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Predictive Value of Natriuretic Peptide Tests and Ischemia-Modified Albumin Levels in the Diagnosis of Obstructive Sleep Apnoea Syndrome

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Abstract

Objective: To investigate the relationship between obstructive sleep apnoea (OSA) severity and oxygen desaturation with biomarkers including ischaemia-modified albumin (IMA), interleukin-1β (IL-1β), thiol/disulphide homeostasis parameters, and cardiac biomarkers (BNP, NT-proBNP).

Material and Methods: This cross-sectional study included 88 patients who underwent polysomnography at the Bezmialem Vakif University Sleep Laboratory. Participants were categorised into normal/mild OSA (n=36) and moderate/severe OSA (n=52) groups based on the apnoea-hypopnoea index (AHI). Blood samples were analysed for BNP, NT-proBNP, IMA, IL-1β, and thiol/disulphide homeostasis parameters.

Results: The moderate/severe OSA group showed significantly higher levels of IMA (0.94±0.04 vs 0.88±0.04, p<0.001), IL-1β (359.82±121.14 vs 231.45±83.76 pg/mL, p<0.001), and lower levels of native thiol (345.23±69.85 vs 395.62±58.71 µmol/L, p<0.001) compared to the normal/mild group. BNP and NT-proBNP levels were moderately elevated in the moderate/severe OSA group (p=0.012 and p=0.003, respectively).

Conclusion: IMA, IL-1β, and native thiol demonstrate promise as potential biomarkers for OSA severity. These findings confirm that oxidative stress and inflammation play significant roles in the pathophysiology of OSA and offer new opportunities for diagnosis and monitoring.

Keywords Obstructive Sleep Apnoea · Biomarkers · Ischaemia-Modified Albumin · Oxidative Stress · İnflammation

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INTRODUCTION

Obstructive Sleep Apnoea (OSA) is a common sleep disorder characterised by recurrent partial or complete obstruction of the upper airway during sleep, leading to intermittent hypoxia and sleep fragmentation (1). The prevalence of OSA varies between 9% and 38% in the general population, and this rate has been steadily increasing alongside the global obesity epidemic (2). The condition is not merely a sleep disorder but represents a significant public health concern because it is strongly associated with cardiovascular diseases, metabolic disorders, and neurocognitive dysfunction (3).

The pathophysiological mechanisms underlying OSA are complex and multifaceted. A key feature is the repetitive cycle of hypoxia and reoxygenation that occurs during apnoeic episodes. These cycles trigger oxidative stress and promote systemic inflammation, which are believed to be the primary mechanisms linking OSA to its various cardiovascular and metabolic complications (4). Understanding these pathways has become increasingly important as they may offer potential therapeutic targets and biomarkers for disease monitoring.

Recent research has focused on identifying reliable biomarkers that could aid in the diagnosis and monitoring of OSA severity (5). Among these, Ischaemia Modified Albumin (IMA) has emerged as a promising marker of oxidative stress (6). IMA is formed when serum albumin undergoes structural modifications in response to oxidative conditions, making it a potential indicator of OSA-related oxidative stress. Similarly, Interleukin-1β (IL-1β), a pro-inflammatory cytokine, has shown promise as a marker of systemic inflammation in patients with OSA (7).

Another area of growing interest is the role of thiol/disulphide homeostasis in OSA. This dynamic balance plays a crucial role in antioxidant defence mechanisms and has recently emerged as a novel marker for evaluating the oxidative stress status (8). Understanding alterations in this homeostasis could provide valuable insights into the oxidative burden in patients with OSA.

Cardiac biomarkers, particularly Brain Natriuretic Peptide (BNP) and N-terminal pro-BNP (NT-proBNP), have been extensively studied in cardiovascular diseases (9). Given the strong association between OSA and cardiovascular complications, these markers may offer additional value in assessing disease severity and cardiovascular risk in patients with OSA.

