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Hypoxia-Induced Inflammatory Mechanisms in Obstructive Sleep Apnea Syndrome

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Abstract

The most common sleep related respiratory disorder, which recurs with upper airway obstruction during sleep and intermittent hypoxia resulting in loss of normal sleep architecture is called Obstructive Sleep Apnea Syndrome (OSAS). These periods of hypoxia are recognized to activate systemic inflammatory pathways, oxidative stress, endothelial dysfunction and autonomic disbalance and increase risk of cardiovascular disease. This study aimed to gain insight into the inflammatory pathways activated by hypoxia in OSAS and their association with clinical and laboratory parameters and cardiovascular outcomes. Prospective observational case–control study done in Tikrit Teaching Hospital in Iraq, from January 2024 to January 2025 . A total 200 patients with OSAS as diagnosed by nocturnal polysomnography and 100 healthy control subjects matched for age and sex between the age of 25 to 55 years were included in this study. Results All patients underwent clinical examination, polysomnography and determination of the following: inflammatory cytokines (IL 6, TNF α, IL 1β), acute-phase reactants (hs CRP), oxidative stress markers (MDA, total antioxidant capacity) and hypoxia-inducible factor-1α (HIF 1α), adhesion molecules (ICAM 1 and VCAM 1) and cardiovascular analysis [blood pressure recordings, HRV heart rate variability)] evaluation of flow-mediated dilation)]. The results showed a significant increase in inflammation and oxidative stress markers, adhesion molecules and BP and decrease in antioxidant capacity, endothelial dysfunction and HRV membranes in patients with OSAS compared to controls ($p < 0.001$). We found associations between the different markers showing high inter-correlations between AHI, ODI and systemic biomarkers among the patients, suggesting that IH may also be a dose-response to inflammation and vascular dysfunction. Finally, OSAS is a “multisystem” disease that results in systemic inflammation and endothelial dysfunction, and autonomic nervous system imbalance due to IH. This indicates the need for timely identification and intervention using targeted treatments to prevent future cardiovascular issues.

Keywords: Obstructive Sleep Apnea, Intermittent Hypoxia, Inflammation, Oxidative Stress, Endothelial Dysfunction, Cardiovascular Risk.

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1. Introduction

One of the universally accepted respiratory syndromes, Obstructive Sleep Apnea Syndrome (OSAS) is frequent in children, as well as older people, all over the world. It is a syndrome of repeated partial or complete upper airway obstruction during sleep, accompanied by intermittent hypoxia, sleep fragmentation and swings in intrathoracic pressure [1]. This pathophysiological malrotation wreaks havoc not only on sleep quality, but also on a series of changes in multiple organ systems. Some of the health problems associated with OSAS are strongly related to increased risk of heart disease, poor glucose utilisation (type 2 diabetes and insulin resistance), mental health problems, memory loss and chronic inflammation. Of these, the inflammatory events caused by hypoxia are the more promising common pathway that links SO to its systemic comorbidities in OSAS [2,3].

Episodes of hypoxia are present in OSAS, periods of reduced O2 level, followed by reoxygenation. It is another response than to that provoked by chronic sustained hypoxia and powerfully induces cellular stress responses. Cyclic hypoxia/reoxygenation (H/R) occurs which leads to the production of reactive oxygen species (ROS) that causes oxidative stress, triggering multiple signaling pathways involved in inflammation [4]. Of these, the NF-κB signaling pathway, which is involved in the regulation of the production of TNF-α, IL-6, IL-1β and other pro-inflammatory cytokines has been studied most extensively. These cytokines lead to chronic low-grade systemic inflammation and many specialists agree that it is one of the main mechanisms for the development of metabolic and cardiovascular diseases in OSAS. In addition, the majority of the hypoxia stimuli (1 min) induced adhesion molecules (ICAM-1 and VCAM-1) which are involved in the recruitment of leukocytes to Microvasculature and increased hyperemia [5,6].

Oxidative stress and NF-κB activation have also been documented as being important in inflammation in OSAS and HIFs play a large role in this process as well. Hypoxia stabilizes the HIF-1alpha, which controls the transcription of genes involved in Angiogenesis, Metabolism and Inflammation (e.g.). HIF-1α activation leads to vascular remodeling, endothelial dysfunction and pro-inflammatory activities in various organs [7]. This oxidative stress, HIF signaling and release of inflammatory cytokines is the 'double-edged sword' responsible for this. This congregates and becomes vicious circle when tissue injury causes inflammation, oxygen depletion and attack by tissue consumption. The chronic inflammatory condition is considered as the main factor linking the intermittent hypoxemia of OSAS to the high risk of atherosclerosis, hypertension, acute myocardial infarction (MI) and stroke observed in these patients [8].

