia that occurs in OSAS is intermittent hypoxia characterized by reoxygenation cycles following brief desaturations. Intermittent hypoxia plays an important role in the start of the inflammatory process in OSAS (12, 13). The importance of the inflammatory process in the pathogenesis of OSAS has been supported by studies showing high levels of proinflammatory cytokines, chemokines and adhesion molecules in the circulation (14). However, the mechanism underlying the inflammatory process has not yet been fully explained.

Several parameters have been investigated in studies performed in order to elucidate the pathogenesis of chronic inflammation in OSAS, one such being the acute phase reactant CRP. The results of studies concerning CRP levels in OSAS are questionable. There are studies reporting an increase in CRP levels. At the same time, CRP levels have also been reported to be correlated with the severity of OSAS (15). In contrast, there are also studies showing no increase in CRP levels (16, 17). However, in a meta-analysis by Nadeem *et al*, higher CRP values were reported in patients with OSAS in the majority of studies (18).

C-reactive protein is more an inflammatory mediatory marker of acute inflammatory events. Red cell distribution width can provide more important information than CRP in the evaluation of chronic inflammatory events. RDW is an inexpensive, easily obtained parameter that that provides information about erythrocyte dimensions. Several studies performed in recent years have reported that RDW increases in conditions such as coronary artery disease, cerebrovascular diseases, heart failure and diabetes, and also that high RDW values in these diseases are correlated with mortality and morbidity (19–21). In the light of these studies, RDW emerges as a novel prognostic marker reflecting chronic inflammation and oxidative stress. Since OSAS is also a condition characterized by increased oxidative stress and chronic inflammation, increased RDW levels in these patients may be associated with the severity of the disease and the development of complications. In this study, we determined significantly higher RDW values in patients with OSAS compared to the control group. Additionally, we determined that RDW levels were positively correlated with AHI, mean desaturation rate and TST90. These results show that RDW values are directly associated with disease severity.

Our results showed that magnesium levels in patients with OSAS were significantly lower compared to the control group. At the same time, we determined that magnesium levels were associated with the severity of the disease. Various studies have shown that magnesium deficiency is a risk factor, as a cause of chronic inflammatory stress, in several diseases including metabolic syndrome, cardiovascular diseases and diabetes mellitus (22–24). Karamanlı *et al* reported significantly lower magnesium levels in patients with OSAS compared to a control group and that this exhibited a negative correlation with AHI and CRP (9). We also determined a negative correlation between magnesium levels in patients with OSAS and AHI, mean desaturation rate and TST90.

We also determined that magnesium levels exhibited a negative correlation with RDW. However, the reason for this change in magnesium levels in patients with OSAS has not yet been explained. The most commonly implicated factor is inflammation, although we do not yet know whether low magnesium in OSAS is a cause or the result of inflammation. From another perspective, considering the role of magnesium in muscle activity, we thought that low magnesium in patients with OSAS might be associated with muscle overactivity in order to overcome apnoea. However, since our study contains no

detailed information capable of illuminating this, further studies concerning the role of muscle activity in patients with OSAS in low magnesium levels are now needed.

CONCLUSION

We determined that serum magnesium levels decreased in the presence of OSAS and that this is related to the severity of OSAS. Similarly, we observed that RDW values increased in patients with OSAS and exhibited a significant correlation with AHI. Also, RDW and Mg levels were found to be negatively correlated. To our knowledge, this is the first study in the literature that demonstrates the association between RDW and Mg levels in the same patient population. Polysomnography will remain the gold standard in the diagnosis of OSAS, but low magnesium values and elevation in RDW values in a patient with suspected OSAS must alert the clinician to the administration of polysomnography.

ACKNOWLEDGEMENT

The authors wish to thank all the patients included in this study.

AUTHORS' NOTE

Compliance with ethical standards: 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.

Statement of Author Contributions: All authors participated in the design, interpretation of the studies, analysis of the data, review of the manuscript and approved final version; KK, MSS, OA and MSG conducted the study. KK and MSS wrote the manuscript. The authors declare that they have no conflicts of interest.

Human Research Ethics Clearance: Ethical committee approval was granted from the local Ethics Committee with admission number 2017:1-1.