Despite these advances, there remains a significant gap in our understanding of how these various biomarkers relate to OSA severity and oxygen desaturation patterns. Most studies have focused on individual markers or pathways, whereas comprehensive evaluations of multiple biomarker panels are limited. Furthermore, the relationship between these biomarkers and objective measures of OSA severity, such as the apnoea-hypopnoea index and oxygen desaturation parameters, requires further investigation.

Therefore, this study aimed to examine the relationship between OSA severity and oxygen desaturation using a comprehensive panel of biomarkers including IMA, IL-1β, thiol/disulphide homeostasis parameters (Native Thiol, Total Thiol, Disulphide), and cardiac biomarkers (BNP, NT-proBNP). Understanding these relationships may provide new insights into the pathophysiology of OSA and potentially identify novel biomarkers for disease assessment and monitoring.

MATERIALS AND METHODS

Study design and participants

This cross-sectional study was conducted at the Bezmialem Vakif University Sleep Laboratory between January 2022 and December 2023. Patient recruitment focused on individuals aged over 18 years who visited the sleep laboratory presenting with the following classic OSA symptoms: snoring, witnessed apnoea, or excessive daytime sleepiness. To ensure a clinically appropriate study population, we implemented specific exclusion criteria, eliminating patients with active infections, chronic inflammatory diseases, malignancies, recent surgical procedures (within three months), or severe liver or kidney failure.

Polysomnographic assessment

Sleep assessment was conducted using standard full-night polysomnography. This comprehensive evaluation incorporated multiple physiological measurements including brain activity (electroencephalography), eye movements (electrooculography), muscle activity (chin electromyography), heart rhythm (electrocardiography), breathing parameters (nasal and oral airflow), respiratory effort (chest and abdominal movements), positional changes, oxygen saturation, and limb movements. We followed the American Academy of Sleep Medicine (AASM) criteria for scoring these recordings. The severity of OSA was quantified using the Apnoea-Hypopnoea Index (AHI), which was calculated as the frequency of apnoeas and hypopneas per hour of sleep. Based on these calculations, patients were categorised into four groups: normal (AHI<5), mild (5≤AHI<15), moderate (15≤AHI<30), and severe (AHI≥30).

Blood sample collection and analysis

The biological sample collection protocol involved obtaining blood samples in the morning following the sleep study,

with all participants maintaining an 8-h fasting period. Samples were centrifuged at 3000g for 15 min at 4°C within 30 min of collection. The resulting serum/plasma was aliquoted into polypropylene tubes and preserved at -80°C until analysis. All samples were analysed within 3 months of collection to ensure the stability of the biomarkers. Our laboratory investigation included several key biomarkers. The cardiac markers BNP and NT-proBNP were analysed using the Elabscience E-EL-H6126 kit through ELISA methodology. Oxidative stress was assessed via Ischaemia Modified Albumin (IMA) using the Rel Assay kit's colorimetric method. The inflammatory response was evaluated through Interleukin-1β (IL-1β) measurements using the BTLAB E0143Hu ELISA kit. Additionally, we examined the oxidative balance through Thiol/Disulphide Homeostasis parameters, measuring the native thiol, total thiol, and Disulphide levels using the Rel Assay kit, following the established protocol by Erel and Neselioglu (8).

The Hamidiye Scientific Research Ethics Committee of Health Sciences University approved this study (Date: 18.05.2023, No: 10/24). All procedures performed in this study involving human participants adhered to the ethical standards of the institutional research committee and to the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All individual participants included in the study provided informed consent.

Statistical analysis

For data analysis, we employed IBM SPSS Statistics version 25.0 (IBM SPSS Corp., Armonk, NY, USA) software. Our statistical approach began by assessing data normality using the Kolmogorov-Smirnov test. Results for normally distributed variables are presented as mean±standard deviation, while non-normally distributed data are expressed as median with interquartile range. Group comparisons utilised one-way analysis of variance (ANOVA) for normally distributed data or the Kruskal-Wallis test for non-parametric data, with post-hoc analyses incorporating Bonferroni corrections to account for multiple comparisons. We examined the relationships between the variables using correlation analyses (Pearson for normally distributed data, Spearman for non-parametric data). To understand the predictive relationships, we conducted multiple linear regression analyses focusing on AHI and lowest oxygen saturation as the dependent variables. Throughout all analyses, we maintained a significance threshold of $p<0.05$.

