ISSN 2307-8960 (online)

# World Journal of *Clinical Cases*

*World J Clin Cases* 2024 December 16; 12(35): 6754-6863

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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Thrice Monthly Volume 12 Number 35 December 16, 2024

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## RESPONSIBLE EDITORS FOR THIS ISSUE



**NAME OF JOURNAL**
*World Journal of Clinical Cases*

**ISSN**
ISSN 2307-8960 (online)

**LAUNCH DATE**
April 16, 2013

**FREQUENCY**
Thrice Monthly

**EDITORS-IN-CHIEF**
Bao-Gan Peng, Salim Surani, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati

**EDITORIAL BOARD MEMBERS**
https://www.wjgnet.com/2307-8960/editorialboard.htm

**PUBLICATION DATE**
December 16, 2024



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*World J Clin Cases* 2024 December 16; 12(35): 6754-6759

DOI: 10.12998/wjcc.v12.i35.6754

ISSN 2307-8960 (online)

EDITORIAL

# Update on the aetiopathogenesis of obstructive sleep apnea: Role of inflammatory and immune mediated mechanisms

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**Specialty type:** Anesthesiology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's classification**

**Scientific Quality:** Grade D, Grade D

**Novelty:** Grade C, Grade C

**Creativity or Innovation:** Grade C, Grade C

**Scientific Significance:** Grade C, Grade C

**P-Reviewer:** Qiang Z; Zhang YD

**Received:** March 10, 2024

**Revised:** August 19, 2024

**Accepted:** September 9, 2024

**Published online:** December 16, 2024

**Processing time:** 228 Days and 3.4 Hours

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## Abstract

Obstructive sleep apnea (OSA) is often a lifestyle disease associated with obesity, which is rapidly evolving as a major health concern with diverse multisystemic implications. To prevent and mitigate its adverse effects and reduce its burden on society, its aetiopathogeneses must be precisely understood. Numerous studies focusing on the range of diverse anatomic, functional, and lifestyle factors have already been carried out to determine the possible contributory roles of these factors in OSA. Recently, evidence to validate the role of inflammatory pathways and immune mechanisms in the aetiopathogeneses of OSA is being developed. This allows for further research and translation of such knowledge for targeted therapeutic and preventive interventions in patients with or who are at risk of developing OSA.

**Key Words:** Sleep apnea; Obstructive; Polysomnography; Mendelian randomization analysis; Cytokines; C-reactive protein



**Core Tip:** Although sleep-disordered breathing is any abnormal respiration that occurs during sleep, obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder. Its pathogenesis involves a complex interplay of anatomical and functional factors, along with immune cell dysfunction owing to chronic intermittent hypoxia-induced oxidative stress. Thus, to develop specific therapeutic modalities and enhance clinical outcomes in patients with or who are at risk of OSA, these mechanisms must be understood.

**Citation:** Nag DS, Varghese K, Swain A, Patel R, Sahu S, Sam M. Update on the aetiopathogenesis of obstructive sleep apnea: Role of inflammatory and immune mediated mechanisms. *World J Clin Cases* 2024; 12(35): 6754-6759
**URL:** https://www.wjgnet.com/2307-8960/full/v12/i35/6754.htm
**DOI:** https://dx.doi.org/10.12998/wjcc.v12.i35.6754

## INTRODUCTION

Sleep-disordered breathing is any abnormal respiration taking place during sleep. Obstructive sleep apnea (OSA), the most common sleep-related breathing disorder, is characterized by recurrent partial or complete obstruction of the upper airway, which results in hypopnea and apnea. This causes sleep fragmentation, intermittent hypoxia, and hypercapnia, which leads to increased sympathetic nervous system activity[1]. Excessive daytime sleepiness in conjunction with OSA is termed OSA syndrome (OSAS)[2].

Comprehensive in-laboratory polysomnography is the gold standard method employed to diagnose sleep-disordered breathing. The apnea–hypopnea index (AHI) is the main outcome utilized to define OSA severity. An airflow reduction of 90% or more for at least 10 s is termed apnea, and the recommended definition of hypopnea is at least 30% airflow reduction for ≥ 10 s with a ≥ 3% decrease in oxygen saturation or arousal. OSA severity based on AHI scores is defined as follows: No OSAS if AHI < 5, mild OSAS if AHI 5–15, moderate OSAS if AHI 15–30, and severe OSAS if AHI > 30[3].

The prevalence of OSA has increased (in developed countries—males 15%, females 5%), and associated morbidity and mortality in adults have been increasing[4,5]. OSA has significant implications for cardiovascular health, neurocognitive function, mental illness, quality of life, and driving safety[6]. OSA is an independent risk factor for hypertension, coronary artery disease, and stroke[7-9]. Moreover, OSA is associated with metabolic syndrome (insulin resistance and type 2 diabetes mellitus), in which adipokines and oxidative stress have been implicated[10,11]. Recent studies revealed that OSA is associated with immune cell dysfunction[12,13]. Furthermore, OSAS has shown an association with cardiovascular disease and cancer[13-15]. Research on how the complicated interaction between inflammatory mediators and immune cells impact the development and severity of OSA is also evolving[13]. Additional genomic association studies in large cohorts can offer additional insights into the role of signal variants in certain specific genes, which may predict their role in affected families[13]. Mendelian randomization has employed epidemiological causality to define the specific impact of the characteristics of the immune cells and their role in OSA[13].

