Periodico di Mineralogia Volume 94, No. 6, 2025
ISSN: 0369-8963

THE EFFECT OF POSITIVE AIRWAY PRESSURE THERAPY IN OBSTRUCTIVE SLEEP APNEA ON ASYMMETRIC DIMETHYL ARGININE (ADMA) LEVELS

Dr. Mustafa Murat ÖZTÜRK[1]

1 Kırşehir Ahi Evran Universty, Vocational School of Health Services,
https:// orcid.org/0000-0002-2302-0018, mustafa.ozturk@ahievran.edu.tr

ABSTRACT

Objective: Obstructive sleep apnea (OSA) is a common sleep disorder characterized by recurrent upper airway obstructions and hypoxemia, which increases the risk of cardiovascular morbidity. Endothelial dysfunction is known to be an important biological mechanism in OSA. Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase, is associated with endothelial damage. The aim of our study was to determine the relationship between serum ADMA levels and OSA and to investigate the effect of positive airway pressure therapy.

Methods: Patients who underwent polysomnography (PSG) recording at the Sleep Disorders Center were included in the study. Ethical committee approval was obtained for the study protocol. The patients' age, gender, habits, comorbidities, height, weight, body mass index (BMI), neck circumference, waist circumference, and PSG parameters were recorded on the study form. The patient and control groups were randomly selected so that no significant differences were found between them in terms of age, gender, body mass index, and symptom frequency ($p>0.05$).

OSA cases with an AHI value above 30 were included in the study. The control group was selected from simple snoring cases with an AHI <5. Blood samples were taken in the morning on an empty stomach following PSG recording. Blood samples taken from the peripheral vein in the patient and control groups were centrifuged at 3000 rpm for 10 minutes, and the separated serum was stored at -80°C until the time of analysis. Patients diagnosed with OSA and planned to receive positive airway pressure (PAP) therapy were designated as the treatment group. Blood samples were collected in the morning after a 1-night fast from patients who had used adequate PAP therapy for 3 months. Following centrifugation, the samples were stored at -80°C. ADMA levels were measured in the blood samples taken from the patients on the morning of the test using the ADMA direct ELISA kit (Immunodiagnostic AG) with an enzyme-linked competitive immunoassay method.

Findings: Serum ADMA levels were found to be high in patients diagnosed with OSA. PAP therapy reduced serum ADMA levels in patients diagnosed with OSA. Thus, PAP therapy helped reduce systemic oxidative stress in serum.

Conclusion: Our study found that serum ADMA levels in OSA patients can be used as a biomarker for diagnosis. Furthermore, 3 months of PAP therapy eliminated OSA symptoms while also statistically significantly reducing serum ADMA levels.

 https://doi.org/10.5281/zenodo.18067672

Keywords: Sleep apnea, oxidative stress, ADMA, PAP therapy.

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by recurrent upper airway obstructions, recurrent hypoxemia, and awakenings; it is associated with increased cardiovascular morbidity and mortality (1). Endothelial dysfunction is an important pathophysiological intermediate step in OSA; decreased nitric oxide (NO) bioavailability is one of the key factors in this process. Asymmetric dimethylarginine (ADMA) is an endogenous L-arginine analog that inhibits NO synthesis, and elevated ADMA levels have been associated with vascular risk (2,3). Because of this mechanism, ADMA has been investigated as both a marker and a potential target in the vascular complication pathway of OSA.

Pathophysiology: OSA, ADMA, and NO Systems

Repeated cycles of hypoxia-reoxygenation lead to increased oxidative stress, inflammation, and protein methylation; alterations in protein-arginine methyltransferase (PRMT) activity and/or dimethylarginine dimethylaminohydrolase (DDAH) enzyme function may affect ADMA production and clearance. Elevated ADMA contributes to endothelial dysfunction, vasoconstriction, and a tendency toward thrombosis by blocking NO synthesis (2,3,4). This biological rationale underlies the association between elevated ADMA in OSA variants and clinically adverse outcomes.

