



RELATIONSHIP BETWEEN SERUM ASYMMETRIC DIMETHYLARGININE LEVEL AND OBSTRUCTIVE SLEEP APNEA SYNDROME SEVERITY

SERUM ASİMETRİK DİMETİL ARJİNİN DÜZEYİ VE OBSTRÜKTİF UYKU APNE SENDROMU AĞIRLIĞI ARASINDAKİ İLİŞKİ

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Abstract

Aim: The repetitive hypoxemia can induce oxidative stress mechanisms. Oxidative stress increases serum asymmetric dimethylarginine (ADMA) levels in patients with obstructive sleep apnea syndrome (OSAS). To investigate the relationship between serum levels of ADMA and OSAS severity. **Methods:** 330 patient's records, who underwent overnight polysomnography (PSG) were retrospectively examined. The patients who had an abnormal serum glucose, lipid, thyroid, renal and liver function tests levels, had excluded. 72 patients had participating criteria. Patients were categorized into five groups according to apnea/hipopnea index (AHI). Measurement of ADMA levels were performed by ELISA kit.

Results: The mean age was $44,19 \pm 14,24$ years. 31,9 % of the patients were female. Patients in normal group, severe, medium, mild and positional-REM dependent OSAS group were 26,4%, 25%, 6,9 %, 16,7% and 25%; respectively. A significant positive correlation was found between AHI and ADMA ($r= 0,483$; $p<0,001$). Appropriate cut-off criterion was set at 1,39 for ADMA. Sensitivity for this value was 73,58 % (95 % Confidence Interval (CI): 61,71- % 85,45 %) and specificity was 94,74 % (95 % CI: 84,70- % to 100%). Accuracy or correct classification rate was found to be 79,17 %. The positive predictive value was 97,5 % and negative predictive value was 56,25 %. The positive likelihood ratio (LR+) was 13,98 ($LR+ > 10$) and the negative likelihood ratio was ($LR- 0,28$ ($R- < 1$)).

Conclusions: ADMA was found to be a strong and good diagnostic tool among patients with normal levels for glucose, lipid, TSH, creatinine and liver function tests.

Keywords: Obstructive sleep apnea, hypoxemia, ADMA

Öz

Amaç: Obstrüktif Uyku Apne Sendromu (OUAS) olan hastalarda ortaya çıkan tekrarlayan hipoksemi ve reoksijenasyon oksidatif stres mekanizmalarını tetikleyebilir. Oksidatif stres OUAS hastalarında Asimetrik dimetilarginin (ADMA) düzeylerini artırır. Çalışmamızda Serum Asimetrik Dimetil Arjinin (ADMA) düzeyi ve Obstrüktif Uyku Apne Sendromu (OUAS) ağırlığı arasındaki ilişkiyi incellemeyi amaçladık.

Yöntemler: Polisomnografi yapılan 330 hasta kayıtları retrospektif olarak değerlendirildi. Anormal serum glukozu, lipid, tiroid, böbrek ve karaciğer bozuklukları olan hastalar çalışma dışı bırakıldı. Kabul kriterleri 72 sağladı. Hastalar apne hipopne indekslerine göre beş gruba ayrıldılar. Asimetrik Dimetil Arjinin ölçümüleri ELISA kiti ile yapıldı.

Bulgular: Ortalama yaşı $44,19 \pm 14,24$ idi. Hastaların %31,9'u kadınlandı. Hastalar normal, ağır, orta, hafif, rem-pozisyonel olarak gruplandı; %26, %25, %6,9, %16,7 ve %25 oranlarında dayandılar. AHI ve ADMA arasında anlamlı korelasyon saptandı ($r= 0,483$; $p<0,001$). ADMA için uygun cut-off değeri 1,39 olarak belirlendi. Bu değer için duyarlılık %73,58 (%95 güven aralığı (CI): 61,71- % 85,45 %), özgünlük %94,74 (95 % CI: 84,70- %100%) idi. Doğruluk ya da doğru sınıflandırma oranı %79,17 olarak bulundu. Pozitif kestirim değeri %97,5 ve negatif kestirim değeri ise %56,25 idi. Pozitif olabilirlik oranı (LR+) 13,98 ($LR+>10$) ve negatif olabilirlik oranı (LR-) 0,28 ($LR-<1$) olarak saptandı.