This article aims to elaborate on the aetiopathogenic mechanisms of OSA, especially emphasizing the role of inflammatory and immune-mediated mechanisms.

## AETIOPATHOGENESIS

### *Current evidence*

The available evidence reveals that OSA is a multifactorial disease[16]. This current evidence is summarized in Table 1 (Multifactorial causes of OSA).

These factors can be broadly categorized as anatomical and functional factors. The main known cause of OSA is the impaired anatomy of the upper airway. Anatomical causes such as a narrow pharyngeal airway, a longer airway, and certain pharyngeal lumen shapes are all associated with the propensity for pharyngeal collapse during sleep[17].

The functional factors comprise impaired pharyngeal dilator muscle function, premature awakening to mild airway narrowing (low respiratory arousal threshold), and unstable control of breathing[2,15].

On falling asleep, the central respiratory drive and pharyngeal dilator muscle activity in OSA patients is decreased. This along with some degree of upper airway narrowing increases their upper airway resistance. Currently, the balance between the airway forces that tend to close or open the airway tilts unfavorably against the forces that attempt to keep the airway open. This eventually results in partial or complete airway collapse, which leads to hypopnea or total apnea. Based on this, two authors independently searched PubMed databases from inception to January 14, 2024. Furthermore, this review considers the study by Zhao *et al*[13].

## EVOLVING EVIDENCE

### *Role of inflammatory and immune-mediated mechanisms*

**Activation of inflammatory pathway and systemic inflammatory response:** The core of OSA pathogenesis is the regular intermittent hypoxia-induced oxidative stress and formation of superoxide ions. This establishes a chronic proinflammatory state with activation of inflammatory pathways and subsequent endothelial and immune cell dysfunction[18].

The proinflammatory transcription factor, nuclear kappa factor B, and an elevated level of proinflammatory cytokines, including tumour necrosis factor alpha, interleukins 6 (IL-6), and 1 beta (IL-1β), serve as key mediators of inflammation, which, when activated, orchestrate a cascade of the immune response[19,20].

Studies revealed that IL-6 and IL-8 are higher in patients with OSA and correlate with AHI[21,22]. A metanalytic investigation into causal analysis between altered levels of ILs and OSA demonstrated that although most ILs (IL-1β, IL-2,

**Table 1 Multifactorial causes of obstructive sleep apnea**

| Anatomic factors | Nonanatomic factors | Functional factors | Miscellaneous |
|---|---|---|---|
| Micrognathia, retrognathia; facial elongation; mandibular hypoplasia; adenoid and tonsillar hypertrophy; inferior displacement of the hyoid | Central fat distribution; obesity, BMI > 30 kg/m$^2$; advanced age; male gender; supine sleeping position; pregnancy | Impaired pharyngeal dilator muscle function; low respiratory arousal threshold; unstable control of breathing | Alcohol use; smoking; sedatives and hypnotics use; hereditary |

BMI: Body mass index.

IL-4, IL-6, IL-8, IL-12, IL-17, IL-18, and IL-23) increased and IL-10 Levels decreased in OSA, a significant causal relationship could not be found. Interestingly, the same study reported that treatment of OSA lowers IL-1β, IL-6, and IL-8 [23].

**Biomarkers of inflammation and OSA:** Recent research has shown that OSA is associated with biomarkers of inflammation. The inflammatory biomarkers of interest include C-reactive protein (CRP), fibrinogen, and erythrocyte sedimentation rate (ESR)[24-26]. Combination of these biomarkers has also been studied, which potentially helps to screen and monitor patients with OSA[27]. A study by Elfeky *et al*[27] found that along with comorbidities, ESR, CRP, and systemic inflammatory markers such as SIRI (systemic inflammatory response index) correlate with OSA severity. The positive correlation of SIRI with OSA severity is in agreement with another recent study by Díaz-García *et al*[28], which postulated that activation of inflammasomes is critical in OSA pathophysiology.

**Neutrophil lymphocyte ratio and OSA:** A meta-analysis that investigated the association of neutrophil lymphocyte ratio (NLR) with OSA revealed that the NLR of patients with OSA is higher than that of controls. The findings of the meta-analysis suggest that NLR is a reliable marker that can be utilized to predict disease progression and detect systemic inflammation in patients with OSA[29]. As both neutrophils and lymphocytes play vital roles in the release of inflammatory mediators, their ratios or absolute counts can indicate the inflammatory status[30]. Moreover, the reduction in the inflammatory markers with continuous-positive airway pressure therapy validates its role in OSA[30].