Furthermore, intermittent hypoxia that occurs in OSAS affects the autonomic nervous system (ANS) and increases sympathetic activity, which are both factors that contribute to the ongoing inflammation. The activation of the sympathetic nervous system (SNS) raises the levels of circulating catecholamines, which are known to cause cardiovascular stress and to alter the immune cells towards a pro-inflammatory state. Additionally, there was higher serum concentration of inflammatory mediators like CRP, tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and chemokine in moderate to severe OSAS patients than in healthy controls [9]. These are not only footprints of inflammation but also have been shown to be the cause of the pathogenic mechanism of OSAS related complications. Additionally, iatrogenic intermittent hypoxia results in adipokine dysregulation and a global inflammatory state with elevated adipokine levels (leptin and resistin) which may cause insulin resistance [10].

There is one interesting change which is hypoxic inflammation neurocognitive changes with OSA. CH has been associated with neurological and cognitive impairment and an increased risk of neurodegenerative diseases [11]. This is another mechanism by which neuroinflammation develops in patients with OSA, due to induced hypoxia. The inflammatory cytokines penetrate the BBB and induce interlaced memory loss, ADD and mood disorders [12]. These data reveal the systemic effects of hypoxia induced inflammation and indicate early diagnosis and treatment of OSAS should be necessary to avoid irreparable consequences [13].

Understanding underlying mechanism of hypoxia induced inflammation in OSAS is important as this will be needed to understand the pathogenesis of the disease and direct research towards novel treatment. There

are currently treatments such as CPAP (Continuous Positive Airway Pressure) that minimize and improve IH and inflammation in the body. Other pharmacological interventions and lifestyle factors against oxidative stress, NF-Î°B transduction and HIF regulation are also being investigated which might be added into the therapeutic arsenal and prognosis of the patients [14,15]. The purpose of this review is to: Review the mechanisms of hypoxia-induced inflammation in OSA; Evaluate the systemic effects of this inflammation, and; Explore the possibility of preventing and/or modulating comorbid condition(s) associated with OSA.

2. Methodology

2.1 Study Design and Setting

Design of the study: Prospective observational case control study was conducted in Tikrit Teaching Hospital, Salah ad Din government, Iraq. The research was conducted between January 2024 to January 2025 , to clarify the inflammatory mechanisms associated with IH among patients with OSAS. The study was approved by the Iraqi ethical review board of Tikrit Teaching Hospital and written consent was obtained from all the participants. The study was designed to ensure the reliability of data, valid internal control and relevant comparisons between OSAS patients group and control subjects.

2.2 Participants and Sampling

Three hundred participants from both sex, aged between 25-55 years were enrolled for this study. The sample consisted of patients referred to the sleep clinic of the hospital. Adult patients with suspected clinical OSAS (as indicated by frequent snoring or sleep pauses reported by bed partner, and excessive daytime sleepiness) with a prior overnight polysomnography (PSG) diagnosis of OSAS as defined by the American Academy of Sleep Medicine (AASM) criteria were included in the OSAS group. Participants with the following conditions were excluded: chronic inflammatory diseases (e.g. rheumatoid arthritis), smoking or recent respiratory infection (within 6 weeks of screening visit), pregnancy, active malignancy, systemic steroids or immunosuppressants that may interfere with inflammatory markers.

The subjects were split into two groups: OSAS group and control group. Twenty percent of patients (200) were diagnosed with OSA using PSG. The control group separated with 100 normal healthy volunteers, who do not have clinical evidence of SDB found on their polysomnography and age as well gender matched and were the staff members from the hospital and community. In addition, sleep questionnaires and initial home sleep apnea testing (where required) ensured that controls were negative for OSAS.

2.3 Data Collection Procedures

2.3.1 Clinical Assessment

Clinically examination was carried on all patients at baseline. It consisted in full medical history focusing on the main complaints related to sleep disordered breathing (snoring, witnessed apnea and nocturnal choking), daytime somnolence scale that was assessed by Epworth Sleepiness Scale (using ESS) and comorbid conditions such as hypertension, diabetes mellitus and cardiovascular disease. BMI and neck circumference (NC), waist/hip ratio (WHR) have been found to be correlated with severity of OSAS.