Sonuç: ADMA test yöntemi; normal glukoz, lipid, tiroid, karaciğer ve böbrek fonksiyon testine sahip hastalarda, güçlü ve iyi bir tanı testi kriteri olma özelliklerine sahip olabilir.

Anahtar Kelimeler: Obstrüktif uyku apne sendromu, hipoksemi, ADMA



Introduction

Obstructive Sleep Apnea Syndrome (OSAS) is the most commonly observed reason for the lack of sleep (insomnia) in the adulthood phase, concerning many systems in the body, which progresses along with the repeating obstruction of the upper airway during sleep¹⁻³. OSAS is also the source of serious morbidity and mortality with its cardiovascular results as well as its social and neuropsychological results⁴⁻⁶.

Hypoxia and reoxygenation which show up and repeat in the patients suffering from an obstructive sleep apnea induce oxidative stress mechanisms⁷.

Decreasing dimethylarginine dimethylaminohydrolase (DDAH) and increasing Protein arginine N-methyltransferase 1 (PRMT-1) enzymes as a result of the oxidative stress appeared in the OSAS cause the Asymmetric Dimethylarginine (ADMA) level rise, increased ADMA serum levels decrease Nitric acid (NO) levels inhibiting Endothelial NOS (e-NOS) activity and causes endothelial dysfunction with the said mechanism.

Golden standard in OSAS is Polysomnography (PSG)⁸. However, the technical hardware requirement and the fact that the survey takes a long time causes that the process when the patients with obstructive sleep apnea syndrome take diagnosis and start the treatment is prolonged.

Our purpose is to investigate the employability of the ADMA in foreseeing the presence and severity of OSAS.

Materials and Methods

This study has been carried out on successive 330 persons who have been applied to the Sleep Clinic of Chest Diseases in the Medical Faculty of Düzce University between August 2011 and August 2013 with complaints of sleep disorders and undergone a polysomnography throughout the night with the informed consent of the relevant patients. A 9 ml of blood taken for hemogram and biochemistry has been put

into K3 EDTA and biochemistry tubes in the morning at the end of the night through which the polysomnography was applied. Other parameters than ADMA have been studied without losing time by means of the Pentra DX 120-Pentra XL 80 devices available in the Microbiology-CBC-Biochemistry Laboratories. Samples taken to be able to measure ADMA values have been frozen at 80° C after they were centrifuged and their plasma has been extracted by a single physician. ADMA levels have been directly measured from the blood of the selected patient group employing ELISA kit (from Immunodiagnostik AG), enzyme-linked immunosorbent assay method.

Patient files have been examined retrospectively. Cases with apnea-hypopnea index ≥ 5 were considered to be OSAS. Three patients due to their central sleep apnea, and 253 persons because of their laboratory anomalies such as high glucose, lipid levels have been extracted from the study. According to the AHI indexes, 72 patients involved in the study have been divided into groups with the following numbers: 19 normal, 12 light sleep apnea, 5 mild sleep apnea, 18 severe sleep apnea and 18 positional/REM-related sleep apnea.

