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Article

Comparative Analysis of Apnea-Hypopnea Duration and Oxidative Stress Markers for Diagnosis and Classification of Obstructive Sleep Apnea

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Abstract

Background/Objectives: Obstructive sleep apnea (OSA) diagnosis relies primarily on the apnea-hypopnea index (AHI), which measures event frequency but not duration. This study aimed to evaluate the diagnostic and classificatory potential of apnea and hypopnea duration (AHD) and oxidative stress markers in OSA. **Methods:** This case-control study included 47 patients with newly diagnosed OSA and 12 healthy controls. Participants underwent polysomnography and oxidative stress assessment through measurement of total-thiol, native-thiol, disulfide, myeloperoxidase, paraoxonase, catalase, malate dehydrogenase, total antioxidant status (TAS), total oxidant status (TOS), and oxidative stress index (OSI). The patient group was classified and compared based on OSA severity. **Results:** Total AHD of the severe OSA group was significantly longer than both other groups ($p < 0.001$). TAS levels of both OSA groups were significantly lower compared to controls ($p = 0.006$). TAS demonstrated moderate correlations with polysomnography parameters. A total AHD value of >12 min discriminated OSA with 100% sensitivity and specificity. A total AHD value of >80 min distinguished severe OSA with 100% sensitivity and 97.22% specificity. **Conclusions:** Total AHD is a valuable parameter for OSA diagnosis and severity classification, demonstrating superior discriminatory performance compared to the widely-used AHI. Although TAS was associated with OSA presence, oxidative stress parameters have limited utility for assessing OSA severity.

Keywords: obstructive sleep apnea; apnea-hypopnea duration; oxidative stress; total antioxidant status; polysomnography; diagnosis; classification; biomarkers

1. Introduction

Obstructive sleep apnea (OSA) is a condition in which breathing functions during sleep are temporarily interrupted. It is characterized by recurrent episodes of apnea or hypopnea caused by upper airway obstruction, usually due to functional or anatomical disorders [1]. OSA prevalence in the adult population is approximately 2–4%, but the prevalence in some countries is reported to exceed 50% [2].

Currently, OSA diagnosis, classification and management are based on the apnea-hypopnea index (AHI), which is calculated from events detected within one hour during sleep, typically using overnight polysomnography [3]. However, AHI is primarily a measure of the frequency of respiratory events, and is incapable of single-handedly defining severity or duration. The limited

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relationship between disease severity and AHI measurements [3,4] has led to the search for additional parameters in the management of OSA.

Apneas and hypopneas lead to intermittent fluctuations in blood oxygenation, and some events can be defined as hypoxemia or hypercapnia [7]. As a result of inconsistent oxygen levels, reactive oxygen species (ROS) are released and increase systemic oxidative stress (OxS) [8]. ROS can react with nucleic acids, proteins, and lipids, leading to DNA changes, cellular damage, apoptosis and inflammation [9,10].

In this study, we aimed to determine whether AHD and OxS markers could be used to direct the management of OSA patients. Firstly, we investigated AHD and OxS markers in individuals with and without OSA. Secondly, we assessed whether AHD and OxS marker levels were associated with OSA severity and AHI. Thirdly, we analyzed potential relationships between AHD and OxS.

2. Materials and Methods

2.1. Study Design and Setting

This was a case-control study carried out in the Sleep Polyclinic at the Department of Chest Diseases of Bezmialem Vakif University Hospital, Istanbul, Turkey, from February 2020 to February 2021.

2.2. Participants

A total of 47 patients who had been newly diagnosed with OSA (patient group) and 12 healthy individuals without OSA (control group) were included. Study candidates were excluded if they were aged <18 or >80 years, and when they had a history of ischemic heart disease, cerebrovascular events, diabetes, peripheral artery disease, acute or chronic infection, collagen tissue disease, inflammatory bowel disease, malignancy, hypo-hyperthyroidism, liver and kidney disease, active bleeding, thrombosis or anemia.

2.3. OSA Diagnosis, Management, and Related Variables

Participants in the patient and control groups all applied to the sleep outpatient clinic with a clinical suspicion of OSA. They underwent a detailed physical examination in addition to height, weight, neck and waist circumference measurements. Daytime sleepiness was estimated on the Epworth Sleepiness Scale (ESS) [3].

