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# Melatonin as a Therapeutic Adjunct in Obstructive Sleep Apnea: A Review of Potential Benefits

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Obstructive sleep apnea (OSA) is a prevalent sleep disorder characterized by recurrent upper airway obstruction, leading to intermittent hypoxia, sleep fragmentation, and increased risk of cardiovascular, metabolic, and neurocognitive complications. Chronic intermittent hypoxia (CIH), a hallmark of OSA, contributes significantly to oxidative stress, systemic inflammation, endothelial dysfunction, and neuronal injury. These mechanisms underlie the development of comorbidities such as hypertension, diabetes mellitus, dyslipidemia, and cognitive impairment. While continuous positive airway pressure is the standard treatment, poor adherence highlights the need for adjunctive therapies. Melatonin, a neurohormone with potent antioxidant, anti-inflammatory, and neuroprotective properties, has emerged as a promising therapeutic agent for mitigating CIH-related complications. Preclinical studies demonstrate that melatonin reduces oxidative stress and inflammation, improves endothelial function, and ameliorates metabolic dysfunction, including insulin resistance and lipid dysregulation. Additionally, melatonin has shown potential in preventing CIH-induced cognitive decline by reducing hippocampal oxidative damage, preserving synaptic plasticity, and enhancing neurogenesis. These neuroprotective effects may counteract the cognitive impairments frequently observed in OSA patients. This narrative review examines the impact of melatonin administration on cardiovascular, metabolic, and neurocognitive sequelae of OSA, focusing on its molecular mechanisms of action and therapeutic potential. While preclinical studies provide compelling evidence for its efficacy, clinical trials are needed to establish optimal dosing, safety, and long-term benefits of melatonin therapy in OSA patients. Integrating melatonin as an adjunctive therapy may offer a novel approach to reducing the burden of OSA-related diseases. **Sleep Med Res 2025;16(2):84-92**

**Keywords** Obstructive sleep apnea; Melatonin; Oxidative stress; Continuous positive airway pressure.

## INTRODUCTION

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder defined by intermittent episodes of partial or complete upper airway obstruction. Fragmentation of sleep in addition to excessive daytime sleepiness, snoring, and awakening with choking or gasping are common manifestations that herald OSA [1]. Narrow or collapsible upper airway anatomy, impaired contractile function of pharyngeal dilator muscles, low arousal threshold, and high loop gain contribute to the disruption in ventilation seen in OSA [2]. Untreated OSA has been associated with increased morbidity and mortality from cardiovascular, neuropsychiatric, renal, pulmonary, and metabolic disorders [3]. Diseases such as coronary heart disease, congestive heart failure, arrhythmias, hypertension, aortic aneurysm, stroke, type 2 diabetes mellitus (T2DM), depression, cognitive impairment, and cancer may accompany

 

the diagnosis of OSA [4,5]. This relates to the pathogenesis of OSA, which involves periodic interruptions in airflow, reductions in blood oxygen saturation, and subsequent respiratory effort related arousals.

Chronic intermittent hypoxia (CIH) plays a significant role in the development of organ damage associated with OSA. OSA is characterized by recurrent respiratory pauses, known as apneas and hypopneas, caused by upper airway collapses during sleep. These events lead to repetitive episodes of hypoxia, resulting in decreased blood oxygen saturation and increased partial pressure of carbon dioxide in arterial blood [6]. This cyclical desaturation and reoxygenation process induces oxidative stress, leading to the production of reactive oxygen species (ROS) and the activation of inflammatory pathways [7-9]. In addition to these effects, arousals due to increased respiratory effort during sleep contribute to systemic inflammation, endothelial dysfunction, and heightened sympathetic neural activity [5,10]. This sympathetic overactivity activates the renin-angiotensin-aldosterone system, which may induce myocardial remodeling, vascular endothelial injury, blood pressure fluctuations, platelet activation, and disruptions in glycemic and insulin homeostasis [5,11,12]. CIH has also been associated with alterations in cellular immune function, which is implicated in cancer pathogenesis [13,14]. The production of ROS, activation of white blood cells, inflammatory responses, gene expression alterations, and impaired vascular function collectively liken cyclical CIH in OSA to ischemia-reperfusion injury (IRI). This connection underlies the cardiovascular, cerebrovascular, and gastrointestinal comorbidities associated with OSA. Addressing the consequences of OSA resulting from CIH presents a promising target for therapeutic interventions [5,11,12,15-17]. Suboptimal adherence to continuous positive airway pressure (CPAP) has thus prompted the development of therapeutic alternatives to ameliorate the consequences of CIH during sleep [7,18-21].

