Review / *Derleme*

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The Central Role of Oxidative Stress in the Pathogenesis of Obstructive Sleep Apnea Syndrome: Mechanisms, Biomarkers, and Clinical Implications

Obstrüktif Uyku Apnesi Sendromunun Patogenezinde Oksidatif Stresin Merkezi Rolü: Mekanizmalar, Biyobelirteçler ve Klinik Sonuçlar

Mustafa Murat Öztürk

Kırşehir Ahi Evran Üniversitesi, Sağlık Hizmetleri Meslek Yüksekokulu, Elektronörofizyoloji Programı, Kırşehir, Türkiye

Abstract

Obstructive sleep apnea (OSA) syndrome is an increasingly prevalent sleep disorder characterized by recurrent upper airway obstructions and associated intermittent episodes of hypoxia. OSA is associated with cardiovascular, metabolic, and neurological morbidity. Recent evidence indicates that the oxidative stress and inflammation caused by intermittent hypoxia play a central role in the pathophysiological consequences of OSA. This review aims to summarize the mechanistic links between OSA and oxidative stress, biomarkers, clinical implications, and treatment approaches. Future research directions are also discussed in light of emerging data from human and animal studies.

Keywords: Obstructive sleep apnea, oxidative stress, reactive oxygen species

Öz

Obstrüktif uyku apne (OSA) sendromu, tekrarlayan üst solunum yolu tıkanıklıkları ve buna bağlı aralıklı hipoksi ataklarıyla karakterize, giderek yaygınlaşan bir uyku bozukluğudur. OSA, kardiyovasküler, metabolik ve nörolojik morbidite ile ilişkilidir. Son yıllarda, aralıklı hipoksinin neden olduğu oksidatif stres ve enflamasyonun OSA patogenezinde merkezi bir rol oynadığına dair güçlü kanıtlar ortaya çıkmıştır. Bu derleme, OSA ile oksidatif stres arasındaki mekanik bağlantıları, biyobelirteçleri, klinik sonuçları ve tedavi yaklaşımlarını özetlemeyi amaçlamaktadır. Gelecekteki araştırma alanları da insan ve hayvan çalışmalarından elde edilen kanıtlar ışığında tartışılacaktır.

Anahtar Kelimeler: Obstrüktif uyku apnesi, oksidatif stres, reaktif oksijen türleri

Introduction

Obstructive sleep apnea (OSA) syndrome is a respiratory disorder characterized by recurrent partial or complete obstruction of the upper airway during sleep, resulting in cumulative physiological disruptions. Clinically, the condition typically presents with loud snoring, repeated arousals, excessive daytime sleepiness, and a marked decrease in attention, memory, and executive functions (1). In recent years, large cohort studies have emphasized that OSA is not merely a sleep disorder but a systemic disease with multifaceted links to cardiometabolic disorders such as hypertension, atherosclerosis, ischemic stroke, heart failure, atrial fibrillation, insulin resistance, and metabolic syndrome (2). Intermittent hypoxia (IH) is central to this broad spectrum of OSA comorbidities. Through frequent nocturnal oxygen fluctuations, IH severely disrupts cellular metabolism. This cycle of hypoxia and reoxygenation creates irregularities in mitochondrial membrane flow, increases NADPH oxidase (NOX) activation (especially NOX2), and leads to excessive reactive oxygen species (ROS) production (3). ROS accumulation triggers the production of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), as well as endothelial dysfunction by activating transcription factors such as nuclear factor kappa B (NF-κB)

Address for Correspondence/Yazışma Adresi: Mustafa Murat Öztürk, Kırşehir Ahi Evran Üniversitesi, Sağlık Hizmetleri Meslek Yüksekokulu, Elektronörofizyoloji Programı, Kırşehir, Türkiye

E-mail: mustafa.ozturk@ahievran.edu.tr **ORCID-ID:** orcid.org/0000-0002-2302-0018

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and hypoxia-inducible factor 1-alpha (4). The same process reduces nitric oxide (NO) bioavailability, accelerates lipid peroxidation [yielding byproducts such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE], and promotes vascular wall stiffening.