For OSA diagnosis, the participants were hospitalized in our sleep laboratories for a full-night monitoring with a polysomnography system (EMBLA S4000; Remlogic, Denver, CA, USA) equipped with a software (Compumedics E series Polysomnography (E3142); Compumedics Inc., Melbourne, Australia) following conventional methods [11]. Computer records were manually checked for verification.

2.4. Definitions

An apnea event was defined as a decrease in respiratory airflow ≥90% for ≥10 seconds with continued respiratory effort. A hypopnea event was defined as a decrease in respiratory airflow of ≥30% for ≥10 seconds followed by a decrease in SaO_2 of ≥3% or an electroencephalogram arousal [11]. The AHI was defined as the number of apnea & hypopnea events per hour of sleep, and calculated by dividing the total number of events by total sleep time [13].

OSA diagnosis and OSA severity were determined based on AHI according to the guideline by American Academy of Sleep Medicine Clinical Practice (2018) [16]. Accordingly, AHI < 5 was defined as no OSA [control group, n = 12 (20.34%)], 5 ≤ AHI < 15 was defined as mild OSA [n = 18 (30.51%)], 15 ≤ AHI < 30 as moderate OSA [n = 6 (10.17%)] and AHI ≥ 30 as severe OSA [n = 23 (38.98%)].

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2.5. Laboratory Parameters

Laboratory analyses were studied with the remaining blood samples after routine biochemical analyses were performed before polysomnography. Venous blood samples were obtained after overnight fasting. The blood parameters studied were as follows: T-Thiol, N-thiol, disulfide, myeloperoxidase, paraoxonase, catalase, malate dehydrogenase, total antioxidant status (TAS), total oxidant status (TOS). Oxidative stress index (OSI) was calculated using the following formula: OSI (arbitrary unit) = TOS (μmol H_2O_2 Eq/L) / TAS (μmol Trolox Eq/L) [31].

2.6. Statistical Analysis

Statistical results were interpreted based on the $p < 0.05$ (two-tailed) threshold. All analyses were performed on the SPSS software, v25.0 (IBM, NY, USA). The Shapiro-Wilk test was used to determine whether continuous variables were normally distributed. Pearson or Spearman correlation coefficients were calculated to evaluate relationships between continuous variables.

Data are given as mean ± standard deviation or median (minimum - maximum) for continuous variables according to normality of distribution, while frequency (percentage) was used for categorical variables. One-way analysis of variance (ANOVA), Kruskal-Wallis and chi-square tests were used to analyze the variables. Pairwise adjustments after 3-group comparisons were done with the Bonferroni correction. Prediction performance of total AHD value was assessed with the Receiver Operating Characteristic (ROC) curve analysis.

3. Results

3.1. Patient Characteristics

The groups were similar with respect to age ($p = 0.714$). Males represented 69.49% of all participants, 41.67% of the control group, 66.67% of the mild & moderate OSA group, and 86.96% of the severe OSA group. The percentage of male sex in the severe OSA group was significantly higher than the control group ($p = 0.020$).

3.2. Polysomnography Results

Patient characteristics and polysomnography results are depicted in Table 1. Notably, the severe OSA group had longer periods of <90% SaO_2 ($p < 0.001$), <88% SaO_2 ($p < 0.001$), average apnea ($p < 0.001$) and longest apnea ($p < 0.001$), as well as higher ODI ($p < 0.001$). The lowest SaO_2 value of the severe OSA group was significantly lower than the other two groups ($p < 0.001$).

Table 1. Summary of patients' characteristics and polysomnography results with regard to severity of sleep apnea.