The descriptive statistics have been calculated for all data in the study (mean, standard deviation, median, minimum, maximum, percent values). Levene and Shapiro-Wilk tests have been carried out in order to control the homogeneity of variances and normality assumptions. One-Way ANOVA (post hoc Tukey test) and Kruskal-Wallis (post-hoc Dunn's test) tests have been employed in the comparison between the groups. McSweeney and Porter's Rank ANCOVA (post hoc Bonferroni test) tests have been carried out in order to eliminate the effects of confounding factors between the groups. Fisher-Freeman-Halton test has been utilized in order to examine the relationships between categorical variables. Degree and direction of the relationship between two variables have been found by Partial Correlation test while controlling the effect of confounding factor. ROC analysis



has been performed in order to determine the suitable cut-off value for the diagnostic test. $p<0.05$ was considered to be statistically significant. PASW 18 software program and specially written macros have been utilized. The Research and Ethics Committee of the Düzce University approved the study (March 2012/93).

Results

Our patients were grouped as 26.4% normal ($n=19$), 25% severe ($n=18$), 25% position-rem dependent ($n=18$), 16.7% mild ($n=12$), 6.9% moderate ($n=5$) OSAS according to AHI. Mean age was 44.19 ± 14.24 . There was a statistically significant difference between the groups as of age ($p=0.041$). The difference was detected between the normal and moderate groups ($p=0.035$). The age variable was detected as the confounding factor. 3. 9% of the patients participating in our survey were women ($n=23$). No statistically significant difference was detected between the groups in respect of gender ($p=0.525$). There was not a difference between the groups in respect of BMI ($p=0.551$). There was a difference between REM, N1, N2, N3 durations of the groups ($p=0.093$).

Statistical analysis was performed by eliminating the age effect in all group comparisons. When the effect of confounding factor (age) and average and minimum oxygen values are under control, a positive correlation was detected between the ADMA and AHI values ($r= 0.483$, $p<0.001$).

In respect of ADMA levels, it was seen that there was a statistically significant difference between the groups ($p<0.001$) (Table 1). As a result of multiple-comparisons, a statistically significant difference was detected between the severe and positional-rem dependent patient groups and normal, mild and moderate, moderate vs severe, OSAS patient groups. The results of comparison of differences between the groups in respect of min SO₂, mean SO₂, desaturation index, nighttime passed as <%90 was given Table 2. It was found that there were statistically significant difference between the groups in respect of mean SO₂, min SO₂ desaturation index, night time passed as <%90 levels. Moreover, negative correlations were detected between ADMA and average SO₂ ($r=-0.311$, $p=0.011$) and Min SO₂ ($r=-0.291$, $p=0.014$). A positive correlation was detected between ADMA and desaturation index ($r= 0.439$, $p<0.001$). But the significant relationship between the percentage of nighttime saturation as <90 and ADMA was not detected ($p>0.05$).

Table 1. ADMA levels of the groups

Group	n	Mean± SD	Median	Min	Max	p
Normal	19	0,87±0,34	0,88	0,28	1,41	
Mild	12	1,24±0,71	0,94	0,38	2,26	
Moderate	5	0,89±0,13	0,89	0,71	1,04	<0,001
Severe	18	2,19±0,16	2,17	1,98	2,47	
Pos-Rem	18	2,02±0,50	2,13	0,08	2,41	
Total	72	1,55±0,71	2,02	0,08	2,47	

SD: Standard Deviation; $p<0.001$ values for the comparison of normal vs. severe, pos-rem, mild vs. severe, moderate vs. severe; $p=0.004$ value for the comparison of moderate vs. pos-rem; $p=0,011$ value for the comparison of mild vs. pos-rem



Table 2. The descriptive statistics of Min SO₂, mean SO₂, desaturation index, nighttime passed as <%90 according to groups