Recent experimental models have shown that IH not only induces oxidative stress but also impairs mitochondrial biogenesis, exacerbates endoplasmic reticulum stress, dysregulates autophagic balance, and triggers epigenetic changes associated with clinical severity (5). Over the long-term, these mechanisms severely compromise cardiovascular integrity. Impaired endothelial function, increased arterial stiffness, autonomic nervous system dysfunction, and shifts in metabolic homeostasis drive the systemic effects of OSA (6).

Understanding the relationship between OSA and oxidative stress is important not only for elucidating the pathophysiology of the disease but also for identifying novel therapeutic targets. Anti-inflammatory molecules, NOX inhibitors, mitochondria-targeted antioxidants (e.g., Mitochondria- targeted Coenzyme Q 10 (MitoQ). agents that modulate the hypoxic response, and non-invasive approaches that improve sleep architecture are among the potential therapeutic options (7). This review discusses the molecular mechanisms of IH, ROS sources, oxidative stress biomarkers, clinical outcomes, and current treatment strategies.

Materials and Methods

This narrative review is based on a comprehensive literature search of the PubMed, Scopus, and Web of Science databases. Studies published in English were screened using the keywords “obstructive sleep apnea”, “oxidative stress”, “biomarkers”, “pathogenesis”, and related terms.

Articles were evaluated according to their scientific relevance, methodological quality, and their contribution to understanding the molecular mechanisms and clinical implications of oxidative stress in OSA. Priority was given to original research articles, clinical studies, and recent review papers addressing oxidative stress pathways, associated biomarkers, and their potential role in disease pathogenesis and management.

Statistical Analysis

As this study is a narrative review based on previously published literature, no statistical analysis was performed.

Oxidative Stress and Its Cellular Basis

Oxidative stress refers to an imbalance between oxidant molecules [primarily ROS and reactive nitrogen species (RNS)] and cellular antioxidant defense systems, in favor of the oxidants. Under physiological conditions, redox signaling plays an essential regulatory role; however, excessive oxidant generation or impaired antioxidant capacity disrupts cellular homeostasis and promotes tissue injury.

In OSA, recurrent cyclical IH and reoxygenation act as a major trigger for oxidative stress by activating mitochondrial and enzymatic oxidant-producing pathways. This process contributes to endothelial dysfunction, inflammation, and progressive organ damage. An overview of the major oxidative stress-related mechanisms involved in OSA is presented in Figure 1.

Intermittent Hypoxia and Oxidative Stress Mechanisms in Obstructive Sleep Apnea Syndrome

Oxidative stress in OSA primarily arises from repetitive cycles of IH and reoxygenation, which markedly increase the production of ROS and RNS. While low levels of ROS are involved in physiological processes such as cellular signaling and vascular regulation, sustained hypoxia-induced oxidant generation overwhelms antioxidant defenses and leads to pathological redox imbalance (8).

The principal cellular sources of ROS in OSA include the mitochondrial electron transport chain (ETC), particularly complexes I and III, and enzymatic systems such as NOX isoforms (NOX1, NOX2, and NOX4), xanthine oxidase, and inducible NO synthase (9). Mitochondrial electron leakage during hypoxia–reoxygenation cycles represent a major source of superoxide anion ($O_2^{\bullet -}$), while NOX enzymes amplify inflammatory ROS production, especially in endothelial cells and immune cells (10).

ROS, including $O_2^{\bullet -}$, hydrogen peroxide, and hydroxyl radicals ($\bullet OH$), along with RNS such as peroxynitrite ($ONOO^-$), induce oxidative damage to DNA, proteins, and lipids. This process leads to the generation of lipid peroxidation products such as MDA and 4-HNE, further exacerbating inflammation and vascular injury (11).

To counteract oxidative damage, cells rely on a coordinated antioxidant defense system. Enzymatic antioxidants—including superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx)—work alongside non-enzymatic molecules such as glutathione, vitamins C and E, carotenoids, flavonoids, and coenzyme Q10 to maintain redox balance (12). In OSA, oxidative stress emerges from the combined effects of increased oxidant production and insufficient or exhausted antioxidant capacity, a dual mechanism that underlies persistent oxidative injury in chronic disease states (8).