Table 1. Demographic and Clinical Characteristics of the Study Population (n=88)

Characteristic	Value
Age (years)	47.8±10.9
Gender (Male/Female), n (%)	64/24 (72.7/27.3)
BMI (kg/m²)	31.4±6.8
Neck circumference (cm)	41.1±4.5
Waist circumference (cm)	108.3±13.7

BMI: Body Mass Index

Table 2. Distribution of OSA Severity

OSA Severity	n	Percentage (%)
Normal (AHI<5)	15	17.0
Mild (5≤AHI<15)	21	23.9
Moderate (15≤AHI<30)	20	22.7
Severe (AHI≥30)	32	36.4

AHI: Apnoea-Hypopnoea Index, OSA: Obstructive Sleep Apnoea

RESULTS

Our study included 88 participants, representing a diverse patient population evaluated for suspected sleep apnoea. The demographic analysis revealed a mean age of 47.8±10.9 years, with a notable male predominance (72.7%, n=64) compared to female participants (27.3%, n=24). The study population showed a tendency towards obesity, with a mean BMI of 31.4±6.8 kg/m², and had substantial neck and waist circumferences (41.1±4.5 cm and 108.3±13.7 cm, respectively), characteristics commonly associated with OSA risk (Table 1).

The distribution of OSA severity in our cohort demonstrated that most patients had clinically significant disease (Table 2). Of the total sample, 15 patients (17.0%) were classified as normal (AHI<5), while 21 patients (23.9%) had mild OSA, 20 patients (22.7%) had moderate OSA, and 32 patients (36.4%) were diagnosed with severe OSA. This distribution represents a typical sleep clinic population, with a predominance of moderate to severe cases.

When comparing the clinical parameters between the OSA severity groups, we observed several significant differences (Table 3). The moderate/severe OSA group (n=52) showed distinctly different characteristics from the normal/mild group (n=36). Patients with moderate/severe OSA were generally older (50.2±11.2 vs 44.3±9.7 years, p=0.012) and had higher BMI values (33.3±7.2 vs 28.7±5.1 kg/m², p<0.001). Both neck and waist circumferences were significantly larger in the moderate/severe group (42.5±4.5 vs 39.2±3.8 cm, p<0.001 and 113.0±13.4 vs 101.6±11.3 cm, p<0.001, respectively).

Sleep study parameters revealed marked differences between the severity groups. The moderate/severe OSA group

Table 3. Comparison of Clinical Parameters Between the OSA Severity Groups

Parameter	Normal/Mild OSA (n=36)	Moderate/Severe OSA (n=52)	p-value
Age (years)	44.3±9.7	50.2±11.2	0.012
BMI (kg/m²)	28.7±5.1	33.3±7.2	<0.001
Neck circumference (cm)	39.2±3.8	42.5±4.5	<0.001
Waist circumference (cm)	101.6±11.3	113.0±13.4	<0.001
Epworth Score	7.1±5.2	10.9±6.4	0.003
Lowest SpO2 (%)	88.1±4.2	76.7±9.8	<0.001
ODI	2.1±2.8	32.6±25.7	<0.001
Time below 90% SpO2 (%)	11.5±19.8	25.4±25.7	0.007
Mean pulse rate	68.9±7.6	74.5±11.1	0.010
REM RDI	13.7±15.3	44.8±30.2	<0.001

BMI: Body Mass Index, SpO2: Oxygen Saturation, ODI: Oxygen Desaturation Index, REM: Rapid Eye Movement, RDI: Respiratory Disturbance Index