Decreased serum ADMA levels may increase NO bioavailability and improve endothelial function; this mechanism may contribute to the positive effects of PAP on blood pressure, vascular reactivity, and long-term cardiovascular risk. However, it has been observed that PAP cannot be expected to lower ADMA in all patients, and its efficacy is closely related to patient compliance, obesity level, accompanying metabolic disorders, and treatment duration (5,6). Although broader meta-analyses discuss the potential benefits of PAP in clinical outcomes (e.g., mortality, cardiovascular events), direct evidence confirming the mediating role of ADMA is limited.

METHOD

Patient Selection

Sixty cases with AHI> 15 after PSG, who were referred to the Sleep Disorders Center with complaints such as snoring, increased daytime sleepiness, witnessed apnea, and morning dry mouth, were included in the study group. Sixty cases with AHI|< 5 after PSG were included in the control group. Individuals who smoked or consumed alcohol, or who had known chronic comorbidities (diabetes mellitus, hypertension, congestive heart failure, etc.) were excluded from the study. The study group received 3 months of PAP therapy after diagnosis. Ethical committee approval was obtained for our study, and written informed consent detailing the study objectives and procedures was obtained from all participants.

Biochemical Analysis

Blood samples were taken from the study group twice, after PSG and at the 3rd month of PAP treatment, with a minimum of 8 hours of fasting. Blood samples were taken from the control group after the PSG procedure with a minimum of 8 hours of fasting. After peripheral

 https://doi.org/10.5281/zenodo.18067672

sample collection, samples were centrifuged at 3000 rpm for 10 minutes, plasma and serum were separated, and stored at -80°C for approximately 6 months until analysis. Serum ADMA levels were measured using the competitive enzyme-linked immunosorbent assay (ELISA) method. The analysis protocol was applied based on the manufacturer's recommendations and previously published validation studies. Standards, controls, and serum samples were added to the wells of the microtiter plate. An ADMA-specific antibody was added and incubated at room temperature for 1 hour. After washing, an enzyme-conjugate was added and left to incubate again. Substrate was added, and color development was measured at 450 nm. Serum ADMA concentrations (µmol/L) were calculated based on absorbance results (7,8).

Low and high level quality control sera were tested in each analysis. The acceptable coefficient of variation (CV) was determined to be <10% in accordance with the literature (8). Duplicate measurements were performed on all samples.

Statistical Method

Data obtained from OSA and control group cases within the scope of the study were analyzed and interpreted using the IMB SPSS Statistics-29 package program to determine the effectiveness of the treatment applied. Before selecting the test statistic appropriate for the hypothesis, it was examined whether the data met the conditions for parametric testing. IBM SPSS Statistics 29 is produced by IBM (International Business Machines Corporation). The company is headquartered in New York, USA. For this purpose, the kurtosis and skewness values of the data, which are one of the determinants, were examined. For kurtosis and skewness values, the range of values (-2.00) to (+2.00) suggested by George et al. (2010) was considered (9). ADMA levels were expressed as mean ± standard deviation. Intergroup differences were evaluated using the Student t-test according to the distribution of the data. $p < 0.05$ was considered statistically significant. The diagnostic performance of the biomarkers was evaluated using ROC (Receiver Operating Characteristic) curve analysis. The area under the curve (AUC) was used as a measure of the test's discriminatory power, and AUC values were interpreted according to the method defined by Hanley & McNeil (10).

FINDINGS

Of the total 120 subjects participating in the study, 74 were male and 46 were female. The mean age of the patients was determined to be 44.19 ± 14.14 years. The patients had a mean body mass index (BMI) of 33.1 ± 7.4 kg/m². The basic demographic characteristics of the groups are detailed in Table 1.

 https://doi.org/10.5281/zenodo.18067672

ISSN: 0369-8963

Table 1: Demographic distribution of individuals comprising the OSA group and the control group.

	Control (N=60)	**Patient (N=60)**	**p**
Yaş	44,19 ± 14,14	47 ± 8,12	0,098
Gender			
Female	22 (%36,6)	24 (%40)	1
Male	38 (%63,4)	36 (%60)	

Table 2: Comparison of the control group and the patient group before treatment.