	Total (n=59)	No OSA (n=12)	Mild & Moderate OSA (n=24)	Severe OSA(n=23)	*p*
Age	43 (20 - 79)	40.5 (25 - 55)	43 (20 - 61)	45 (29 - 79)	0.714
Sex					
Male	41 (69.49%)	5 (41.67%)	16 (66.67%)	20 (86.96%)*	**0.020**
Female	18 (30.51%)	7 (58.33%)	8 (33.33%)	3 (13.04%)	
Epworth Sleepiness Scale score	10.61 ± 5.64	8.08 ± 4.34	9.83 ± 5.18	12.74 ± 6.11	0.058
Body mass index, kg/m²	31.36 ± 5.98	30.44 ± 3.92	30.35 ± 6.85	32.90 ± 5.79	0.293
Neck circumference, cm	39.24 ± 4.75	35.83 ± 1.75	38.00 ± 5.04	42.30 ± 3.69*#	**<0.001**
Waist circumference, cm	105.97 ± 14.44	97.75 ± 8.37	102.83 ± 14.91	113.52 ± 13.23*#	**0.002**

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Total sleep time, min	367.55 ± 44.65	359.79 ± 42.48	361.17 ± 57.27	378.26 ± 26.97	0.243
Sleep efficiency, %	91.9 (65.1 - 99.8)	87.35 (75.9 - 99.4)	90.5 (65.1 - 98.4)	94.3 (79.6 - 99.8)	0.077
Stage REM latency, min	153.46 ± 86.58	137.67 ± 74.29	166.98 ± 80.43	147.59 ± 99.35	0.588
REM sleep duration, min	35.5 (0 - 79)	48.5 (20 - 76)	37 (0 - 77)	22 (0 - 79)	0.051
Stage 1 sleep duration, min	3 (1 - 12)	2.5 (1 - 7)	3.5 (1.5 - 12)	2 (1 - 7)#	**0.021**
Stage 2 sleep duration, min	285 (154.5 - 387)	243.5 (199.5 - 314)	280.5 (154.5 - 371)	311.5 (241.5 - 387)*#	**0.001**
Stage 3 sleep duration, min	46.5 (0 - 113)	60.25 (9.5 - 113)	54.75 (0 - 101)	39 (0 - 108.5)	0.090
REM sleep time, %	10.2 (0 - 19.4)	13.35 (6.8 - 19.4)	10.85 (0 - 18.3)	6 (0 - 19.1)*	**0.009**
Stage 1 sleep time, %	0.8 (0.2 - 4.3)	1.0 (0.3 - 2.1)	0.9 (0.3 - 4.3)	0.5 (0.2 - 2.0)#	**0.016**
Stage 2 sleep time, %	75.8 (51.3 - 98.0)	71.25 (51.3 - 86.5)	74.45 (55.9 - 94.6)	83.5 (61.3 - 98.0)*#	**0.006**
Stage 3 sleep time, %	12.2 (0 - 29)	17 (2.5 - 29)	13.85 (0 - 26.7)	10.5 (0 - 27.5)	0.083
Lowest SaO_2%	83 (38 - 93)	91 (76 - 93)	86.5 (43 - 93)	76 (38 - 86)*#	**<0.001**
Time below 90%, min	24 (0 - 301)	0 (0 - 253)	1 (0 - 183)	116 (7 - 301)*#	**<0.001**
Time below 88%, min	7 (0 - 271)	0 (0 - 88)	0 (0 - 41)	52 (2 - 271)*#	**<0.001**
Oxygen desaturation index	5.6 (0 - 77.7)	0.3 (0 - 1.3)	2.55 (0 - 14.3)	43.9 (8.7 - 77.7)*#	**<0.001**
Average heart rate	67.98 ± 9.42	69.00 ± 6.94	67.25 ± 6.34	68.22 ± 12.91	0.865
Average apnea duration, sec	27.00 ± 5.13	23.75 ± 4.14	25.50 ± 4.26	30.26 ± 4.74*#	**<0.001**
Longest apnea duration, sec	53 (22 - 159)	33 (23 - 58)	48 (22 - 82)	77 (43 - 159)*#	**<0.001**
REM					
Number of apneas	9 (0 - 107)	1 (0 - 9)	5 (0 - 47)*	23 (0 - 107)*#	**<0.001**
Number of hypopneas	0 (0 - 13)	0 (0 - 5)	0 (0 - 6)	0 (0 - 13)	0.204
Number of apneas & hypopneas	12 (0 - 107)	2 (0 - 14)	9 (0 - 49)	23 (0 - 107)*#	**<0.001**
Apnea-hypopnea index	18.69 (0.00 - 114.78)	2.12 (0.00 - 12.00)	13.45 (0.00 - 54.29)	71.49 (0.00 - 114.78)*#	**<0.001**
Total apnea duration, min	3 (0 - 67)	0 (0 - 3)	2 (0 - 26)	12 (0 - 67)*#	**<0.001**
Total hypopnea duration, min	0 (0 - 7)	0 (0 - 3)	0 (0 - 3)	0 (0 - 7)	0.488
Total apnea & hypopnea duration, min	4 (0 - 67)	0 (0 - 6)	3 (0 - 27)	14 (0 - 67)*#	**<0.001**
Respiratory disturbance index	19.5 (0 - 114.8)	2.1 (0 - 12.0)	13.9 (0 - 54.3)	71.5 (0 - 114.8)*#	**<0.001**