Given the challenges associated with CPAP adherence, researchers have explored alternative therapies that target the physiological disruptions caused by CIH, including interventions aimed at restoring circadian clocks. One such approach involves the administration of melatonin (N-acetyl-5-methoxytryptamine), the primary neuroendocrine hormone synthesized in the pineal gland. Melatonin plays a crucial role in the regulation of circadian rhythms, and its disruption may exacerbate sleep fragmentation and misalignment in OSA patients. Emerging evidence suggests that melatonin secretion is disrupted in individuals with OSA. Circadian clock dysregulation has been associated with metabolic disturbances due to disruptions in the secretion of hormones essential for glucose and lipid metabolism. It has been found that melatonin secretion follows a disease severity-dependent pattern, with lower nighttime melatonin levels observed in patients with moderate to severe OSA compared to normal controls [22]. Melatonin levels can serve as a marker of circadian phase disturbances in OSA patients, suggesting that circadian dysregulation may contribute to disease severity and treatment resistance [23]. Numerous studies have also highlighted the interaction between circadian disruptions and hypoxia. OSA and circadian clock disruption share a bidirectional relationship, likely mediated by CIH, which activates hypoxia-inducible factors (HIFs) and disrupts clock gene expression. MicroRNAs (such as miRNA-181) and sirtuins (SIRTs) may interact with clock-regulating pathways, further exacerbating circadian misalignment in OSA patients, while inflammation triggered by sympathetic activation and cytokine fluctuations also contributes to this dysregulation [24]. These findings highlight the potential chronobiological dysfunction in OSA and support the rationale for investigating melatonin as a therapeutic adjunct. Apart from its role in regulating biological functions through circadian rhythms, melatonin has also demonstrated potential benefits in detoxifying free radicals and reducing inflammatory responses [25-28]. While the exact underlying mechanisms remain a subject of study, melatonin has shown promise in mitigating effects of CIH such as hypertension, vascular inflammation, endothelial dysfunction, myocardial IRI, local inflammation, and lipid peroxidation [25,28-34]. Studies are now evaluating the role of melatonin against the consequences of CIH as seen in the pathogenesis of OSA. Ongoing research aims to evaluate the impact of melatonin on various aspects of health, including cardiovascular, neurologic, psychiatric, gastrointestinal, metabolic, and oncologic effects. These findings emphasize the importance of considering melatonin's antioxidant and anti-inflammatory properties, in addition to its chronobiotic effects, in OSA management. This review thus examines the potential of melatonin administration as a therapeutic strategy in OSA.

## POTENTIAL OF MELATONIN ON CARDIOVASCULAR DISEASES IN THE SETTING OF OSA

Ample evidence has explored the relationship between OSA and cardiovascular diseases such as hypertension, coronary artery disease, atrial fibrillation, stroke, myocardial infarction, and heart failure [35]. In a meta-analysis using prospective observational studies, a diagnosis of severe OSA increases risk of all-cause mortality by 67% and risk of cardiovascular mortality by 265% [36]. This has led to the consideration of OSA as an independent cardiovascular risk factor [35-39]. CIH has been studied as a contributing factor to the association between OSA and cardiovascular disease. As stated, the changes in oxygen concentration, carbon dioxide concentration, and blood pH brought about by repeated cycles of desaturation and re-oxygenation of oxyhemoglobin increase oxidative stress and stimulate systemic inflammation via the activation of inflammatory signaling pathways mediated by HIF-1 and HIF-2 [40,41]. CIH increases HIF-1α and decreases HIF-2α protein levels [42]. There is thus HIF-