Mitochondrial Sources

IH disrupts the efficiency of oxidative phosphorylation by causing irregular electron flow in the mitochondrial ETC. During periods of hypoxia, electron accumulation occurs particularly at steps I and III of the ETC; during the reoxygenation phase, these accumulated electrons rapidly interact with oxygen, significantly increasing $O_2^{\bullet -}$ formation (13). This process constitutes the most fundamental source of oxidative stress in the hypoxia–reoxygenation cycles specific to IH.

Chronic IH exposure is associated with more persistent effects beyond an acute increase in ROS production. These include mitochondrial dysfunction, decreased ATP synthesis, collapse of the mitochondrial membrane potential, decreased complex I activity, and suppression of mitochondrial biogenesis (14). Mitochondrial DNA is highly susceptible to oxidative damage because it lacks protective histones. Under IH conditions, a decrease in mitochondrial DNA copy number and impaired DNA replication have been reported, along with the accumulation

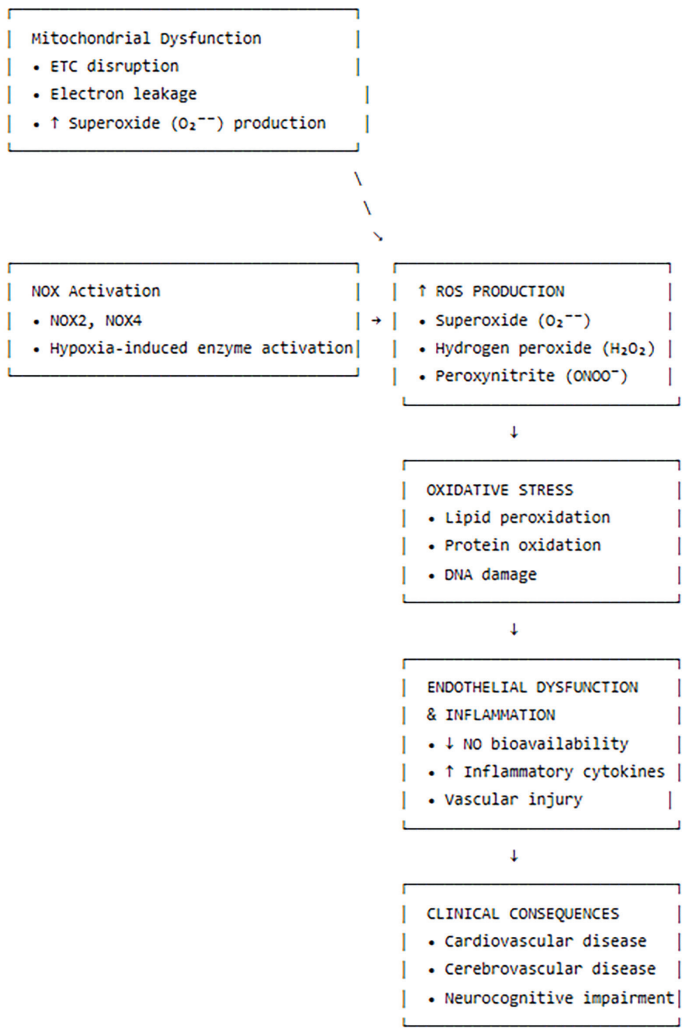

Figure 1. Schematic overview of oxidative stress pathways in obstructive sleep apnea.
ETC: Electron transport chain, NO: Nitric oxide, NOX: NADPH oxidase, ROS: Reactive oxygen species.

of 8-hydroxy-2'-deoxyguanosine (8-OHdG), an indicator of oxidative DNA damage (15).

