



# A SYSTEMIC REVIEW ON SLEEP APNEA AND ASTHMA EXACERBATIONS

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## ABSTRACT

Obstructive sleep apnea syndrome (OSAS) may be a risk factor for exacerbations of asthma, according to recent evidence. In patients with simultaneous OSAS, inflammation (local and systemic), neuromechanical reflex bronchoconstriction, gastric reflux, and the indirect effect of OSAS-induced cardiac dysfunction on dyspnea have all been proposed as processes that contribute to deteriorating asthma control. Leptin-related alterations in airways, vascular endothelial growth factor-induced airway angiogenesis, and OSAS-induced weight gain could potentially have a common mechanism underlying these two illnesses. Asthmatics are more likely than the general population to experience OSAS symptoms, according to multiple research. Nasal obstruction, a decrease in pharyngeal cross sectional area, and an increase in upper airway collapsibility are common asthmatic traits that exacerbate symptoms of OSAS. It is crucial to understand the nature of the connection between OSAS and asthma since it has significant treatment ramifications.

## INTRODUCTION

Breathing difficulties connected to sleep comprise a range of conditions. OSA, or obstructive sleep apnea, is the most severe and intricate type of persistent clinical condition. This is typified by recurrent episodes of upper airway blockage, which can lead to either a considerable decrease in airflow (hypopnea) or a temporary cessation of breathing (apnea) during sleep. Loud snoring, oxygen desaturation, frequent awakening, and disturbed sleep are all possible symptoms of OSA. In addition, sleep disturbances lead to hypersomnolence, poor daytime concentration, and a lower standard of living. For the most part, OSA is still an underdiagnosed and unrecognized condition<sup>1</sup>.

Recurrent episodes of upper airway blockage during sleep lead to either transient stoppage of breathing (apnea) or a significant decline in breathing (hypopnea) in OSAS patients. This pattern is characterized by oxyhemoglobin desaturation, prolonged inspiratory efforts against the blocked airway, and waking from

sleep. The initial course of treatment for sleep apnea is continuous positive airway pressure, or CPAP.<sup>1</sup> It does this by forming a "pneumatic splint," which keeps the upper airway open while you sleep.

Expert Panel Report 3 (EPR3) from the August 2007 National Asthma Education and Prevention Program urges doctors to assess symptoms that may indicate OSAS in patients with unstable, poorly managed asthma, especially those who are fat or overweight. There is currently little evidence linking OSAS to asthma, and not many studies have looked into this<sup>2</sup>.

## PREVALENCE

Globally, the general population's prevalence of OSA ranges from 0.3% to 5.1%.<sup>[1]</sup> The range of OSA in India was 4.4% to 13.7% (4.4%–19.7% for men and 2.5%–7.4% for women) in various investigations. The prevalence of OSA rises with age, especially in persons over 60<sup>4</sup>.

## POSSIBLE MECHANISMS BY WHICH OSAS WORSENS ASTHMA

Chronic asthma is a prevalent illness of the airways that is characterized by intricate interplay between underlying inflammation, hyperresponsiveness, and restriction of airflow. The deterioration of asthma control in patients with simultaneous OSAS has been attributed to a number of mechanisms, including neuromechanical reflex bronchoconstriction, gastric reflux, systemic and local inflammation, and the indirect influence of OSAS-induced cardiac dysfunction on dyspnea. We review the current understanding of each of these pathways and propose new ones, including leptin-related alterations in the airways, airway angiogenesis, and weight gain caused by OSAS<sup>5</sup>.

Due to partial or total airway blockage during apneas, patients with OSAS have an increase in vagal tone as they sleep. The Müller maneuver, which entails exerting inspiratory force against a closed glottis, and this strong vagal stimulation work similarly. In individuals with sleep apnea, an increase in vagal tone during apnea episodes may act as a trigger for nocturnal asthma attacks. Actually, a number of studies have demonstrated that elevated vagal tone activates the muscarinic receptors in the central airways, which causes bronchoconstriction<sup>4</sup> and nocturnal asthma. Moreover, inhaled anticholinergic medications that inhibit elevated vagal tone enhance forced expiratory flow, reduce early morning drops in peak expiratory flow, and guard against nocturnal asthma attacks<sup>6</sup>.