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Non-REM					
					<0.00
Number of apneas	59 (3 - 577)	8.5 (3 - 23)	40.5 (11 - 148)*	372 (141 - 577)*#	**1**
Number of hypopneas	4 (0 - 64)	1.5 (0 - 4)	4 (0 - 36)	11 (0 - 64)*	**0.003**
					<0.00
Number of apneas & hypopneas	67 (3 - 582)	10.5 (3 - 24)	49.5 (30 - 184)*	408 (173 - 582)*#	**1**
	13.69 (0.69 -	1.98 (0.69 -		69.91 (32.44 -	**<0.00**
Apnea-hypopnea index	94.12)	4.13)	9.00 (4.69 - 31.19)*	94.12)*#	**1**
					<0.00
Total apnea duration, min	29 (1 - 295)	2.5 (1 - 8)	17.5 (3 - 68)*	179 (51 - 295)*#	**1**
Total hypopnea duration, min	2 (0 - 29)	0 (0 - 2)	3 (0 - 22)	6 (0 - 29)*	**0.002**
Total apnea & hypopnea					**<0.00**
duration, min	34 (1 - 295)	3.5 (1 - 10)	20.5 (10 - 90)*	192 (76 - 295)*#	**1**
					<0.00
Respiratory disturbance index	12.8 (0.7 - 94.1)	2 (0.7 - 4.1)	9.15 (4.7 - 31.2)*	69.2 (5.0 - 94.1)*#	**1**
Total					
					<0.00
Number of apneas	73 (3 - 605)	9.5 (3 - 25)	51.5 (16 - 150)*	400 (165 - 605)*#	**1**
Number of hypopneas	4 (0 - 77)	2 (0 - 7)	4.5 (0 - 36)	11 (0 - 77)*	**0.012**
					<0.00
Number of apneas & hypopneas	86 (4 - 610)	12 (4 - 28)	56 (35 - 186)*	430 (207 - 610)*#	**1**
	14.60 (0.77 -	1.92 (0.77 -		70.63 (30.55 -	**<0.00**
Apnea-hypopnea index	92.78)	4.68)	10.44 (5.16 - 29.56)*	92.78)*#	**1**
					<0.00
Total apnea duration, min	36 (1 - 347)	2.5 (1 - 9)	21.5 (4 - 68)*	193 (62 - 347)*#	**1**
Total hypopnea duration, min	2 (0 - 32)	0.5 (0 - 4)	3.5 (0 - 22)	6 (0 - 32)*	**0.007**
Total apnea & hypopnea					**<0.00**
duration, min	40 (1 - 347)	3.5 (1 - 11)	24 (14 - 90)*	206 (86 - 347)*#	**1**
					<0.00
Respiratory disturbance index	14.6 (0.8 - 92.8)	1.9 (0.8 - 4.7)	10.45 (5.2 - 29.6)*	70.6 (30.5 - 92.8)*#	**1**

Data are given as mean ± standard deviation or median (minimum - maximum) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. *: Significantly different from the control group, #: Significantly different from the Mild & Moderate group. Abbreviations: OSA: Obstructive sleep apnea, REM: Rapid eye movement, SaO2: Arterial oxygen saturation.