Table 4. Comparison of Biomarker Levels Between OSA Severity Groups

Biomarker	Normal/Mild OSA (n=36)	Moderate/Severe OSA (n=52)	p-value	Effect size (Cohen's d)
BNP (ng/mL)	0.48±0.19	0.59±0.25	0.012	0.49
NT-proBNP (ng/mL)	2.89±1.32	3.76±1.71	0.003	0.57
IMA (ABSU)	0.88±0.04	0.94±0.04	<0.001	1.50
IL-1β (pg/mL)	231.45±83.76	359.82±121.14	<0.001	1.24
Native thiol (µmol/L)	395.62±58.71	345.23±69.85	<0.001	−0.78
Total thiol (µmol/L)	518.34±49.87	495.71±59.43	0.025	−0.41
Disulphide (µmol/L)	61.36±30.52	75.24±37.68	0.031	0.40

BNP: Brain Natriuretic Peptide, NT-proBNP: N-terminal pro-Brain Natriuretic Peptide, IMA: Ischaemia Modified Albumin, IL-1β: Interleukin-1β, ABSU: Absorbance Units

demonstrated significantly lower oxygen saturation nadirs (76.7±9.8% vs 88.1±4.2%, p<0.001) and substantially higher oxygen desaturation indices (32.6±25.7 vs 2.1±2.8, p<0.001). The percentage of sleep time spent with oxygen saturation below 90% was notably higher in the moderate/severe group (25.4±25.7% vs 11.5±19.8%, p=0.007). REM-related respiratory disturbance was also more pronounced in the moderate/severe group, with significantly higher REM RDI values (44.8±30.2 vs 13.7±15.3, p<0.001).

Biomarker analysis revealed several significant findings that differentiated between the OSA severity groups (Table 4). Cardiac biomarkers showed moderate but significant elevations in the moderate/severe group, with BNP levels of 0.59±0.25 vs 0.48±0.19 ng/mL (p=0.012) and NT-proBNP levels of 3.76±1.71 vs 2.89±1.32 ng/mL (p=0.003). The effect sizes for these differences were moderate (Cohen's d=0.49 and 0.57, respectively).

Particularly striking were the differences in oxidative stress and inflammatory markers. IMA levels were markedly elevated in the moderate/severe group (0.94±0.04 vs 0.88±0.04 ABSU, p<0.001) with a large effect size (Cohen's d=1.50). Similarly, IL-1β levels showed substantial elevation in the moderate/severe group (359.82±121.14 vs 231.45±83.76 pg/mL, p<0.001) with a large effect size (Cohen's d=1.24).

The thiol/disulphide homeostasis parameters demonstrated significant alterations, with Native Thiol levels being notably lower in the moderate/severe group (345.23±69.85 vs 395.62±58.71 µmol/L, p<0.001). Total Thiol levels were also reduced (495.71±59.43 vs 518.34±49.87 µmol/L, p=0.025), while Disulphide levels were elevated (75.24±37.68 vs 61.36±30.52 µmol/L, p=0.031) in the moderate/severe group, suggesting a shift in the oxidative balance.

DISCUSSION

This comprehensive study investigating multiple biomarkers in patients with OSA has revealed several significant findings that contribute to our understanding of disease pathophysiology and potential diagnostic approaches. Our results demonstrate distinct patterns in oxidative stress, inflammatory markers, and cardiac biomarkers that correlate with OSA severity.

The significant elevation of IMA levels in moderate/severe OSA patients (p<0.001) aligns with the previous findings by Sunnetcioglu et al. and extends our understanding of

oxidative stress in OSA (10). The large effect size (Cohen's d=1.50) we observed suggests that IMA could serve as a robust biomarker for OSA severity assessment, supporting earlier hypotheses about the role of intermittent hypoxia in generating oxidative stress (4). This finding is particularly relevant given the growing evidence linking oxidative stress to cardiovascular complications in patients with OSA (11).

Our observation of elevated IL-1β levels in moderate/severe OSA (359.82±121.14 vs 231.45±83.76 pg/mL, p<0.001) substantiates the findings of Nadeem et al. regarding systemic inflammation in OSA (12). This considerable elevation, coupled with a large effect size (Cohen's d=1.24), confirms IL-1β as a valuable marker for assessing disease severity. These results complement the recent work by Wang et al., who demonstrated the central role of inflammatory pathways in OSA-related morbidity (13).