## NEURAL RECEPTOR AND MECHANICAL EFFECT

Neural receptors in the laryngeal area and at the glottic inlets play a role in the neural reflex mechanism as well. These receptors have strong reflex bronchoconstrictive action. In anesthetized and decerebrate cats, Nadal et al.'s research shown that mechanical irritation of the laryngeal mucosa raised total lung resistance distal to the larynx. The superior laryngeal nerve is the reflex's afferent limb, while the vagus nerves are its efferent limb. Additionally, efferent parasympathetic nerve fibers that supply the trachea and bronchi become more active in response to stimulation of the larynx. Consequently, bronchoconstriction generated by neural reflex may be stimulated by repeatedly stimulating these neural receptors during episodes of loud snoring and obstructive apnea<sup>6</sup>.

It can follow that the larger negative intrathoracic pressure created during obstructive apneas enhances pulmonary capillary blood volume. This rise was seen in nocturnally symptomatic asthmatic subjects, and it may be linked to the detrimental effect of reduced lung capacity on the development of nocturnal bronchoconstriction in sleep apnea patients<sup>7</sup>.

Another theory is that the hypoxia caused by obstructive apneas stimulates the carotid body, which in turn causes reflex bronchoconstriction. Denjean et al found that moderate hypoxia improved the bronchial reactivity to methacholine in sheep and that this effect was eliminated in all animals after carotid chemodenervation. It has been demonstrated by other researchers that hypoxia exacerbated the bronchoconstricting reflex, the histamine response in dogs under anesthesia, and the bronchial reaction to a histamine aerosolized dose in sheep that were awake. Furthermore, a hypoxia-induced increase in bronchial reactivity to methacholine was identified in asthmatic individuals. Evidence suggests that a vagal route may be used by hypoxia to modify the airway responsiveness to constricting stimuli<sup>8</sup>. It is most likely the stimulation of the peripheral carotid body chemoreceptors that triggers this vagal reaction.

## GASTROESOPHAGAL REFLUX DISEASE

Those with OSAS have a higher incidence of GER. According to studies by Green et al. and Valipour et al., GER was a complication in 62% and 58% of OSAS patients, respectively. It has been proposed that obesity contributes to the same risk factors for both GER and OSAS; nevertheless, even after adjusting for body mass index and alcohol consumption, OSAS patients still show considerably higher rates of GER than the general population.<sup>26</sup> This condition is believed to be brought on by GER-favoring elevated transdiaphragmatic pressure and decreased intrathoracic pressure that occur during apneic episodes. Additional potential reasons encompass dilation of the stomach, reduction in gastric motility, and temporary relaxation of the lower esophageal sphincter due to an anomaly in the autonomic nervous system brought on by the apneic episodes<sup>9</sup>.

GER that happens while you sleep is a well-known cause of nocturnal asthma. It can also cause asthma symptoms by triggering vagal reflexes brought on by acid exposure to the esophagus. In fact, persons with asthma experience a marked increase in airway resistance following acid instillation into the midesophagus. Similar effects of acid instillation into the esophagus on canine airway resistance were seen; vagotomy eliminated this reaction. An additional mechanism of GER-induced bronchoconstriction is microaspiration of the gastric acid content. Proton pump inhibitor therapy for GER has been shown to lessen nighttime symptoms, lessen asthma flare-ups, and enhance asthma-related quality of life. Additionally, there have been reports that surgical therapy for GER lowers the need for medication and asthma symptoms<sup>10</sup>.

### LOCAL AIRWAY INFLAMMATION

Obstructive sleep apnea syndrome has been proven to be related with inflammation of both the upper and lower respiratory tracts. Pentane, exhaled nitric oxide,<sup>42</sup> IL-6, and 8-isoprostane<sup>43</sup> are examples of oxidative stress and inflammatory markers that have been detected in the expired air of OSAS patients. These markers may indicate the existence of airway inflammation in OSAS<sup>11</sup>.