Varible	**Control (N=60)**	**Pre-treatment Patient (N=60)**	**P**
AHI	2,77 ± 0,23	40,46 ± 3,93	<0,001
ADMA (µmol/L)	0,84 ± 0,02	2,32 ± 0,04	<0,001
MİN SPO_2	88,03 ± 0,35	78,97 ± 1,36	<0,001
ORT SPO_2	92,34 ± 0,33	87,71 ± 0,6	<0,001

AHI and ADMA levels were found to be statistically higher in the patient group compared to the control group, while minimum spO2 and average spO2 levels were found to be lower. The statistical data obtained are detailed in Table 2.

 https://doi.org/10.5281/zenodo.18067672

Table 3: Comparison of the control group and the patient group after PAP therapy.

Variable	Control (N=60)	Post-Treatment Patient (N=60)	p
AHI	2,77 ± 0,23	2,76± 0,22	0,965
ADMA (µmol/L)	0,84 ± 0,02	1,22± 0,03	0,902
MİN SPO_2	88,03 ± 0,35	88,09 ± 0,34	0,908
ORT SPO_2	92,34 ± 0,33	92,43 ± 0,34	0,856

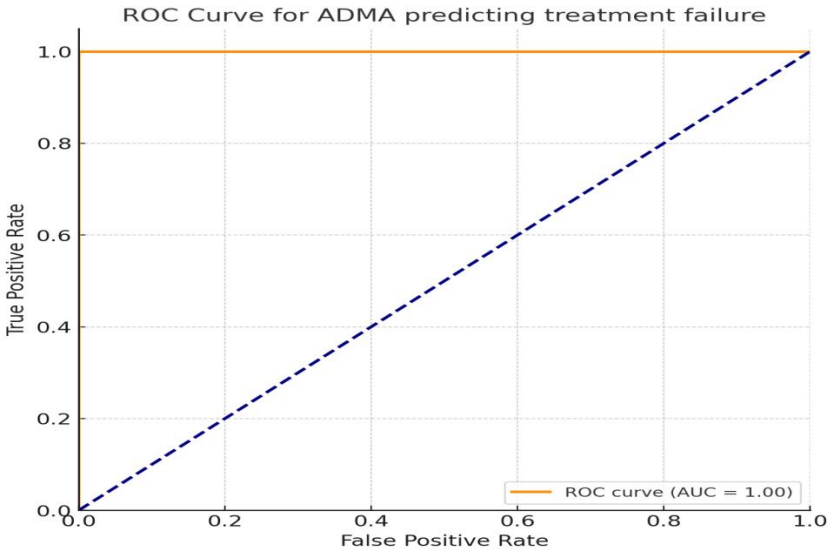
Statistically similar values were found for apnea-hypopnea index, serum ADMA, minimum spO_2, and average spO_2 values in the control group and patient groups after PAP therapy. The statistical data obtained are detailed in Table 3.

Table 4. Examination of differences in variables obtained in patient groups before and after treatment.

Varible	Pre-treatment Patient (N=60)	Post-treatment Patient (N=60)	P
AHI	40,47 ± 3,93	2,77 ± 0,23	<0,001
ADMA (µmol/L)	2,32 ± 0,04	1,22± 0,03	<0,001
MİN SPO_2	78,97 ± 1,36	88,09 ± 0,34	<0,001
ORT SPO_2	87,71 ± 0,6	92,43 ± 0,34	<0,001

The mean AHI before treatment was 40.47 ± 3.93, and the mean AHI after PAP treatment was 2.77 ± 0.23. The minimum SpO2, mean SpO2, and serum ADMA level detected before treatment improved to a statistically significant degree after 3 months of PAP therapy. The data obtained before and after treatment are detailed in Table 4.

 https://doi.org/10.5281/zenodo.18067672



Graph 1: ROC curve regarding the predictive power of ADMA levels for treatment failure.