Increased ROS accumulation triggers cytochrome c release, activating mitochondria-dependent apoptosis. This is supported by experimental models demonstrating that IH induces a pro-apoptotic shift in the Bcl-2- associated X protein/ B-celllymphoma 2 (Bax/ Bcl-2) balance, increases caspase-3 activation, and compromises cellular integrity (16). Therefore, IH is associated not only with oxidative stress but also with chronic disruption of mitochondrial integrity.

NADPH Oxidase

The NOX enzymes are among the primary oxidative enzyme complexes responsible for the production of extracellular $O_2^{\bullet-}$ and are particularly abundant in endothelial cells, neutrophils, and monocytes. IH significantly upregulates NOX2 and NOX4 expression via increased sympathetic nervous system activation, elevated angiotensin II levels, and increased inflammatory cytokines such as TNF-α and IL-6 (17). This increases basal ROS production and heightens cellular sensitivity to hypoxia–reoxygenation cycles.

NOX-derived ROS are key triggers of endothelial dysfunction, primarily by reducing NO bioavailability in the endothelium. Specifically, $O_2^{\bullet-}$ reacts with NO to form $ONOO^-$. This potent oxidant causes nitration damage, markedly reduces vascular relaxation capacity, and impairs endothelial NO synthase function through a phenomenon known as "uncoupling" (18). Furthermore, NOX activation contributes to structural remodeling of the vessel wall by promoting proliferation of vascular smooth muscle cells (19).

In chronic IH models, NOX2 has been identified as the predominant ROS source, and NOX2 inhibition has been shown to improve endothelial function, reduce oxidative damage, and significantly attenuate vascular inflammation (20). Therefore,

NOX activation is considered a key pathobiological driver in both the onset and progression of IH-related vascular damage.

Ischemia–Reperfusion-Like Processes and Other Sources

IH and sleep fragmentation in OSA activate multiple sources of oxidative stress. Xanthine oxidase activation, combined with ROS production by neutrophils and macrophages, leads to increased local and systemic oxidative load (21). Xanthine oxidase produces $O_2^{\bullet-}$ and H_2O_2 during purine metabolism. This mechanism is particularly critical in vascular endothelial and cardiovascular tissue damage (22).

In addition, the NAD^+/SIRT (sirtuin) balance plays an important role in regulating cellular energy metabolism and antioxidant defense pathways. IH can reduce NAD^+ levels and impair SIRT activity, which contributes to increased oxidative stress by hindering mitochondrial ROS scavenging capacity (23).

Endoplasmic reticulum stress and mitochondria–endoplasmic reticulum interactions are also mechanisms that increase oxidative load in the context of OSA. The endoplasmic reticulum stress response (specifically the unfolded protein response) is associated with excessive ROS production, and mitochondria-associated membranes facilitate ROS signaling and cellular apoptotic responses (24). Collectively, these pathways contribute to the development of both vascular and metabolic complications in individuals with OSA.

Biomarkers: Diagnosis, Severity Assessment, and Prognosis

Both direct and indirect biomarkers are used to assess oxidative stress in OSA. Significant changes in most of these markers have been reported due to IH-associated ROS increase, systemic inflammatory activation, and impaired antioxidant defense capacity. The categories of commonly used biomarkers and their relationship with OSA are summarized below.

Although no single gold-standard biomarker of oxidative stress in OSA has been established, current evidence suggests that certain markers may hold greater clinical promise. Among these, circulating asymmetric dimethylarginine and 8-isoprostane appear particularly relevant due to their reproducibility, association with disease severity, and links to endothelial dysfunction. When combined with inflammatory markers such as high-sensitivity CRP, these biomarkers may offer a more pragmatic and clinically informative approach than relying on a single oxidative stress indicator.

Lipid Peroxidation Products

MDA and 4-HNE levels are significantly elevated in OSA patients. Meta-analyses have reported a dose-response relationship between MDA levels and OSA severity and demonstrated that continuous positive airway pressure (CPAP) treatment reduces these levels (25).

Protein Oxidation

Protein carbonyls are relatively stable and easily measurable indicators of oxidative stress. Current literature demonstrates that protein carbonylation is increased in OSA patients and positively correlates with disease severity (26).