The mechanical stress that the high negative pressures transferred against a closed airway channel as a result of the severe inspiratory effort caused by snoring and obstructive apneas impose on the mucosa is one theory for the airway inflammation in OSAS. The mucosa of the nose and throat becomes locally inflamed as a result of this repetitive mechanical damage to the upper airway. The local nasal mucosa of OSAS patients has been shown to have increased levels of polymorphonuclear leukocytes and inflammatory mediators, including bradykinin and vasoactive intestinal peptide (VIP). Chronic inflammation of the soft palate with increasing interstitial edema has also been documented. The uvula exhibits enlargement of the mucous glands and T cell infiltration of the lamina propria<sup>12</sup>.

Also described are inflammatory alterations in the muscles of the upper airways.<sup>49</sup> It has been shown that bronchial inflammation with higher neutrophil counts in produced sputum from OSAS patients occurs in a manner akin to that seen in asthma of the upper and lower airways as a continuum.

It is commonly known that airway inflammation can impact not only the diameter and flow rates of the airways but also the underlying bronchial hyperresponsiveness, which increases the vulnerability to bronchospasm, a key factor in the pathophysiology of asthma. Thus, asthma may be triggered by the localized airway inflammation observed in OSAS.

### SYSTEMIC INFLAMMATION

Increased blood concentrations of cytokines and chemokines are indicative of persistent, low-grade systemic inflammation in persons with OSAS, even in the absence of an overt inflammatory insult. Additionally, increased levels of C-reactive protein (CRP), a measure of inflammation and cardiovascular risk, are linked to OSAS in adults. According to earlier research, the severity of OSAS is directly correlated with CRP levels. Additionally, a significant reduction in CRP levels was observed after one month of continuous positive airway pressure treatment for OSAS. The oxidative stress brought on by oxygen desaturation during sleep apneas appears to be the source of this systemic inflammation, at least partially. The elevations in serum TNF- $\alpha$  that are associated with OSAS are especially intriguing in relation to airway smooth muscle. Airway

smooth muscle has TNF receptors, and it has been demonstrated that exogenous TNF- $\alpha$  increases the contractility of mouse airways in vitro in response to a range of contractile agonists. Conversely, oxidative stress brought on by OSAS and an increase in IL-8 could be a factor in bronchial inflammation. Lastly, this combination of cytokines may amplify various other proinflammatory effects, such as greater activation of resident airway cells including mast cells, fibroblasts, and epithelial cells, and endothelial activation for leukocyte recruitment<sup>13</sup>.

In relation to airway smooth muscle, the higher levels of serum TNF- $\alpha$  associated to OSAS are particularly noteworthy. TNF receptors are found in airway smooth muscle, and it has been established that exogenous TNF- $\alpha$  improves the contractility of mouse airways in vitro in response to multiple contractile agonists. Conversely, increased IL-8 levels and oxidative stress brought on by OSAS may be factors in bronchial inflammation. Lastly, the combination of these cytokines may exacerbate further proinflammatory effects, like heightened activation of resident airway cells like mast cells, fibroblasts, and epithelial cells, as well as greater activation of endothelium activation for leukocyte recruitment.

## CARDIAC DYSFUNCTION

Numerous cardiovascular effects of OSAS have been demonstrated, which could make a coexisting airway blockage more difficult for asthmatic patients. Ischemic heart disease and congestive heart failure (CHF) are associated with an increased risk of OSAS. Furthermore, dogs that experience induced obstructive sleep apnea experience left ventricular impairment.<sup>64</sup> Several mechanisms are hypothesized to be responsible for this scenario. Numerous epidemiologic, animal, and human intervention studies have demonstrated that OSAS has a role in the onset of systemic hypertension, which is a prelude to congestive heart failure (CHF). Elevated sympathetic nerve activity is recognized to be cardiotoxic in patients with congestive heart failure (CHF). Possible contributing factors include recurrent hypoxemia, hypercapnia, and baroreflex suppression brought on by recurrent spikes in nocturnal blood pressure. Additionally, hypoxemia may cause oxidative vascular wall damage on its own<sup>15</sup>.