The number of apnea & hypopnea events, AHI value, apnea duration, total AHD, and RDI values (REM, non-REM and total sleep) of the severe OSA group were significantly higher than the other two groups ($p < 0.001$ for all). When the severe OSA group was compared to controls, we found that severe OSA patients had more hypopnea events and greater hypopnea duration in the non-REM period ($p = 0.003$ and $p = 0.002$, respectively) and the total sleep period ($p = 0.012$ and $p = 0.007$, respectively). All OSA-related parameters in the mild & moderate OSA group were significantly higher compared to the control group ($p < 0.001$ for all variables and all three periods).

3.3. Laboratory Data

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Laboratory data and the differences between groups are presented in Table 2. The mean TAS levels of the severe and mild & moderate OSA groups were significantly lower compared to the control group (p = 0.006).

Table 2. Summary of laboratory measurements with regard to severity of sleep apnea.

	Total (n=59)	Controls (n=12)	Mild & Moderate OSA (n=24)	Severe OSA (n=23)	*p*
Total Thiol, mmol/L	970.69 (866.78 - 1021.99)	975.19 (925.30 - 1008.42)	963.69 (866.78 - 1004.00)	975.35 (897.46 - 1021.99)	0.292
Native Thiol, mmol/L	460.85 ± 28.21	464.93 ± 25.67	452.46 ± 30.77	467.47 ± 25.45	0.163
Disulfidet, mmol/L	253.87 ± 3.18	254.06 ± 1.80	254.62 ± 3.22	253.00 ± 3.59	0.217
Total antioxidant status, mmol Trolox Eq/L	1.13 ± 0.07	1.18 ± 0.07	1.12 ± 0.06*	1.11 ± 0.06*	**0.006**
Total oxidant status, μmol H_2O_2 Eq/L	13 (7 - 48)	11 (8 - 48)	13.5 (7 - 31)	15 (7 - 46)	0.596
Oxidative stress index, AU	1.19 (0.56 - 4.42)	0.94 (0.63 - 4.36)	1.17 (0.56 - 2.61)	1.36 (0.58 - 4.42)	0.400
Myeloperoxidase, pM	41 (2 - 403)	28 (4 - 341)	42.5 (2 - 179)	44 (8 - 403)	0.640
Paraoxonase, U/L	83 (12 - 321)	121.5 (35 - 186)	55 (12 - 290)	72 (27 - 321)	0.175
Catalase, kU/L	28 (5 - 153)	21.5 (5 - 153)	27.5 (6 - 76)	29 (12 - 137)	0.724
Malate dehydrogenase, U/mL	14.22 ± 3.61	13.33 ± 3.77	15.38 ± 3.42	13.48 ± 3.54	0.125

Data are given as mean ± standard deviation or median (minimum - maximum) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. *: Significantly different from the control group, #: Significantly different from the Mild & Moderate group. Abbreviations: AU: Arbitrary unit, OSA: Obstructive sleep apnea.

3.4. Diagnostic Performance of Total AHD

Total AHD, with a cut-off value of >12 min, was able to distinguish patients with OSA from those without OSA with 100% sensitivity and 100% specificity (100% accuracy) [AUC (95.0% CI) = 1.000 (1.000 - 1.000), p < 0.001]. Total AHD with a cut-off value of >80 min was able to distinguish patients with severe OSA from those with mild & moderate OSA and without OSA with 100% sensitivity, 97.22% specificity, 98.31% accuracy, 95.83% PPV and 100.00% NPV [AUC (95.0% CI) = 0.999 (0.995 - 1.000), p < 0.001] (Table 3).

Table 3. Performance of the total apnea & hypopnea duration to predict sleep apnea.

	OSA (AHI≥5)	Severe OSA (AHI≥30)
Cut-off	>12 min	>80 min
Sensitivity	100.00%	100.00%
Specificity	100.00%	97.22%
Accuracy	100.00%	98.31%
PPV	100.00%	95.83%
NPV	100.00%	100.00%
AUC (95.0% CI)	1.000 (1.000 - 1.000)	0.999 (0.995 - 1.000)
p	**<0.001**	**<0.001**

Abbreviations: AUC: Area under ROC curve, AHI: Apnea-hypopnea index, CI: Confidence interval, NPV: Negative predictive value, OSA: Obstructive sleep apnea, PPV: Positive predictive value.