2.3.2 Polysomnography (PSG)

Overnight polysomnography was performed in all OSA patients with a digital sleep laboratory (Alice 6 LDx, Philips Respironics) following manufacturers' instructions. Recorded parameters were electroencephalogram (EEG), electrooculography (EOG), submental and tibial electromyogram (EMG)air flow (pressure thermistor), respiratory effort (thoracic and abdominal bands), heart rate (EGG) and five-lead continuous pulse oximetry. The sleep stages were visually scored following the American Academy of Sleep Medicine (AASM) scoring manual and the diagnosis of OSAS was based on Apnea–Hypopnea Index (AHI). OSAS was defined as mild (AHI 5-15 events/hour), moderate (AHI 15-30 events/hour) and severe (AHI >30 events/hour).

2.4 Biochemical and Inflammatory Parameter Assessment

2.4.1 Blood Sampling

All participants with OSAS and controls were subjected to venipuncture in the morning following the night of polysomnography (between 07:00 and 09:00). B) were collected in EDTA and serum separator tubes, processed within 1 h and then stored at −80°C until analysis. Routine precautions were followed for reducing pre analytical variability.

2.4.2 Inflammatory and Oxidative Stress Biomarkers

A large number of biomarkers were identified that are associated with pro inflammatory pathways, including concentrations of pro inflammatory cytokines in the serum (e.g., IL 6, TNF α, IL 1β) using high sensitivity enzyme linked immunosorbent assays (ELISAs) (e.g., Quantikine HS, R&D Systems).

C reactive protein (hs CRP) was measured using a high sensitivity immunoturbidimetric assay (e.g., Tina quant hs CRP, Roche Diagnostics). Oxidative stress, we measured plasma levels of malondialdehyde (MDA) by thiobarbituric acid reactive substances (TBARS) assay and total antioxidant capacity was determined by colorimetric assays (from e.g., Cayman Chemical kits). Hypoxia inducible factor (HIF), serum HIF 1α was measured by sandwich ELISA assay (Ela science). The clinical research was done by using commercially available ELISA kits for adhesion molecules (ICAM 1 and VCAM 1) and serum.

The parameters were chosen because of their role in inflammatory signaling, oxidative stress, endothelial dysfunction, and hypoxia response pathways of OSAS pathophysiology.

2.4.3 Additional Physiological Measurements

They also received cardiovascular assessments, such as resting blood pressure (Omron HEM 907XL), heart rate variability (HRV; measure of autonomic activity) and flow mediated dilation at the brachial artery (measure of endothelial function) by high resolution ultrasound (GE LOGIQ P9), in addition to biochemical markers. These results indicated that IH and inflammation caused systemic modifications.

2.5 Statistical Analysis

Results collected data were analyzed via SPSS ver. 23. The continuous data were reported as means ± standard deviation or median (interquartile range) according to their distribution. Independent t tests or Mann Whitney U tests were used to compare the OSAS and control groups. Spearman or Pearson correlation test was used to test the relationship between the PSIG indices (AHI and ODI) and inflammatory markers. Multivariate regression models were used to control for possible confounding variables including age, BMI and comorbidities. All statistical procedures were performed on 2 sides and a p value<0.05 was considered significant.

3. Results

3.1 Demographic and Clinical Characteristics

Subjects' detailed demographic and clinical features are presented in Table 1 and in Figure 1. The OSAS group (n=200) and control group (n=100) were matched in terms of age distribution and gender, however significant differences existed for BMI, neck circumference and ESS which are all indicators of the clinical impact of OSAS.