1-mediated activation of pro-oxidant enzymes with reduced HIF-2-mediated transcription of antioxidant genes [41,42]. This increases ROS generation. The production of ROS is associated with an increased concentration of inflammatory mediators such as nuclear factor kappa B (NF-κB), tumor necrosis factor (TNF-α), interleukin 6 (IL-6), and inducible nitric oxide synthase (iNOS) [43]. Increased ROS generation also promotes sympathetic excitation and chemoreceptor activation [35,40,41,44,45]. This triggers a cascade of events which may lead to endothelial dysfunction, inflammation, plaque formation, arrhythmia, and ischemia as seen in the pathogenesis of cardiovascular disease [5,46]. Researchers are actively investigating the molecular mechanisms that underlie both intermittent hypoxia (IH) and cardiovascular pathology as potential targets for therapeutic interventions. Growing evidence has thus emerged to support melatonin as a potential therapeutic candidate.

Melatonin administration can exhibit cardioprotective effects against inflammation, fibrosis, disruptions in calcium homeostasis, and IRI in animal models of OSA [47]. One study utilized adult male Sprague-Dawley (SD) rats exposed to CIH for 4 weeks to mimic severe OSA. Systolic pressure, levels of lipid peroxidation, and heart-to-body weight (HW/BW) ratio, which was used to gauge cardiac hypertrophy, were less elevated in the hypoxic rats treated with melatonin compared to the hypoxic rats treated with vehicle (ethanol in normal saline). The levels of proinflammatory cytokines (TNF-α, IL-6) and fibrotic mediators (pro-collagen I, PC1; and transforming growth factor beta-1, TGFβ) were lower in the melatonin-treated group compared with normoxic control, whereas these parameters were significantly increased in the vehicle-treated group. Additionally, increased expression of antioxidant enzymes (catalase, CAT; and manganese-superoxide dismutase, MnSOD) and decreased expression of ROS-generating enzyme subunits (p22 and NOX2 in nicotinamide adenine dinucleotide phosphate [NADPH] oxidase) were found in the melatonin-treated group in contrast to the vehicle treated group. Melatonin administration was also associated with smaller infarct sizes and more desirable sarcoplasmic reticulum calcium (SR-$Ca^{2+}$) handling during IRI. These findings support the prophylactic use of melatonin in OSA patients to confer protection against CIH-induced myocardial dysfunction characterized by vascular inflammation, oxidative stress, fibrosis, impaired SR-$Ca^{2+}$ handling, and exacerbated IRI [48].

A similar study investigated the potential of melatonin to diminish CIH-induced cardiac hypertrophy by inducing autophagy via the adenosine monophosphate-activated protein kinase (AMPK) pathway. Male SD rats were treated with CIH under normoxia and received melatonin or the same dose of saline by daily intraperitoneal injection. As stated in the study, the increase in markers of myocardial hypertrophy such as serum atrial natriuretic peptide level, HW/BW ratio, cardiomyocyte area, and fibrotic area induced by CIH exposure was reversed with melatonin treatment [49]. Melatonin administration also led to enhancement of AMPK-mediated autophagy, which has known to mitigate cardiac hypertrophy, maintain cardiac function and morphology during heart failure and pressure overload, and protect against CIH-induced myocardial damage [50,51]. Increased levels of pro-autophagic protein Beclin-1, increased cleavage of microtubule-associated proteins 1A/1B light chain 3B (LC3), and reduced accumulation of stress-inducible sequestosome 1 (p62) were indicative of this protective effect. The results suggest the therapeutic potential and protective function of melatonin to induce AMPK-mediated autophagy and autophagy-regulated apoptosis against CIH-induced cardiac hypertrophy seen in OSA [52].