Airway obstruction is a result of CHF, as demonstrated by clinical and experimental observations. Growing clinical data suggests that hyperresponsiveness to cholinergic stimulation, which causes the smooth muscles in the airways to constrict, is a critical aspect of bronchial narrowing in CHF. The airway hyperresponsiveness linked to congestive heart failure (CHF) has been attributed to multiple processes. These include the down-regulation of pulmonary  $\beta$ -receptors and concurrent reductions in adenylyl cyclase activity, which lead to a notable attenuation of cAMP-mediated airway relaxation. Additional processes include thickening of bronchial walls, nonspecific activation of bronchial C-fibers, altered salt and water transport in the epithelium, and elevated endothelin levels, which cause pulmonary edema-induced constriction of airways. By exacerbating cardiac dysfunction, OSAS may exacerbate airway hyperresponsiveness (AHR) in individuals with asthma<sup>16</sup>.

## VASCULAR ENDOTHELIAL GROWTHFACTOR (VEGF) AND AIRWAY ANGIOGENESIS

A glycoprotein that is sensitive to hypoxia and promotes vascular growth is called VEGF. Tumor growth, wound healing, and neovascularization during embryonic development all depend on VEGF. A growing amount of research suggests that VEGF might be a significant factor in the etiology of bronchial asthma and might be involved in bronchial hyperresponsiveness and inflammation. According to a recent study, VEGF plays a crucial part in the vascular remodeling associated with asthma. Furthermore, a relationship between the degree of airway obstruction and elevated VEGF levels in asthmatic patients has been discovered<sup>17</sup>.

According to recent research, VEGF concentrations in OSAS patients are high and are correlated with the severity of the disease as measured by the degree of nocturnal oxygen desaturation and the apnea-hypopnea index (AHI). The most likely cause of VEGF release in OSAS is hypoxia, which is brought on by recurrent hypoxia during the night and hypoxia-inducible factor (HIF)-mediated gene expression<sup>18</sup>. Changes in other mediator systems may possibly be the secondary cause of the VEGF increase in OSAS. The gene expression

of VEGF may be enhanced by endothelin and free oxygen radicals, both of which have been found to be higher in patients with OSAS.

Furthermore, the downregulation of nitric oxide synthesis observed in OSAS may lessen the inhibitory effect of nitric oxide on VEGF gene activation. Although there is probably a connection, there is currently insufficient evidence to link OSAS patients' higher VEGF levels to the bronchial inflammation and hyperresponsiveness that are essential to asthmatic airway inflammation<sup>19</sup>.

## LEPTIN HYPOTHESIS

Leptin is a protein generated by adipose tissue that circulates systemically and acts on the hypothalamus to induce satiety and enhance metabolism. Nevertheless, serum leptin concentrations are considerably raised in obese people, suggesting leptin resistance in obesity, comparable probably to the insulin resistance observed in patients with type II diabetes. In addition to its effects on the regulation of body weight, leptin is also proinflammatory promoting the release of proinflammatory cytokines such as IL-6 and TNF- $\alpha$  by adipocytes<sup>20</sup>. Leptin receptors are expressed by hematopoietic cells, and monocytes and macrophages produce more cytokines in response to leptin stimulation of LPS. Leptin-exposed CD41 T cells also exhibit enhanced T-cell mitogen-induced proliferation.

Regarding the function of leptin in the etiology of asthma, a novel theory is beginning to take shape. Even after adjusting for body mass index (BMI), leptin was shown to be higher in the serum of male asthmatic children compared with that of nonasthmatic children. Leptin injection to mice in a murine model resulted in an increase in serum IgE levels and airway hyperresponsiveness to inhaled methacholine, indicating a potential function for leptin in heightened mast cell activation<sup>21</sup>.

Leptin levels are almost 50% higher in obese male patients with OSAS than in similarly obese males without OSAS. Clinical research has shown that OSAS patients have higher serum leptin levels than nonapneic patients with comparable obesity levels. This has been shown in multiple case-control studies<sup>22</sup>. Furthermore, a noteworthy inverse relationship ( $r = -0.73$ ,  $p < 0.001$ ) was discovered between plasma-soluble leptin receptor levels and the apnea-hypopnea index, which was not influenced by BMI. While the precise mechanism is yet unknown, the elevated levels may be due to the hypoxic stressors typical of OSAS, which raises leptin secretion. It is hypothesized that leptin resistance may result from OSAS since patients with the condition have higher leptin levels than obese nonapneic people.