	Normal (n=19)	Mild (n=12)	Moderate (n=5)	Severe (n=18)	Pos-rem (n=18)	Total (n=72)	p
<i>meanSO₂*</i>							
Mean± SD	96,11±1,05	95,25±1,71	95,60±0,55	94,17±1,92	96,00±0,97	95,42±1,57	
Median (min- max)	96 (94-98)	96 (91-97)	96 (95-96)	95 (89-96)	96 (95-98)	96 (89-98)	0,001
<i>minSO₂£</i>							
Mean± SD	87,68±6,31	86,58±3,48	85,00±5,10	75,28±10,55	84,83±6,58	83,50±8,63	
Median (min- max)	89 (73-95)	86,5 (79-92)	84 (78-90)	80 (55-88)	86 (71-94)	85 (55-95)	<0,001
<i>desaturation index</i> ¢							
Mean± SD	2,69±3,49	7,23±4,23	14,78±14,97	51,26±29,77	14,58±9,67	19,40±24,85	
Median (min- max)	1,4 (0-14,5)	7,05 (1,3-15,4)	8,6 (1,5-39,1)	58,6 (0-104,3)	16,6 (0,8-34)	8,15 (0-104,3)	<0,001
<i>uykudesattime</i> ª							
Mean± SD	0,65±0,97	2,38±1,66	4,82±4,65	20,76±13,24	5,20±4,03	7,39±10,54	
Median (min-max)	0,2 (0-3,8)	2,4 (0,3-6,4)	2,1 (0,6-11,4)	19,5 (0-41)	4,9 (0-13,8)	2,5 (0-41)	<0,001

SD: Standard Deviation, Min-Max: Minimum-Maximum; *: p=0,002 value for the comparison of normal vs. severe; p=0,005 value for the comparison of severe vs. pos-rem; £: p<0,001 value for comparison of normal vs. severe; p=0,004 value for the comparison of mild vs. severe; p=0,010 value for the comparison of severe vs. pos-rem; ¢: p≤0,001 value for the comparison of normal vs. severe and pos-rem; ¤: p=0,001 value for the comparison of groups mild vs. severe; p=0,019 value for the comparison of severe vs. pos-rem; ª: p<0,001 value for the comparison of normal vs. severe and pos-rem; p=0,001 value for the comparison of mild vs. severe; p=0,017 value for the comparison of severe vs. pos-rem

The differences between the groups in respect of serum glucose (p=0,727), total cholesterol (p=0,504) and ldl (p=0,518) values were not significant.

It was determined that ADMA test method can be used as a diagnosis criteria (area under the curve (AUC)=0,84, p<0,001). Best cut-off value for ADMA was determined as 1,39. For this value, the sensitivity was 73,58% (95% Confidence Interval (CI): %61,71-%85,45) and Specificity was 94,74% (95% CI: 84,70%-100%) (Figure 1). Accuracy or true classification rate was found as 79,17%. Positive predictive value was 97,5% and negative predictive value was 56,25%. Positive likelihood ratio (LR+) was detected as 13,98 (LR+>10) and negative likelihood ratio (LR-) was detected as 0,28 (LR-<1). According to the results, ADMA test has the properties of a strong and good diagnostic test.

Discussion

As a result of our study, a significant correlation has been observed between minimum oxygen saturation, mean oxygen saturation, Oxygen desaturation Index and AHI values. It has been determined that the ADMA test method has the features to be a strong and good diagnostic test criteria in people whose fasting blood glucose, LDL, triglyceride, TSH, creatinine, liver function tests are within normal limits.

OSAS is a disease characterized by recurred airflow restriction or block due to contraction of the airways^{9,10}. Excessive daytime sleepiness arising due to fragmentation of sleep gives rise to failure at work, work and traffic accidents, repetitive nocturnal hypoxia leads to certain physiological diseases.