The graph shows the relationship between sensitivity (TPR) and false positive rate (FPR) across all possible threshold values to evaluate the diagnostic accuracy performance of the biomarker. The Area Under the Curve (AUC) obtained in the analysis = 1.00, indicating that ADMA's discriminatory power regarding treatment failure is theoretically at its maximum level. The curve's complete approach to the upper left corner indicates that high sensitivity and specificity are achieved simultaneously, thus demonstrating that the biomarker offers near-perfect predictive accuracy. The ROC curve drawn with our study data reveals that ADMA possesses strong prognostic/diagnostic marker properties in classifying treatment response.

DISCUSSION

This study evaluated the effects of positive airway pressure (PAP) therapy on serum asymmetric dimethylarginine (ADMA) levels and oxygen saturation in patients with obstructive sleep apnea (OSA). Our findings show a significant decrease in AHI values after treatment, a significant decrease in serum ADMA levels, and a significant increase in both minimum and average SpO_2 levels. These results demonstrate that PAP therapy positively affects not only respiratory parameters but also biochemical markers related to endothelial function.

In our study, the mean ADMA level decreased from 2.32 µmol/L before treatment to 1.22 µmol/L after treatment. Previous studies have clearly demonstrated that ADMA reduces nitric oxide (NO) bioavailability by inhibiting endothelial NO synthase, leading to vascular dysfunction and increased cardiovascular risk (7). Therefore, the decrease in ADMA levels with PAP therapy can be interpreted as an important biochemical improvement toward reducing the known cardiovascular risk in OSA patients. Indeed, previous studies reporting ADMA as an independent risk factor for cardiovascular diseases are consistent with our findings (7,8).

 https://doi.org/10.5281/zenodo.18067672

It is known that OSA triggers endothelial dysfunction through repeated hypoxia and reoxygenation processes, and that ADMA levels are affected by these processes (11). In our study, the increase in the minimum SpO_2 level from 78.97 to 88.09 after treatment indicates a significant improvement in oxygenation. The improvement in the suppression of ADMA production with the reduction in hypoxia and the increase in dimethylarginine dimethylaminohydrolase (DDAH) activity can be considered among the pathophysiological reasons for the decrease in ADMA (12). This is supported by studies in the literature indicating that PAP therapy reduces oxidative stress and endothelial damage (8).

The dramatic decrease in AHI after treatment (from 40.47 to 2.77) demonstrates the clinical efficacy of PAP therapy, and it is noteworthy that this improvement parallels ADMA levels. This is consistent with studies reporting a positive correlation between OSA severity and ADMA (11). Our findings suggest that ADMA is not only a biomarker but also a parameter that could potentially be used to evaluate treatment response.

RESULTS

This study evaluated the effect of positive airway pressure (PAP) therapy on asymmetric dimethylarginine (ADMA) levels, an important indicator of endothelial dysfunction, in obstructive sleep apnea syndrome (OSAS). The findings indicate that PAP therapy administered for a specific period resulted in a significant decrease in ADMA levels, consistent with a reduction in the suppression of endothelial nitric oxide synthesis. The existing literature suggesting that increased oxidative stress and endothelial damage associated with intermittent hypoxemia in OUAS is partially reversed with PAP therapy is supported by these results. In this context, our study demonstrates that PAP therapy has positive effects not only on respiratory parameters but also on vascular biomarkers.

A key strength of this study is that the effect of PAP therapy on ADMA was assessed using a pre- and post-treatment matched sample approach. Measurements taken from the same individuals reduced potential bias due to inter-individual variability and allowed for a more accurate determination of treatment-related biochemical changes. Furthermore, the application of PAP therapy according to standard protocols and the analysis of ADMA levels in conjunction with clinical indicators (AHI, desaturation indices, oxygenation parameters) allowed the findings to be comprehensively linked to pathophysiological mechanisms. In these respects, the study has produced strong data supporting the potential of ADMA as a biomarker in OSA, both diagnostically and in terms of treatment response.