The proinflammatory effects of leptin, when combined with the elevated serum leptin levels seen in OSAS, imply that this hormone may have a role in the worsening of asthma in OSAS. An essential causal linkage between the morbidities of OSAS and asthma may exist between higher leptin levels in OSAS patients and airway hyperresponsiveness and inflammation<sup>23</sup>.

## WEIGHT GAIN

It has been demonstrated that the recurrent hypoxic episodes and sleep disruption associated with OSAS cause glucose intolerance and elevated insulin resistance. According to certain research, the degree of insulin resistance and the severity of OSAS are correlated. The release of inflammatory cytokines originating from adipocytes, such as IL-6, TNF- $\alpha$ , and leptin, as well as stimulation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system may be linked to the rise in insulin resistance in OSAS. Because circulating insulin increases hunger and encourages fat storage, patients with insulin resistance may continue to gain weight. Patients with OSAS have been reported to secrete less growth hormone. Due to the lipolytic activity of growth hormone, suppressing growth hormone secretion in untreated OSAS leads to decreased lipolysis, which in turn encourages fat storage and weight gain<sup>24</sup>.

## WHY ASTHMATIC ARE MORE PRONE TO DEVELOP OSAS?

According to recent investigations, snoring and observed apneas—symptoms of OSAS—are prevalent among asthmatics. Others have seen increased daytime sleepiness in asthmatic patients and have discovered a similar association between asthma and observed apneas, possibly suggesting the presence of a sleep disturbance. It has also been discovered that snoring is highly common in atopy young women and that there is a strong correlation between snoring and asthma.

An attended polysomnogram is still the gold standard for diagnosing OSAS (PSG). To date, there have been no reports of population-based investigations involving laboratory PSG in asthmatic patients, most likely because such an undertaking is quite expensive.

According to recent report from the National Sleep Foundation analysis, 26% of all adults would be considered to be at high risk for OSAS based on the Berlin Questionnaire, which has a strong positive predictive value for the condition. Researchers found that patients with asthma had a greater prevalence of OSAS symptoms than patients in primary care in a study that used the Berlin Questionnaire. According to this study, people with asthma had a higher chance of developing OSAS than patients without asthma<sup>25</sup>.

The higher incidence of nasal obstruction in asthmatic patients may be the cause of the high prevalence of OSAS symptoms in these patients. The primary breathing pathway during sleep is through the nose, and in those who are prone to it, nasal blockage exacerbates sleep disordered breathing. Common illnesses like sinusitis and rhinorrhea can lead to nasal congestion, which in turn can exacerbate upper airway obstruction in OSAS. Upper airway obstruction may also be linked to nasal and nasopharyngeal polyps. Based on clinical investigations, rhinitis is found in most asthma patients.

A major contributing element to the development of OSAS is the increased nasal obstruction in asthmatic patients, which causes an increase in nasal resistance and, ultimately, an increase in the negative pressure in the upper airway during inspiration<sup>26</sup>.

Lower airway cross-sectional area and upper airway patency may be contributing factors to the high incidence of OSAS in asthmatic patients. The persistent inflammation of the airway mucosa seen in asthmatic patients is one factor contributing to this decrease. Another reason why asthmatic patients have decreased airway patency is because of increased fat deposits in the pharyngeal wall caused by weight gain. Weight gain may persist over time as a result of sadness, sleep deprivation leading to increased insulin resistance, activity limitations, and oral steroid use.

Last but not least, OSAS may be brought on by the disturbance of sleep architecture that occurs after recurrent nocturnal asthma episodes. It is true that upper airway collapsibility is increased by chronic sleep loss, particularly sleep fragmentation, which is another factor that contributes to the development of OSAS<sup>27</sup>.

### CONCLUSION

Asthma and OSAS are detrimental. According to recent studies, OSAS symptoms are more prevalent in individuals with asthma than in the general population, and OSAS may be an independent risk factor for asthma exacerbations.

We have demonstrated how OSAS can exacerbate asthma and vice versa, and we have listed possible causes for this interplay. The use of CPAP has been proven in several trials to relieve asthma symptoms; as a result, future research may need to investigate this pathway in order to further validate the theory of a causal relationship between the two disorders and their management.

Professionals need to be aware of the connection between OSAS and asthma as well as the significance of treating patients with asthma who have OSAS.

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