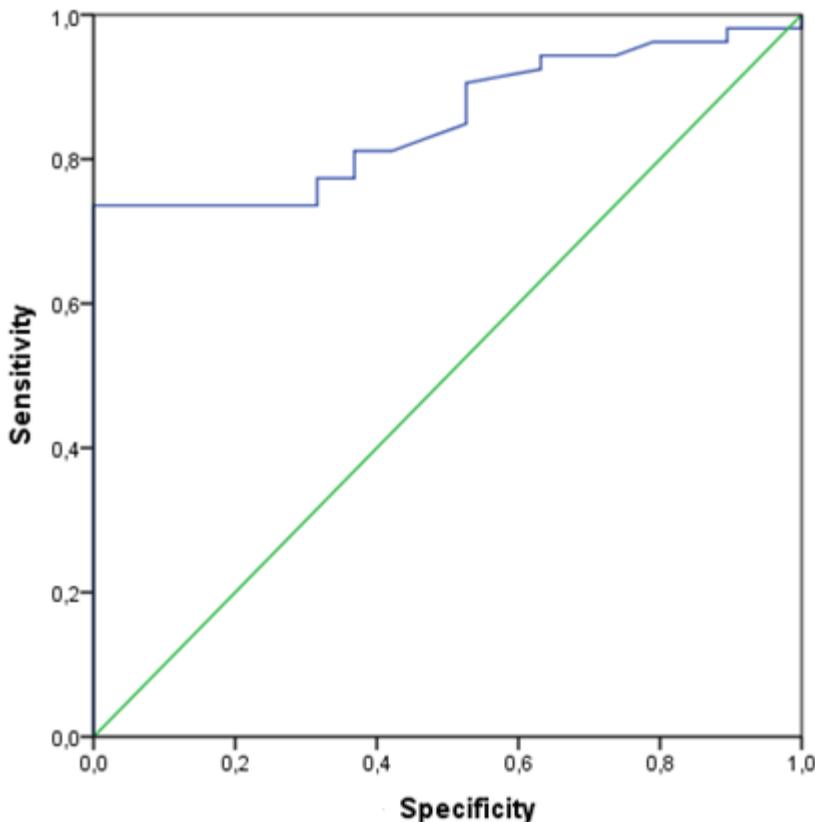


Figure 1. ROC curve of ADMA test

Therefore, patients with OSAS have a high incidence of hypertension, arrhythmias, coronary artery diseases and congestive heart failure^{11,12}. Polysomnography PSG is considered the gold standard in the diagnosis of sleep disordered breathing and is recommended by the American Sleep Disorders Association [American Sleep Disorders Association (ASDA)]^{13,14}.

As polysomnography is a difficult to reach, hard to apply, laborious and expensive test, alternative additional diagnosis methods are being investigated. We do not have a good preliminary test, which shall foresee to which patients primary PSG shall be applied. In our working group, ¼ of the patients to whom PSG was applied were detected to be normal. And this prevents us from making use of the laboratories

effectively, diagnosis and treatment for real patients are delayed.

ADMA is a methylated arginine derivative whose importance is increasing, and which occurs as a result of the protein arginine methyl transferase (PRMT) enzyme adding methyl groups following synthesis with regulation to the arginine residue in the nucleoproteins, and the destruction of these proteins¹⁵. The protein bound ADMA which occurs as a result of the methylation of the protein bound arginine has no inhibitor effect on the NOS enzyme. For this inhibition, free ADMA caused by the proteolysis of methylated protein is required.

A large portion of the free ADMA which occurs in the cell as a result of proteolysis, is immediately destroyed by the dimethylaminohydrolase (DDAH) enzyme in the cell. A small portion however escapes

intracellular degradation and enters the bloodstream. This small amount of ADMA entering the bloodstream, is either excreted unchanged through the kidneys in urine, or is taken back into the cells through liver and kidneys and is metabolized by the DDAH enzyme¹⁶. In cases of increased oxidative stress in the body, an increase in ADMA levels occurs. This increase in ADMA levels may be due to a decrease in DDAH enzyme activity. In the reduction of activity, the oxidation of cysteine in the active area of DDAH is important. This oxidation can be accomplished by NO and thus its activity can be recycled and reduced^{17,18}. Inducible NOS (iNOS) activity increases greatly with inflammation, and NO is produced in very large quantities. The produced NO combines with superoxide (O_2^-) radicals, becoming peroxynitrite ($ONOO^-$) and reduces the half-life of NO (19). The formation of peroxynitrite occurs faster than the capture of superoxide radicals by superoxidizedismutase (SOD). Peroxynitrite binds to the active area of DDAH and reduces its activity, thus leading to an increase in ADMA amount and a reduction in NO levels. Oxidative stress changes the activity of enzymes with a role in ADMA production and leads to a change in ADMA amounts¹⁹. PRMT activity is increased with reactive oxygen species and ADMA levels increase²⁰.