However, the study has some limitations. First, the limited sample size partially reduces the statistical power and generalizability of the results. The relatively short treatment duration did not allow for the assessment of the long-term sustainability of improvements in ADMA levels. Furthermore, the single-center nature of the study limited population diversity, reducing its external validity.

 https://doi.org/10.5281/zenodo.18067672

REFERENCES

1. Patil, S. P., Ayappa, I. A., Caples, S. M., Kimoff, R. J., Patel, S. R., & Harrod, C. G. (2019). Treatment of Adult Obstructive Sleep Apnea With Positive Airway Pressure: An American Academy of Sleep Medicine Clinical Practice Guideline. *Journal of Clinical Sleep Medicine, 15*(2), 335–343. https://doi.org/10.5664/jcsm.7640.
2. Csiszar, B., Marton, Z., Riba, J., Csecsei, P., Nagy, L., Toth, K., … Molnar, T. (2022). *l-arginine, asymmetric and symmetric dimethylarginine for early outcome prediction in unselected cardiac arrest victims: a prospective cohort study*. *Internal and Emergency Medicine, 17*(2), 525–534. https://doi.org/10.1007/s11739-021-02767.
3. Badran, M., Golbidi, S., Ayas, N., & Laher, I. (2015). *Nitric Oxide Bioavailability in Obstructive Sleep Apnea: Interplay of Asymmetric Dimethylarginine and Free Radicals. Sleep Disorders, 2015*, Article ID 387801. https://doi.org/10.1155/2015/387801.
4. Maniaci, A., Iannella, G., Cocuzza, S., Vicini, C., Magliulo, G., Ferlito, S., Cammaroto, G., Meccariello, G., De Vito, A., Nicolai, A., Pace, A., Artico, M., & Taurone, S. (2021). *Oxidative Stress and Inflammation Biomarker Expression in Obstructive Sleep Apnea Patients. Journal of Clinical Medicine, 10*(2), 277. https://doi.org/10.3390/jcm10020277.
5. Benjafield, A. V., Pepin, J.-L., Cistulli, P. A., Wimms, A., Lavergne, F., Sert Kuniyoshi, F. H., … & the medXcloud Group. (2025). *Positive airway pressure therapy and all-cause and cardiovascular mortality in people with obstructive sleep apnoea: a systematic review and meta-analysis of randomised controlled trials and confounder-adjusted, non-randomised controlled studies. The Lancet Respiratory Medicine, 13*(5), 403–413. https://doi.org/10.1016/S2213-2600(25)00002-5.
6. Li, J., Zeng, L., & Feng, T. (2024). The pathophysiological relationship and treatment progress of obstructive sleep apnea syndrome, obesity, and metabolic syndrome. *Chronic Metabolic Diseases.* Advance online publication. https://doi.org/10.14218/CMD.2024.00003.
7. Böger, R. H. (2003). The emerging role of asymmetric dimethylarginine as a novel cardiovascular risk factor. *Cardiovascular Research, 59*(4), 824–833. https://doi.org/10.1016/S0008-6363(03)00500-5.
8. Teerlink T. Measurement of asymmetric dimethylarginine in biological samples. *J Chromatogr B*. 2005;851(1–2):21–9.
9. George, D., & Mallery, M. (2010). SPSS for Windows Step by Step: A Simple Guide and Reference, 17.0 update (10a ed.) Boston: Pearson.
10. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143(1):29-36. **http://doi:10.1148/radiology.143.1.7063747.**
11. Schwedhelm E, Böger RH. The role of asymmetric and symmetric dimethylarginines in renal disease. *Nat Rev Nephrol*. 2011;7(5):275–85. **http://doi:** 10.1038/nrneph.2011.31.
12. Martens-Lobenhoffer J, Bode-Böger SM. Chromatographic methods for the quantification of L-arginine, symmetric dimethylarginine, and asymmetric dimethylarginine in biological fluids. *J Chromatogr B*. 2014;964:214–22. **http://doi:** 10.1016/j.jchromb.2013.10.030.