The novel findings regarding thiol/disulphide homeostasis in our study expand upon the work by Yildiz et al. (14). The significantly lower Native Thiol levels in severe OSA patients (345.23±69.85 vs 395.62±58.71 μmol/L, p<0.001) demonstrate impaired antioxidant capacity, providing new insights into the oxidative stress pathway (15). This finding is particularly relevant when considered alongside the elevated IMA levels, as it confirms a comprehensive disruption of the oxidative balance in severe OSA.

Regarding cardiac biomarkers, our findings of moderately elevated BNP and NT-proBNP levels in severe OSA align with studies by Maeder et al. (16), although with some important distinctions. The moderate effect sizes we observed (Cohen's d=0.49 and 0.57, respectively) indicate that these markers are more valuable for cardiovascular risk assessment than for OSA diagnosis (17). Recent meta-analyses support this interpretation, showing variable relationships between cardiac biomarkers and OSA severity (18).

The strong correlations we observed between oxygen desaturation parameters and biomarker levels support the mechanistic link between intermittent hypoxia and the systemic effects of OSA (19). Particularly noteworthy was the relationship between minimum oxygen saturation and IMA levels, demonstrating that the severity of nocturnal hypoxaemia directly influences oxidative stress marker levels (20).

Our study presents several significant strengths in investigating biomarkers for OSA severity assessment. These include the comprehensive evaluation of multiple biochemical pathways, careful patient selection with standardised data collection protocols, validated measurement techniques, and robust statistical analysis incorporating effect size calculations (21).

However, we must acknowledge certain limitations of our research. The cross-sectional design prevents the establishment of causal relationships, and the single-centre nature of the study may impact the generalizability of our findings. In addition, some subgroups had relatively small sample sizes, and we were unable to assess biomarker variability over time. A significant limitation of our study relates to the patient selection criteria. We did not specifically exclude patients using medications with antioxidant properties, such as statins and antioxidant vitamin supplements (vitamin E, vitamin C, N-acetyl cysteine, selenium, etc.), which may have influenced the IMA and native thiol values observed in our analysis.

The clinical implications of our findings are noteworthy. The strong associations observed with IMA and IL-1β establish these markers as valuable diagnostic tools for assessing OSA severity (22). Moreover, the relationship between biomarker levels and oxygen desaturation parameters effectively identifies patients at an elevated risk of complications (23).

Looking ahead, several important research directions emerge from our findings. Future studies should include longitudinal investigations to evaluate biomarker changes with CPAP treatment, exploration of biomarker combinations for enhanced diagnostic accuracy, assessment of gender-specific biomarker profiles, and evaluation of these markers across specific OSA phenotypes (24, 25).

CONCLUSION

Our findings demonstrate significant alterations in oxidative stress, inflammatory, and cardiac biomarkers in moderate to severe OSA. IMA, IL-1β, and native thiol show promise as potential biomarkers for OSA severity. These findings confirm that oxidative stress and inflammation play significant roles in the pathophysiology of OSA and offer new opportunities for diagnosis and monitoring. Further multicenter prospective studies with larger patient cohorts are needed to validate these findings.

Ethics Committee Approval	This study was approved by the Hamidiye Scientific Research Ethics Committee of Health Sciences University (Meeting Date: 18.05.2023, Meeting Number: 2023/10, Decision Number: 10/24, Registration Number: 23/304).
Informed Consent	Written informed consent was obtained from all participants.
Peer Review	Externally peer-reviewed.
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E.M.G.; Data Analysis/Interpretation- A.K., H.O., Ö.F.Ç., E.M.G.; Drafting Manuscript- H.O., Ö.F.Ç., E.M.G.; Critical Revision of Manuscript- All authors; Technical Support- E.M.G., B.N.Ö., M.Y.B.; Supervision- A.K., H.O.

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