In a study by Christou et al, the antioxidant capacity of patients with OSAS were found to be close to the antioxidant capacity of health individuals. However, in patients with severe OSAS diagnosis, as a reflection of extreme oxidative stress, low antioxidant capacity has been determined²¹.

Some researchers have displayed those pigs exposed to hypoxia have inhibited DDAH activity. DDAH activity and expression has lowered in newborn primary pulmonary

hypertension. This explains the reduction of NOS activity in patients and the increased ADMA levels²².

We also believe that increased ADMA in OSAS can also be explained with another mechanism. The low oxygen levels occurring in OSAS, leads to an increase in hypoxia-inducible factor 1 (HIF-1) levels providing the activation of genes responsible for EPO, VEGF, glucose transporter and glycolytic enzyme transcription. Studies have shown that, with intracellular and extracellular oxidative stress of erythropoietin reduces DDAH enzyme activity²³. Erythropoietin levels have been shown to be higher in OSAS patients than healthy group²⁴. These results are suggestive of increased erythropoietin levels secondary to hypoxia in OSAS patients and oxidative agents inhibition of DDAH enzyme may raise ADMA levels.

Setting off from the point of could there be another alternative examination to PSG, have considered that increased erythropoietin levels secondary to hypoxia in OSAS patients and oxidative agents inhibition of DDAH enzyme may raise ADMA levels and have seen that the results of our study and information in literature support our hypothesis.

When health, mild, moderate, severe, Positional-Rem dependent OSAS groups were compared in our study, we determined a significant difference in terms of ADMA levels between the groups

We determined a significant positive correlation between AHI, defined as the number of apnea and hypopnea, forming the basis of hypoxia in OSAS patients, per sleep hour and ADMA values. In a study by A. Barcelo et al, a tendency to increased ADMA levels in severe OSAS patients was found, but a statistical difference could not be determined. This result is suggestive of increased



ADMA in OSAS patients being due to obesity and metabolic disorders^{25,26}.

However, in our study groups there was no significant difference in terms of BMI and metabolic parameters, and any parameters that could impact the determined ADMA values such as age, average, minimum oxygen values were controlled. Despite the serum markers studied in patients being different, the mediator release mechanism being based on our oxidative stress hypothesis supports our results.

In the study conducted by In et al, a positive correlation was determined between ADMA levels and the duration when the saturation was <%90²⁶. According to our findings, when the confounding factors (age) are eliminated and the groups compared, a significant difference has been determined between the groups in terms of average oxygen saturation (SO_2) and minimum SO_2 . When the confounding factor impact (age) is controlled, a significant negative correlation has been determined between ADMA and minimum SO_2 . An increase in ADMA with the increased lowest oxygen saturation measured overnight of patients has shown a result consistent with our hypothesis.

We have determined a significant positive correlation between the oxygen desaturation index, defined as the number of oxygen desaturations per hour during sleep and ADMA.

Conclusion

In our study, it was determined that ADMA test method has the properties of being a strong and good diagnosis test criteria for people, whose fasting blood glucose, ldl, triglyceride, tsh, creatinine, liver function tests are at normal levels.

PSG is expensive, having limited accessibility and a time-consuming technique. Employment of such technique in the properly selected patient groups will lessen the laboratories patient loads and prevent the real patients from being destitute of diagnosis and therapy for a long time. A study related to this very subject is required, which will be prospective, have more advanced control and also include the results of therapy.

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Author contributions

Both all authors contributed to the drafting and revising of the article. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical approval

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