3.5. Correlation Analyses

There was a significant correlation between AHI and total AHD value in REM sleep (r = 0.867, p < 0.001), non-REM sleep (r = 0.971, p < 0.001), and total sleep (r = 0.974, p < 0.001) (Table 4). Other notable correlations were between TAS and AHI (r = -0.428, p = 0.001) and between TAS and RDI (r = -0.440, p < 0.001) in the non-REM period. When assessed for total sleep duration, TAS was also significantly correlated with AHI (r = -0.441, p < 0.001), AHD (r = -0.407, p = 0.001) and RDI (r = -0.445, p < 0.001) (Table 5).

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Table 4. Correlations between apnea-hypopnea index and apnea & hypopnea duration.

	REM	Non-REM	Total
r	0.867	0.971	0.974
p	**<0.001**	**<0.001**	**<0.001**

Abbreviations r: Correlation coefficient, REM: Rapid eye movement

Table 5. Correlations between Epworth Sleepiness Scale score, polysomnography results and laboratory measurements.

						REM			Non-REM			Total		
		ESS score	ODI	Average apnea duration	Longest apnea duration	AHI	Total AHD	RDI	AHI	Total AHD	RDI	AHI	Total AHD	RDI
ESS score	*r*	-	**0.389**	**0.294**	**0.310**	0.225	0.228	0.226	**0.357**	**0.378**	**0.282**	**0.365**	**0.384**	**0.362**
	p	-	**0.002**	**0.024**	**0.017**	0.086	0.082	0.085	**0.006**	**0.003**	**0.031**	**0.004**	**0.003**	**0.005**
Total Thiol	*r*	0.131	0.073	0.078	0.079	0.084	-0.003	0.068	0.157	0.089	0.144	0.145	0.082	0.143
	p	0.322	0.583	0.558	0.554	0.527	0.984	0.608	0.234	0.503	0.276	0.275	0.537	0.282
Native Thiol	*r*	0.086	0.111	0.173	0.080	0.108	0.013	0.093	0.180	0.118	0.170	0.172	0.114	0.171
	p	0.515	0.401	0.190	0.545	0.416	0.923	0.484	0.171	0.372	0.198	0.192	0.388	0.196
Disulfide	*r*	0.026	-0.196	-0.027	-0.012	-0.102	-0.115	-0.099	-0.108	-0.117	-0.131	-0.133	-0.131	-0.134
	p	0.844	0.137	0.838	0.926	0.442	0.384	0.456	0.417	0.377	0.322	0.314	0.322	0.311
Total antioxidant status	*r*	-0.175	**-0.362**	**-0.266**	-0.250	**-0.382**	**-0.271**	**-0.367**	**-0.428**	**-0.392**	**-0.440**	**-0.441**	**-0.407**	**-0.445**
	p	0.186	**0.005**	**0.042**	0.057	**0.003**	**0.038**	**0.004**	**0.001**	**0.002**	**<0.001**	**<0.001**	**0.001**	**<0.001**
Total oxidant status	*r*	0.078	0.076	0.158	0.081	0.087	0.043	0.079	0.146	0.133	0.161	0.151	0.131	0.149
	p	0.559	0.568	0.233	0.542	0.512	0.745	0.550	0.270	0.315	0.224	0.255	0.323	0.261
Oxidative stress index	*r*	0.097	0.128	0.188	0.110	0.132	0.079	0.122	0.204	0.188	0.221	0.210	0.187	0.209
	p	0.466	0.336	0.154	0.407	0.321	0.551	0.356	0.121	0.154	0.093	0.111	0.157	0.112
Myeloperoxidase	*r*	0.085	0.045	0.108	0.030	0.044	0.017	0.038	0.107	0.113	0.093	0.110	0.105	0.108
	p	0.524	0.736	0.416	0.819	0.738	0.898	0.774	0.421	0.396	0.484	0.409	0.429	0.415
Paraoxonase	*r*	0.106	0.019	-0.009	-0.015	0.074	0.058	0.076	0.013	-0.024	0.039	-0.005	-0.030	-0.002
	p	0.424	0.887	0.948	0.909	0.580	0.660	0.568	0.923	0.854	0.769	0.972	0.821	0.986
Catalase	*r*	0.075	0.041	0.220	0.132	0.050	-0.014	0.036	0.162	0.129	0.186	0.163	0.122	0.162
	p	0.572	0.758	0.093	0.320	0.707	0.917	0.788	0.222	0.330	0.157	0.218	0.357	0.221
Malate dehydrogenase	*r*	0.144	0.048	-0.184	-0.066	0.048	-0.025	0.043	0.073	0.024	0.052	0.078	0.029	0.078
	p	0.276	0.718	0.162	0.618	0.718	0.854	0.748	0.585	0.857	0.698	0.559	0.828	0.559