REFERENCES

1. The International Classification of Sleep Disorders. Diagnostic and Coding Manual. In: ASDA-Diagnostic Classification Steering Committee. 2nd edn. Lawrence, KS: Allen Press Inc.; 1997: 52.
2. Sökücü SN, Karasulu L, Dalar L, Seyhan EC, Altın S. Can red blood cell distribution width predict severity of obstructive sleep apnea syndrome? J Clin Sleep Med 2012; **8:** 521–5.
3. Liu H, Liu J, Xiong S, Shen G, Zhang Z, Xu Y. The change of interleukin-6 and tumor necrosis factor in patients with obstructive sleep apnea syndrome. J Tongji Med Univ 2000; **20:** 200–2.
4. Gorelik O, Izhakian S, Barchel D, Almoznino-Sarafian D, Tzur I, Swarka M, Beberashvili I, Feldman L, Cohen N, Shteinshnaider M. Changes in red cell distribution width during hospitalization for community-acquired pneumonia: clinical characteristics and prognostic significance. Lung 2016; doi: 10.1007/s00408-016-9942–8.
5. Ozsu S, Abul Y, Gulsoy A, Bulbul Y, Yaman S, Ozlu T. Red cell distribution width in patients with obstructive sleep apnea syndrome. Lung 2012; **190:** 319–26
6. Barbagallo M, Dominguez LJ. Magnesium and type 2 diabetes. World J Diabetes 2015; **6:** 1152–7.
7. Kolte D, Vijayaraghavan K, Khera S, Sica DA, Frishman WH. Role of magnesium in cardiovascular diseases. Cardiol Rev 2014; **22:** 182–92.
8. Van den Bergh WM, Algra A, Van der Sprenkel JW, Tulleken CA, Rinkel GJ. Hypomagnesemia after aneurysmal subarachnoid hemorrhage. Neurosurgery. 2003; **52:** 276–81.
9. Karamanli H, Kizilirmak D, Akgedik R, Bilgi M. Serum levels of magnesium and their relationship with CRP in patients with OSA. Sleep Breath 2016. doi: 10.1007/s11325-016-1402-4.
10. Guilleminault C, Tilkian A, Dement WC. The sleep apnea syndromes. Annu Rev Med 1976; **27:** 465–84.
11. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; **328:** 1230–5.
12. Ryan S, Taylor CT, McNicholas WT. Systemic inflammation: a key factor in the pathogenesis of cardiovascular complications in obstructive sleep apnoea syndrome? Thorax 2009; **64:** 631–6
13. Ryan S, McNicholas WT. Intermittent hypoxia and activation of inflammatory molecular pathways in OSAS. Arch Physiol Biochem 2008; **114:** 261–6.
14. Minoguchi K, Tazaki T, Yokoe T, Minoguchi H, Watanabe Y, Yamamoto M, Adachi M. Elevated production of tumor necrosis factor-alpha by monocytes in patients with obstructive sleep apnea syndrome. Chest 2004; **126:**1473–9.
15. Shamsuzzaman AS, Winnicki M, Lanfranchi P, Wolk R, Kara T, Accurso V, Somers VK. Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation 2002; **105:** 2462–4.
16. Ryan S, Nolan GM, Hannigan E, Cunningham S, Taylor C, McNicholas WT. Cardiovascular risk markers in obstructive sleep apnoea syndrome and correlation with obesity. Thorax 2007; **62:** 509–14.
17. Fornadi K, Lindner A, Czira ME, Szentkiralyi A, Lazar AS, Zoller R, Turanyi CZ, Veber O, Novak M, Mucsi I, Molnar MZ. Lack of association between objectively assessed sleep disorders and inflammatory markers among kidney transplant recipients. Int Urol Nephrol 2012; **44:** 607–17.
18. Nadeem R, Molnar J, Madbouly EM, Nida M, Aggarwal S, Sajid H, Naseem J, Loomba R. Serum inflammatory markers in obstructive sleep apnea: a meta-analysis. J Clin Sleep Med 2013; **9:** 1003–12.
19. Siegler JE, Marcaccio C, Nawalinski K, Quattrone F, Sandsmark DK, Maloney-Wilensky E et al. Elevated red cell distribution width is associated with cerebral infarction in aneurysmal subarachnoid hemorrhage. Neurocrit Care 2016. doi: 10.1007/s12028-016-0306-2.
20. Tonelli M, Sacks F, Arnold M, Moye L, Davis B, Pfeffer M. Relation between red blood cell distribution width and cardiovascular event rate in people with coronary disease. Circulation 2008; **117:** 163–8.
21. Magri CJ, Fava S. Red blood cell distribution width and diabetes-associated complications. Diabetes Metab Syndr 2014; **8:** 13–7
22. Qu X, Jin F, Hao Y, Li H, Tang T, Wang H, Yan W, Dai K. Magnesium and the risk of cardiovascular events: a meta-analysis of prospective cohort studies. PLoS One 2013; **8:** e57720
23. Wang J, Persuitte G, Olendzki BC, Wedick NM, Zhang Z, Merriam PA et al. Dietary magnesium intake improves insulin resistance among non-diabetic individuals with metabolic syndrome participating in a dietary trial. Nutrients 2013; **5:** 3910–9.
24. Xu J, Xu W, Yao H, Sun W, Zhou Q, Cai L. Associations of serum and urinary magnesium with the pre-diabetes, diabetes and diabetic complications in the Chinese Northeast population. PLoS One 2013; **8:** e56750.