DNA Damage

The molecule 8-OHdG, a key marker of DNA oxidation, is elevated in both the serum and urine samples of OSA patients. This increase is particularly associated with severe OSA and intense IH exposure. Studies have also shown that 8-OHdG levels decrease with CPAP treatment (27).

Antioxidant Defense Markers:

Total antioxidant capacity (TAC), SOD, catalase, and GPx activities have been investigated in numerous studies. Although findings are heterogeneous, most studies show that antioxidant capacity is reduced in OSA, consistent with increased oxidative load (28). Furthermore, more pronounced decreases in erythrocyte SOD and GPx activities have been reported in severe OSA.

Nitrosative Stress and NO Metabolites

Nitrite/nitrate levels and protein nitrosylation products may be elevated in OSA. $ONOO^-$ formation exacerbates vascular dysfunction by reducing endothelial NO bioavailability (29). Furthermore, nitrosative stress is implicated in the pathogenesis of cardiometabolic comorbidities.

Most of these biomarkers correlate with OSA severity, IH severity, and CPAP compliance. However, their clinical use has not yet been standardized due to differences in measurement methods, biomarker stability, and heterogeneity in study designs.

Table 1 summarizes the main oxidative stress biomarkers used in OSA studies, their measurement methods, and their clinical correlations.

Table 1. Oxidative stress biomarkers commonly used in obstructive sleep apnea.

Biomarker	Measurement method	Clinical correlation
MDA	TBARS method	Lipid peroxidation indicator; correlates with OSA severity
4-HNE	ELISA/GC-MS	Lipid oxidation product
8-OHdG	HPLC/ELISA	DNA oxidation indicator; correlates with apnea-hypopnea index
Protein carbonyl	DNPH method	Protein oxidation
TAC	Spectrophotometric tests	Total antioxidant capacity
SOD, GPx, catalase activities	Enzymatic analyses	Antioxidant defense

4-HNE: 4-hydroxynonenal, 8-OHdG: 8-hydroxy-2'-deoxyguanosine, DNPH: 2,4-dinitrophenylhydrazine, ELISA: Enzyme-linked immunosorbent assay, GC-MS: Gas chromatography-mass spectrometry, GPx: Glutathione peroxidase, HPLC: High-performance liquid chromatography, MDA: Malondialdehyde, OSA: Obstructive sleep apnea, SOD: Superoxide dismutase, TAC: Total antioxidant capacity, TBARS: Thiobarbituric acid reactive substances.

Clinical Effects: Vascular and Metabolic Outcomes

Oxidative stress in OSA leads to multifaceted systemic damage through the ROS increase triggered by IH, endothelial dysfunction, and inflammatory activation. This pathophysiological cascade leads to significant clinical consequences affecting the cardiovascular, metabolic, and neurological systems.

Cardiovascular Effects

Oxidative stress associated with OSA is one of the key determinants of vascular dysfunction, along with increased vascular tone, decreased endothelial NO bioavailability, and increased proinflammatory cytokines (30). Reactive species such as $O_2^{\bullet -}$ and $ONOO^-$ further reduce NO production by inducing endothelial NO synthase "uncoupling." This results in decreased vasodilation capacity, increased arterial stiffness, and elevated blood pressure (31).

Furthermore, lipid peroxidation and endothelial activation accelerate the formation and progression of atherosclerotic plaques. Platelet activation and hyperaggregability are other common oxidative stress-related changes in OSA that increase the risk of cardiovascular events (32).

Metabolic Consequences

Oxidative stress impairs the IRS-1 and PI3K/Akt pathways, which are critical for insulin signaling. This increases insulin resistance by reducing glucose uptake in muscle and adipose tissue (33). Furthermore, increased free fatty acid levels, lipolysis activation, and accelerated steatogenic processes in the liver exacerbate the adverse effects of OSA on metabolic syndrome components. In untreated OSA, chronic inflammation, adipokine dysregulation (particularly increased leptin and decreased adiponectin), and ongoing oxidative damage significantly raise the risk of type 2 diabetes (34).