Abbreviations: AHD: Apnea and hypopnea duration, AHI: Apnea-hypopnea index, ESS: Epworth Sleepiness Scale, ODI: Oxygen desaturation index, r: Correlation coefficient, RDI: Respiratory disturbance index, REM: Rapid eye movement.

4. Discussion

The main findings of the present study were: (i) AHD (average, longest, total) was significantly higher in individuals with OSA compared to controls, regardless of sleep periods. (ii) Almost all AHD parameters of the severe OSA group were significantly higher than the mild & moderate group. (iii) Patients with OSA (regardless of severity) had significantly lower TAS levels than those without OSA. (iv) Total AHD > 12 min was able to distinguish patients with OSA and total AHD > 80 min was able to distinguish patients with severe OSA, with excellent performances. (v) There was a strong positive correlation between total AHD and AHI (regardless of sleep periods). (vi) Additionally, a moderate negative correlation was seen between TAS and total AHD.

Polysomnography is the 'gold standard' for the diagnosis of OSA, and the AHI in nighttime recordings has been used as the main parameter to diagnose and to stratify the severity of the disease [3,19]. Despite hypoxemia being identified as a significant factor in explaining the negative health consequences of OSA, there has been insufficient focus on alterations in the overall duration or average level of desaturation during apnea and hypopnea episodes. There may be a correlation between total AHD and heightened sympathetic nervous system activity over an extended period, resulting in heightened cardiovascular stress [5].

Our results concerning parameters of apnea and/or hypopnea duration (almost all) showed higher values in patients with OSA compared to controls, and in patients with severe OSA compared

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to those with less-severe disease, regardless of sleep periods. Total AHD was a perfect discriminator of OSA presence (cut-off: >12 minutes), and it also demonstrated excellent performance to distinguish severe OSA from less-severe disease and controls (100.00% sensitivity and 97.22% specificity). Also, there was a high (REM period) and very high (non-REM and total sleep periods) positive correlation between total AHD and AHI.

Previously, a retrospective study reported a significant but moderate correlation between mean AHD and AHI. It was shown that patients with longer average AHD (>25s) had significantly higher mean AHI value, ESS score and sleep efficiency, while they also had shorter sleep latency [3]. Muraja-Murro and colleagues demonstrated that there was a noteworthy rise in the overall duration of apnea events, overall duration of hypopnea events, and the total apnea-hypopnea duration (AHD) as a percentage of sleep time, as well as the mean duration of an individual apnea event, in accordance with the severity of OSA [5]. Wu et al. demonstrated that mean AHD (rather than AHI), ODI and lowest oxygen saturation were associated with worse hypertension in patients with OSA [20]. In a large community sample, shorter AHD was interestingly shown to predict higher 11-year mortality rates, even after adjusting for risks associated with AHI and confounders [21].

Although AHI is a widely-accepted parameter, it has several disadvantages. There are also questions about whether AHI can reflect the patient's condition and prognosis in severe disease [5]. Additionally, AHI has been shown to have inter- and intra-night variability, suggesting limited reliability [22,23]. Finally, some studies also have shown that while AHI remains unchanged, subjective symptoms improve in some patients following surgical treatment for OSA [24,25], which may be due to improvements in oxygen parameters after OSA surgery [3].