Table 1. Demographic and Clinical Characteristics of Study Participants

Parameter	OSAS Group	Control Group	p-value
Age (years, mean ± SD)	41.3 ± 8.1	40.7 ± 7.9	0.45
Gender (M/F)	120/80	60/40	0.98
BMI (kg/m², mean ± SD)	31.5 ± 4.2	25.6 ± 3.1	<0.001

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Parameter	OSAS Group	Control Group	p-value
Neck circumference (cm)	42.1 ± 3.5	37.8 ± 2.9	<0.001
ESS score (mean ± SD)	13.4 ± 4.1	5.8 ± 2.6	<0.001

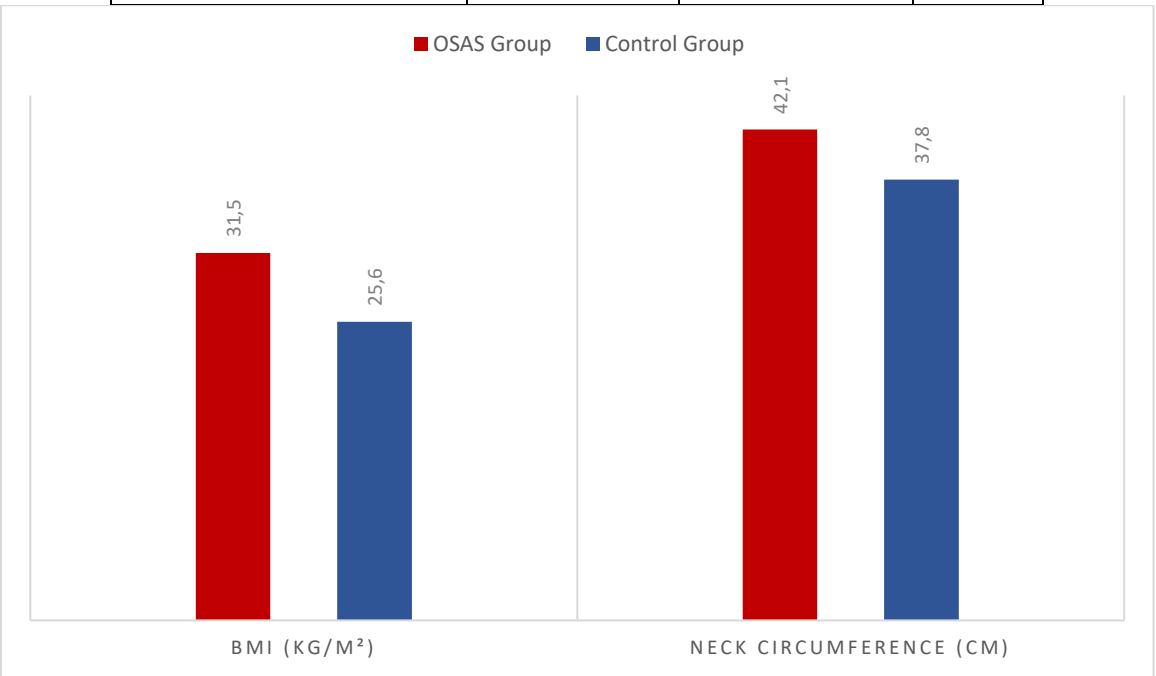


Figure 1. Evaluation of BMI and neck circumference in OSAS as well as control groups.

3.2 Polysomnographic Findings

The AHI and ODI were significantly higher in the OSAS group, indicative of sleep-disordered breathing and intermittent hypoxia. Conversely, the control group had normal sleep architecture was nearly devoid of any respiratory events and maintained a stable oxygen saturation throughout night. These results help to underlie the different characteristic of OSAS patients as compared to healthy subjects.

Table 2. Polysomnographic Parameters in OSAS and Control Groups

Parameter	OSAS Group	Control Group	p-value
Total Sleep Time (min)	362 ± 42	368 ± 35	0.12
Sleep Efficiency (%)	78.5 ± 9.4	85.3 ± 6.1	<0.001
Apnea-Hypopnea Index (events/hr)	28.7 ± 12.5	3.1 ± 1.4	<0.001
Oxygen Desaturation Index (ODI, events/hr)	22.3 ± 10.1	1.8 ± 0.9	<0.001
Mean SpO_2 (%)	92.1 ± 3.5	96.8 ± 1.2	<0.001
Lowest SpO_2 (%)	78.6 ± 6.2	92.5 ± 1.5	<0.001