Neurological Effects

Oxidative stress caused by IH compromises neural integrity through mitochondrial dysfunction, glial cell activation, and neuroinflammation. Both animal and human studies have demonstrated structural and functional impairments, particularly in the hippocampus and prefrontal cortex regions. These changes are associated with deficits in attention, memory, and executive function. Furthermore, oxidative stress has been linked to a reduction in neuronal connectivity and a decrease in hippocampal neurogenesis rate. This is one of the key findings explaining the neurobiological basis of OSA's cognitive effects (35).

These multidimensional effects of OSA demonstrate that oxidative stress serves as both a trigger and perpetuator of systemic pathology. Therefore, oxidative stress markers are considered valuable tools not only for understanding pathophysiology but also for monitoring treatment response.

Treatment Effects and Antioxidant Strategies

Continuous Positive Airway Pressure and Oxidative Stress

CPAP is the standard treatment for OSA and reduces the oxidative stress load by preventing IH. Following CPAP therapy, a decrease in ROS production, an increase in NO bioavailability, and a marked improvement in endothelial function have been reported. These clinical benefits are supported by improvements in flow-mediated dilation, increased circulating NO levels, and decreased lipid peroxidation markers (36).

When evaluated in terms of oxidative stress markers, studies have shown significant decreases in parameters such as MDA, thiobarbituric acid reactive substances, advanced oxidation protein products, 8-OHdG, and TAC following CPAP treatment. However, the magnitude of this effect varies across studies; while no significant reduction was observed in some studies, most demonstrated moderate improvement (37).

The main reasons for this variability are as follows:

- **Treatment Duration:** CPAP therapy lasting eight weeks or longer yields more pronounced improvements in biomarkers compared to shorter-term applications (1).
- **Patient Compliance:** The reduction in oxidative stress is directly correlated with the duration of nighttime usage. Thus, the therapeutic effect is limited in patients with low compliance (38).
- **Biomarker Diversity:** The biochemical markers used in studies vary and may exhibit different sensitivities to CPAP therapy (39).
- **Comorbid Conditions:** Factors such as obesity, metabolic syndrome, diabetes, and smoking independently modulate oxidative stress levels, leading to heterogeneity in the CPAP response (40).

Overall, the literature supports the beneficial impact of CPAP on oxidative stress and inflammation. However, considering the methodological differences, biomarker diversity, and compliance variability, there remains a need for long-term studies utilizing standardized biomarker panels in highly compliant cohorts to more clearly characterize the oxidative stress response to CPAP (41).

Surgery and Oral Appliances

Upper airway surgeries and mandibular advancement appliances may indirectly reduce oxidative load by decreasing apnea severity. However, data are limited, and more studies are needed to determine the long-term effects.

Pharmacological and Nutrition-Based Antioxidant Approaches

Pharmacological approaches targeting oxidative stress in OSA include antioxidant vitamins (C and E), coenzyme Q10, N-acetylcysteine, and melatonin. These agents can reduce ROS production at the cellular level, limit lipid peroxidation and DNA damage, and upregulate antioxidant enzyme activities.

In animal models, N-acetylcysteine or melatonin administration in mice exposed to IH has been shown to decrease mitochondrial ROS production and partially preserve endothelial function (42). Small-scale human studies corroborate these findings. For example, short-term vitamin C and E supplementation has been associated with decreased serum MDA and 8-OHdG levels in OSA patients (43).

However, current clinical evidence remains limited, as most studies have been small, short-term, and conducted in heterogeneous populations. Large-scale, randomized controlled

trials are scarce, and the effect of antioxidant therapy on the clinical outcomes of OSA, particularly cardiovascular events, insulin resistance, or neurological dysfunction, is unclear (44). Furthermore, it is not clearly established whether the combination of antioxidants with CPAP therapy provides additional benefit.

In summary, while antioxidant agents have the potential to modulate oxidative stress associated with OSA, these therapies have not yet been incorporated into standard treatment protocols. More extensive clinical studies are needed to assess their long-term efficacy and safety.