AHD may be the most favorable one of these candidate parameters. This is because it is anticipated that the AHD is just as crucial as the count of apneas and hypopneas in the development of negative health consequences and symptoms associated with OSA. However, it is known that AHD can vary greatly in patients with OSA [5] and patients with high AHI have been sometimes shown to have short AHD [3]. The latter point, however, may explain the presence of more severe symptoms in some patients with low AHI. Furthermore, AHD may provide new and valuable diagnostic information regarding the biological consequences of OSA [5]. One such idea has been emphasized by Zhan et al. [3]. They suggested that these two indices (AHI and AHD) are relatively independent, but may be complementary in the evaluation of patients with OSA, as AHI reflects the frequency of respiratory events and AHD reflects the severity of respiratory events.

In patients with OSA, OxS occurs as a result of intermittent hypoxia during sleep [7]. Biomarkers of OxS have the potential to be used to assess disease severity as well as individual response to treatment in a number of diseases [26–28]. Therefore, the relationship between OxS and OSA has been a subject of interest in recent years. While it has been suggested that individuals with OSA experience a greater burden of OxS, it has also been demonstrated that OxS decreases with continuous positive airway pressure treatment and that antioxidant therapies can be utilized in the management of OSA [9,12,29,30].

In the present study, only the TAS level was found to be lower in OSA patients compared to the control group. TAS levels did not change according to OSA severity. In addition, there were significant negative correlations between TAS levels and ODI (weak), average apnea duration (weak), longest apnea duration (weak), AHI, total AHD and RDI (weak) in the REM period. Similarly, in the non-REM period measurements, TAS was correlated with AHI (moderate), total AHD (weak) and RDI (moderate). In total sleep measurements, TAS demonstrated moderate correlations with AHI, total AHD and RDI.

Cofta et al. showed that TAS levels were lower, and thiobarbituric acid reactive substances were higher, in patients with OSA. Additionally, increased AHI was associated with decreased TAS and increased thiobarbituric acid reactive substance levels [1]. Another study showed that OSA patients had significantly higher plasma concentrations of malondialdehyde and lower glutathione peroxidase and superoxide dismutase activities. Also, significant differences were found in all the above parameters in patients with moderate OSA compared to those with mild OSA [31]. In some

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other studies, increased OxS markers and/or decreased antioxidant markers were found to be associated with the presence and/or severity of OSA [9,11,12]. A limited number of studies have investigated the relationship between OxS markers and AHD. In one of them, Asker et al. reported a mildly significant negative correlation between mean duration of apnea and glutathione peroxidase activity [32].

The inconsistency of the results may be due to the differences in OxS markers used, duration of hypoxia, and selected exclusion criteria. Although most studies reported increased OxS in patients with OSA compared to those without OSA, the exact mechanism by which OSA increases OxS is not known. Comprehending the impact of OxS on the pathophysiology of OSA and its associated complications, as well as its correlation with OSA severity, could aid in the enhancement of OSA-related morbidity and mortality through personalized antioxidant treatments. TAS measurements could be useful in diagnosing and classifying OSA since the imbalance between oxidant and antioxidant statuses may be due to decreased antioxidant capacity induced by respiratory event-related hypoxia.

Limitations of the Study

The study has some limitations. It is a single-center study with a small sample size, especially for controls. Apart from the fact that only individuals who were examined for OSA could be included in the control group, the most important reason for the low number of participants is the wide variety of exclusion criteria. These exclusion criteria were chosen because they could impact OxS parameters. This situation also creates the following limitation: the results obtained relate only to patients that meet the exclusion criteria, not the general population with OSA.

5. Conclusions

Total AHD was associated with the presence of OSA, severity of OSA and AHI. TAS levels were lower in patients with OSA compared to controls. TAS levels were negatively correlated with both AHI and total AHD and RDI. Total AHD seems to be a candidate measure that can be used in the diagnosis of OSA and classification of severity, as determined by excellent discriminatory results, which are appreciably better compared to the widely-used AHI. However, it appears that OxS parameters have limited use in this regard. There is a need for more comprehensive studies on the subject in order to assess the utility of AHD, particularly with population-based studies in patients with OSA.

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