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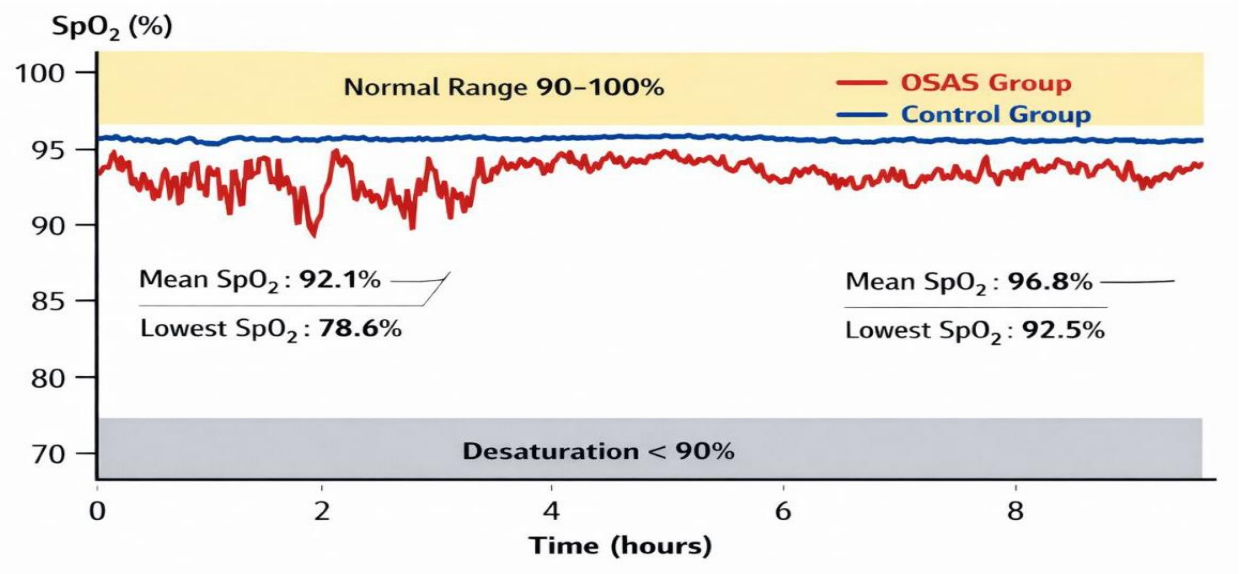


Figure 2. Oxygen saturation patterns overnight in OSAS patients compared to control.

3.3 Inflammatory Biomarkers

Table 3 and Figure 3 indicate that serum inflammatory markers, such as IL-6, TNF-α, IL-1β and hs-CRP level, were significantly elevated in OSAS patients in comparison to controls. The image illustrates the process of intermittent hypoxia leading to inflammation in the whole body.

Table 3. Inflammatory Biomarkers in OSAS and Control Groups

Biomarker	OSAS Group	Control Group	p-value
IL-6 (pg/mL)	12.5 ± 3.8	4.2 ± 1.5	<0.001
TNF-α (pg/mL)	18.7 ± 5.1	7.6 ± 2.3	<0.001
IL-1β (pg/mL)	6.9 ± 2.4	2.1 ± 1.0	<0.001
hs-CRP (mg/L)	5.8 ± 2.2	1.7 ± 0.9	<0.001