Lifestyle Interventions

Weight loss, regular exercise, and smoking cessation are important lifestyle interventions in OSA management that reduce both IH frequency and oxidative stress. Weight loss, particularly in obese patients, reduces the severity of OSA by decreasing the structural load on the upper airway and reducing ROS production caused by IH. In clinical studies, weight loss of approximately 10–15 kg has been associated with a significant decrease in the frequency of hypoxic episodes and reductions in oxidative stress biomarkers such as serum/plasma MDA and 8-OHdG (45).

Regular aerobic exercise is also beneficial in terms of modulating oxidative stress. Exercise improves vascular function and enhances cellular defenses against ROS by upregulating antioxidant enzyme activities. Additionally, smoking cessation may reduce cardiovascular risks associated with OSA by decreasing both systemic inflammation and oxidative load (46).

In summary, lifestyle interventions offer effective and low-risk strategies for reducing OSA severity and modulating oxidative stress. When combined with pharmacological or device therapies, these approaches may enhance clinical benefit.

Experimental Evidence: Animal Models and Cellular Studies

Animal studies using IH models provide important insights into the oxidative stress mechanisms and vascular-structural changes associated with OSA. In these models, IH has been shown to trigger NOX activation, mitochondrial dysfunction, endothelial dysfunction, and increased systolic blood pressure (3). For example, exposure to IH in mice has been found to increase $O_2^{\bullet -}$ production, decrease SOD and glutathione levels, and impair vascular smooth muscle tone (47).

Cell culture experiments also support these mechanisms. When repeated oxygen deprivation is applied to endothelial cells, ROS production increases, NF-κB activation is triggered, and the expression of proinflammatory cytokines (TNF-α, IL-6, and IL-1β) rises (48). This indicates that IH contributes to vascular damage by simultaneously activating inflammatory and oxidative pathways. Findings from animal and *in vitro* models parallel the clinical oxidative stress and vascular complications seen in OSA. Therefore, these models are critical for understanding pathophysiology and testing new treatment strategies.

Implications from Clinical Studies and Evaluation of Evidence

Current human studies consist mostly of prospective, small-scale randomized controlled trials or cross-sectional analyses. Heterogeneous study populations, different biomarker measurement methods, and variability in CPAP compliance limit the comparability of the results obtained (49). However, the general trend in the literature indicates that oxidative stress markers increase with OSA severity, and partial improvement is observed with CPAP therapy (37).

Several critical points regarding study design emerge in the clinical and biomarker-based assessment of oxidative stress in OSA:

Standardized Biomarker Panels: The combined assessment of parameters such as MDA, 8-OHdG, F2-isoprostanes, TAC, SOD, and GPx activities increases the comparability of data from different studies (50).

CPAP Compliance and Treatment Duration: Objective CPAP usage monitoring (e.g., via device data cards) and sufficient treatment duration (generally ≥3 months) are required for an accurate assessment of treatment efficacy (51).

Separation of Comorbidities: Isolating the effects of concomitant conditions such as obesity, type 2 diabetes, hypertension, and cardiovascular disease is crucial to understanding the direct relationship between oxidative stress and OSA.

Follow-up of Long-Term Clinical Outcomes: The correlation of cardiovascular events, mortality, or metabolic parameters with biomarker changes provides critical information for assessing the clinical significance of oxidative stress and treatment responses (51).

This approach will both enhance methodological standardization in future studies and more clearly elucidate the clinical significance of OSA-related oxidative stress.

Recommendations for Future Studies

While current knowledge on oxidative stress associated with OSA and IH is substantial, many questions remain unanswered. The following recommendations are proposed to guide future research and provide clearer, more comparable data:

Large-Scale, Randomized Controlled Trials: The effectiveness of antioxidant agents (e.g., vitamins C and E, coenzyme Q10, N-acetylcysteine, melatonin) and other pharmacological interventions on OSA-related oxidative stress biomarkers and clinical outcomes (cardiovascular events, neurological function, mortality) should be evaluated.