**Immune cell infiltration in OSA:** The entry of neutrophils and macrophages into the mucous membrane of the upper airway causes persistent inflammation tissue inflammation, which leads to changes in airway structure. This contributed to the worsening of OSA severity. Recurrent upper respiratory tract infection due to deranged respiratory immunity further exacerbates the upper airway obstruction[31]. Animal studies have shown that intermittent hypoxia increases oxidative stress and decreases antioxidant activity[30]. Nonetheless, to establish causality, further studies are required [30].

**Endothelial dysfunction in OSA:** Oxidative shear stress to the vascular endothelium results in endothelial dysfunction and vascular remodeling, which contributes to systemic vascular complications and atherosclerosis. These complications, along with the neurohormonal alterations induced by hypoxia-mediated sympathetic overactivity and multiple arousals, cause blood pressure surges resulting in hypertension[32,33]. Cyclical hypoxia in OSA can provoke oxidative stress and adversely impact vascular endothelial function[32].

**Adipokine dysregulation in OSA:** Adipose tissue serves as a reservoir of immune-modulating adipokines. Dysregulation of adipokines in OSA contributes to systemic inflammation, insulin resistance, and dyslipidemia. Leptin, adiponectin, and other adipokines are involved in immune dysregulation and pathogenesis of OSA-related complications [34].

**Circadian rhythm disruption in OSA:** Circadian rhythms are 24-h biological clocks that regulate a myriad of physiological processes, such as the sleep–wake cycle, hormone secretion, and metabolism, and modulate the immune response[35-37]. Research is now being directed to analyze differential genes and associated pathways in patients with OSA as well as its effects on immune cell infiltration. The idea is to examine whether regulation of genes related to circadian rhythm could impact disease progression in OSA[38].

Table 2 (Immune cell and obstructive sleep apnea) summarizes the impact of immune cells on OSA, and Table 3 (Inflammatory mediators and obstructive sleep apnea) summarizes the impact of inflammatory mediators.

## CONCLUSION

OSA pathogenesis involves a complex interplay of anatomical and functional factors along with immune cell dysfunction caused by chronic intermittent hypoxia-induced oxidative stress. This dysregulation contributes to systemic inflammation, endothelial dysfunction, and metabolic disturbances, exacerbating OSA severity and associated comorbidities. Therefore, these mechanisms must be understood to develop targeted therapies and improve clinical outcomes in OSA patients. To establish the specific role of each inflammatory pathway and immune modulator, further large multicentric trials are needed, to develop specific therapeutic interventions necessary to provide clinically relevant benefits.

**Table 2 Immune cell and obstructive sleep apnea**

| Immune cells | Effect |
|---|---|
| Monocyte | There were significant alterations in the distribution of monocyte subsets in response to OSAS, characterized by an increase in intermediate and non-classical monocytes and a decrease in classical monocytes[12] |
| Neutrophils | OSA is independently associated with increased neutrophil counts and inflammation[38] |
| B-lymphocytes | When B cells are depleted or dysregulated, it can lead to an imbalance in the immune system, potentially resulting in increased inflammation as seen in OSA[38] |
| T-lymphocytes | There is an imbalance of CD4+ and CD8+ cells in individuals with OSAS, with a high proportion of CD8+ cells and a low proportion of CD4+ cells. These changes are dependent on the AHI[38] |
| Neutrophil lymphocyte ratio | NLR increases and is directly correlates with AHI[28] |

AHI: Apnea–hypopnea index; OSA: Obstructive sleep apnea; NLR: Neutrophil lymphocyte ratio.

**Table 3 Inflammatory mediators and obstructive sleep apnea**

| Inflammatory Mediators | Effect |
|---|---|
| TNF-α | Elevated levels of inflammatory |
| IL-6, IL-8, CRP, ESR | Markers correlate with severity of OSA[22,25,38] |
| Adipokines | |
| Key adipokines studied include: Leptin, Chemerin, Resistin, Adiponectin, Omentin-1 | OSA is associated with elevated levels of leptin, chemerin, and resistin, and decreased levels of adiponectin and omentin-1. These changes may contribute to metabolic dysfunction, inflammation, and cardiovascular risks[38] |

TNF-α: Tumour necrosis factor alpha; IL: Interleukin; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; OSA: Obstructive sleep apnea.

## FOOTNOTES

**Author contributions:** Nag DS, Varghese K, Swain A, Patel R, Sahu S, Sam M contributed to this paper; Nag DS and Varghese K designed the overall concept and outline of the manuscript; Varghese K, Swain A, Patel R, and Sam M contributed to the discussion and design of the manuscript and review of literature; Nag DS, Varghese K, Swain A, Patel R, Sahu S, and Sam M contributed to the writing and editing of the manuscript; Sahu S, Patel R, and Sam M contributed in the reference indexing and formatting of the manuscript.

**Conflict-of-interest statement:** All authors have no conflicts of interest to disclose.



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**Corresponding Author's Membership in Professional Societies:** Indian Society of Anaesthesiology, S2863.

**S-Editor:** Liu JH
**L-Editor:** A
**P-Editor:** Zhang L

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