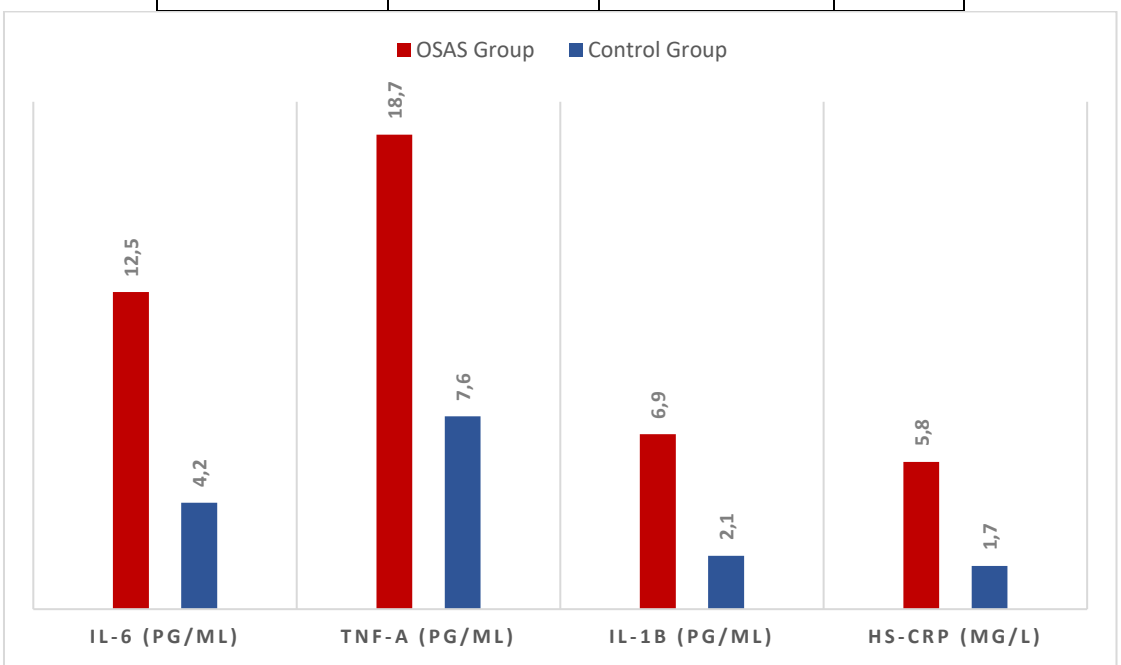


Figure 3. Comparison of pro-inflammatory cytokines between OSAS and control groups.

3.4 Oxidative Stress and Hypoxia-Inducible Factor

As expected, the level of oxidative stress markers and the expression of HIF-1α were significantly increased in OSAS patients (Table 4), supporting the link between intermittent hypoxia and systemic oxidative stress.

Table 4. Oxidative Stress and HIF-1α Levels

Parameter	OSAS Group	Control Group	p-value
Malondialdehyde (MDA, μmol/L)	5.6 ± 1.2	2.8 ± 0.7	<0.001
Total Antioxidant Capacity (TAC, mmol/L)	1.1 ± 0.3	1.8 ± 0.4	<0.001
HIF-1α (ng/mL)	4.7 ± 1.5	1.9 ± 0.8	<0.001

3.5 Adhesion Molecules and Endothelial Function

There was a significant increase in serum VCAM-1 and ICAM-1 levels, which suggest endothelial activation in OSAS patients. In OSAS, flow mediated dilation (FMD) was reduced, indicating endothelial dysfunction (Table 5).

Table 5. Adhesion Molecules and Endothelial Function

Parameter	OSAS Group	Control Group	p-value
ICAM-1 (ng/mL)	310 ± 45	180 ± 30	<0.001
VCAM-1 (ng/mL)	450 ± 60	290 ± 40	<0.001
Flow-Mediated Dilation (FMD, %)	5.2 ± 1.1	8.7 ± 1.5	<0.001

3.6 Cardiovascular Parameters

Resting blood pressure and indices of heart rate variability (HRV) were associated with increased sympathetic activity in the patients with OSAS, consistent with autonomic abnormalities due to hypoxia (Table 6).

Table 6. Cardiovascular Parameters

Parameter	OSAS Group	Control Group	p-value
Systolic BP (mmHg)	136 ± 12	122 ± 10	<0.001
Diastolic BP (mmHg)	86 ± 8	74 ± 7	<0.001
HRV (SDNN, ms)	72 ± 15	102 ± 18	<0.001

3.7 Correlation of Measurable Parameters Associated with Severity of OSAS

Table 7 summarizes the results of the study. Significant positive correlations were found with inflammatory markers, markers of oxidative stress, adhesion molecules and blood pressure with AHI/ODI. A negative correlation was found for antioxidant capacity HRV and FMD with AHI/ODI, which corresponds to a positive association with intermittent hypoxia and systemic inflammation, endothelial dysfunction and autonomic dysregulation.

Table 7. Correlation of OSAS Severity (AHI, ODI) with Inflammatory, Oxidative, Endothelial, and Cardiovascular Parameters

Parameter	Correlation with AHI (r)	p-value	Correlation with ODI (r)	p-value
IL-6 (pg/mL)	0.68	<0.001	0.65	<0.001
TNF-α (pg/mL)	0.61	<0.001	0.59	<0.001

Parameter	Correlation with AHI (r)	p-value	Correlation with ODI (r)	p-value
IL-1β (pg/mL)	0.57	<0.001	0.54	<0.001
hs-CRP (mg/L)	0.63	<0.001	0.60	<0.001
MDA (μmol/L)	0.66	<0.001	0.64	<0.001
TAC (mmol/L)	-0.52	<0.001	-0.50	<0.001
HIF-1α (ng/mL)	0.70	<0.001	0.68	<0.001
ICAM-1 (ng/mL)	0.62	<0.001	0.60	<0.001
VCAM-1 (ng/mL)	0.65	<0.001	0.63	<0.001
FMD (%)	-0.55	<0.001	-0.53	<0.001
Systolic BP (mmHg)	0.60	<0.001	0.57	<0.001
Diastolic BP (mmHg)	0.58	<0.001	0.56	<0.001
HRV (SDNN, ms)	-0.54	<0.001	-0.52	<0.001