Investigation of Genetic and Epigenetic Markers: Responses to IH and oxidative stress levels vary considerably among individuals. The role of genetic polymorphisms and epigenetic modifications in this variability warrants investigation. In particular, the effects of Nrf2, SOD, and NOX genes and miRNA profiles can be investigated.

Implementation of Standardized Biomarker Panels: Multicenter cohort studies using standardized protocols for the measurement of biomarkers such as MDA, 8-OHdG, F2-isoprostanes, TAC, SOD, and GPx will enable the collection of comparable data across different populations.

Personalized Medicine and Biomarker-Based Treatment Strategies: Given the heterogeneous nature of OSA, personalized treatment algorithms based on the individual's

oxidative stress profile should be developed. This approach can optimize combinations of CPAP, lifestyle interventions, and surgical or pharmacological antioxidant treatments.

These recommendations will contribute to a better understanding of OSA-related oxidative stress pathophysiology and facilitate the development of targeted clinical management strategies.

Study Limitations

Despite providing a comprehensive overview of the role of oxidative stress in the pathogenesis of OSA, several limitations should be acknowledged. First, as a narrative review, the present study relies on previously published literature, which may introduce selection bias depending on the availability and scope of existing studies. The heterogeneity of the included studies in terms of study design, sample size, patient characteristics, and methodological approaches may also limit the generalizability of the conclusions.

Second, oxidative stress biomarkers such as MDA, SOD, and GPx are measured using different analytical techniques across studies, which may lead to variability in reported results and complicate direct comparisons between studies. Additionally, variations in OSA severity, the presence of comorbid conditions, and differences in treatment status (particularly the use of CPAP therapy) may influence oxidative stress parameters and contribute to inconsistent findings.

Another limitation is the scarcity of longitudinal and large-scale clinical studies examining the causal relationship between oxidative stress pathways and disease progression. Most available studies are cross-sectional, making it difficult to establish definitive cause–effect relationships. Furthermore, although several biomarkers of oxidative stress have been proposed, there is currently no universally accepted biomarker panel for routine clinical assessment in patients with OSA.

Finally, this review primarily focuses on biochemical and molecular mechanisms and may not fully address all clinical, environmental, and lifestyle factors that can modulate oxidative stress. Future studies, particularly well-designed prospective clinical trials and multi-center investigations, are needed to clarify the precise role of oxidative stress biomarkers and to determine their clinical utility in the diagnosis, prognosis, and therapeutic monitoring of patients with OSA.

Conclusion

OSA increases mitochondrial and enzyme-derived ROS production through IH and sleep disruptions, while simultaneously weakening antioxidant defense mechanisms (8-52). This increased oxidative stress load drives the development of OSA-related morbidities such as vascular dysfunction, systemic inflammation, metabolic disorders, insulin resistance, and cardiovascular complications (30-53).

CPAP therapy can reduce ROS production by decreasing IH and sleep fragmentation, improve endothelial function, and partially improve certain biomarkers (e.g., MDA, 8-OHdG, TAC) (37-54). Similarly, lifestyle interventions such as weight loss, regular exercise, and smoking cessation can reduce both OSA severity and the oxidative burden (55).

However, the efficacy of antioxidant pharmacotherapies (e.g., vitamins C and E, N-acetylcysteine, coenzyme Q10, and melatonin) on oxidative stress and clinical outcomes associated with OSA has not yet been confirmed by robust, large-scale randomized controlled trials beyond the current small-scale studies (56). Therefore, antioxidant approaches remain experimental and have not yet been incorporated into standard treatment protocols in clinical practice.

In summary, the relationship between OSA and oxidative stress is fundamentally characterized by IH-induced increases in ROS and compromised antioxidant defenses. While CPAP therapy and lifestyle interventions can reduce this burden, further high-quality studies are needed to determine the clinical benefit of pharmacological antioxidant treatments.

Footnotes

Authorship Contributions

Concept: M.M.Ö., Design: M.M.Ö., Data Collection or Processing: M.M.Ö., Analysis or Interpretation: M.M.Ö., Literature Search: M.M.Ö., Writing: M.M.Ö.

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