4. Discussion

This study seems to give convincing support that OSAS is part of a cascade of inflammation, oxidative, endothelial and cardiac damage due to the IH. In the present study, in line with reports from prior meta-analyses and clinical studies, OSAS patients were found to have significantly higher systemic inflammation markers such as IL-6, TNF-α, IL-1β and hs-CRP when compared to control subjects. In line with a meta-analysis that identified increased levels of CRP, TNF-α, IL-6, and adhesion molecules in OSA (a state associated with repeated oxygen desaturation), this suggests to be inflammatory milieu in a chronic low-grade inflammation [16]. The results confirm the observations of mechanistic studies that IH mainly induces signaling pathways related to inflammation which participate in the functionality of NF κB and HIF 1α. As a result, they produce pro-inflammatory cytokines and vascular adhesion molecules, and ultimately result in the endothelial cell becoming dysfunctional and triggering early atherosclerotic events [17].

As well as significantly lower total antioxidant capacity, the OSAS group also presented with higher oxidative stress markers, such as malondialdehyde. This seems to follow the hypothesis that ROS are generated during each cycle of hypoxia and reoxygenation, surpassing the ability of the endogenous antioxidant system, and thus resulting in an oxidative attack. Similarly, to other studies, this suggests an increase in ROS production and a reduction of nitric oxide level in OSAS [18,19]. Positive airway pressure therapy may decrease the levels of circulating adhesion molecules with cardiovascular risk markers in patients with OSA from a more comprehensive viewpoint. Also, there was an overexpression of adhesion molecules (ICAM 1, VCAM 1) in the subgroup as reported by large systematic studies [20].

The endothelial function determined by flow mediated dilation (FMD) was significantly reduced in the OSAS patients. In this way, increased oxidative stress and endothelial dysfunction (OS/ED) in OSAS patients are contributory factors to development of future CVD [21]. This finding is consistent with the link between moderate-to-severe OSAS and endothelial dysfunction and arterial stiffness found in metanalysis studies, which has been proposed as a mechanism that contributes to CVD risk [22]. Moreover, both AHI and ODI have also been closely correlated with inflammatory, oxidative stress and endothelial dysfunction and with reduced blood pressure and heart rate associated with autonomic dysfunction, which suggest a pathophysiological axis between autonomic dysfunction, systemic inflammation and vascular damage.

Inflammation is an intermediate risk factor for cardiovascular disease, and these pathophysiologic changes are consistent with previous work, which associated inflammatory markers with OSA's subclinical atherosclerosis (as defined by CIMT) [23]. Furthermore, our biomarker data are also of therapeutic value as previous studies have demonstrated that the intermittent hypoxia occurring with OSA may cause activation and dysfunction of endothelial cells in human coronary arteries [24]. The inflammatory and oxidative pathways triggered by IH, which lead to endothelial dysfunction and autonomic instability in some patients and not others, depending on gender, are likely a common underlying mechanism for increased cardiovascular risk profiles in OSAS patients, as suggested by our findings.

5. Conclusion

Last, but not least, OSA is associated with significant systemic inflammation, oxidative stress, endothelial dysfunction and autonomic instability due to the intermittent hypoxia. These pathological processes are tightly correlated with increased inflammatory cytokines (IL-6, TNF-α, IL-1β), oxidative indices (MDA and HIF-1α) and adhesion molecules (ICAM-1 and VCAM-1) as well as reduction in FMD and changes in cardiovascular parameters (elevation of blood pressure or reduction in HRV) which are closely related to the severity of OSAS. These results offer additional support that OSAS is a multi-systemic condition that has a significant impact on the cardiovascular system. Early detection and early targeted therapies are important, since there are significant links between OSAS severity and systemic biomarkers to reduce long-term morbidity. Complete clinical work-ups such as inflammatory and vascular profiles may be helpful for risk stratification in patients with OSAS and for guiding a comprehensive approach to OSAS care.

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