Another study examined the protective effects of melatonin against oxidative stress, endothelial dysfunction, and inflammation seen in hypertension brought about by CIH [48]. Compared to the vehicle-treated group, expression of NADPH oxidase, proinflammatory mediators (TNF-α; cyclooxygenase-2, COX-2; iNOS) and adhesion molecules (intercellular adhesion molecules-1, ICAM-1; and vascular cell adhesion molecule 1, VCAM-1) were lower with melatonin treatment in the rats exposed to CIH mimicking severe OSA. There were also no significant differences found in systolic pressure between the normoxic control group and the melatonin-treated group. Additionally, higher expression of nitric oxide (NO), endothelial-dependent relaxation, endothelial NO synthase (eNOS) and antioxidant enzymes (glutathione peroxidase, GPx; CAT; and copper/zinc superoxide dismutase, Cu/Zn SOD) were found in the melatonin-treated group compared to the vehicle-treated group. The molecular mechanisms proposed to underlie these effects include receptor-mediated transcriptional regulation of pro-inflammatory (NF-κB; and retinoid-related orphan receptor alpha, RORα) and antioxidant enzymes, increased production of eNOS protein, improved $Ca^{2+}$ handling in endothelial cells, and attenuation of sympathetic activity [48,52-56]. In line with the findings, the ability of melatonin to reduce oxidative stress, vascular inflammation, and endothelial dysfunction via transcriptional regulation of antioxidant enzymes support its use as preventive treatment against the progression of hypertension and other cardiovascular complications in patients with OSA [48].

## POTENTIAL OF MELATONIN ON METABOLIC DISEASES IN THE SETTING OF OSA

Many studies have explored how OSA impacts metabolic function, including its association with diseases such as T2DM and dyslipidemia. In a recent meta-analysis of cohort and cross-sectional studies, OSA was associated with a higher risk of impaired fasting glucose, impaired glucose tolerance, impaired glucose regulation, and diabetes mellitus [57]. Another meta-analysis showed that OSA is associated with more adverse de-

grees of dyslipidemia characterized by high levels of total cholesterol (TC), low density lipoprotein, triglyceride (TG), and low levels of high density lipoprotein [58]. Apart from a correlation between metabolic syndrome (MS) and OSA, these findings reinforce the possibility OSA may exacerbate cardiometabolic risk of obesity and MS [59-62]. CIH plays a significant role in the metabolic consequences associated with OSA. Animal studies have shown that CIH leads to insulin resistance and impaired insulin secretion [63]. This happens because CIH increases lipolysis, glycogenolysis, glucagon secretion, and gluconeogenesis while reducing glucose uptake. These effects are linked to elevated hepatic lipid biosynthesis, increased sympathetic activity, the release of corticosteroids through the hypothalamic-pituitary-adrenal axis, and higher production of leptin [63]. CIH may contribute to dysregulation of lipid metabolism by activating a hepatic transcription factor, sterol regulatory element-binding protein-1c (SREBP-1c), and an SREBP-1c regulated enzyme, stearoyl coenzyme A desaturase 1, which catalyzes TG and phospholipid synthesis. This upregulates lipid biosynthetic pathways in the liver [61,63-65]. Additionally, CIH was found to inactivate lipoprotein lipase, consequently impairing lipoprotein clearance [61,63,66]. Several potential interventions for the effects of CIH and for the role of CIH in the exacerbation of metabolic dysfunction have thus been studied; melatonin administration is among the potential therapeutic candidates.

Numerous reviews have investigated the impact of melatonin administration on enhancing glucose homeostasis by increasing insulin sensitivity, promoting glucose uptake, and reducing insulin resistance and fasting blood glucose levels [67-72]. However, the potential of melatonin as an agent for improving glycemic control is still the subject of ongoing research [73]. One study compared the plasma glucose, TG, and cholesterol levels of twelve groups of Balb/c mice exposed to either sham hypoxia or IH and given either vehicle, N-acetylcysteine, or melatonin. Results showed lower glucose levels in the IH group receiving melatonin compared to the group receiving the vehicle and the group receiving N-acetylcysteine; however, no changes were seen in the lipid profile among all groups. This effect was attributed to the influence of melatonin on glucose homeostasis [74-76]. The study thus concluded that melatonin may have a role in improving glycemic control and in preventing hypoxia-induced hyperglycemia as seen in OSA [74]. A more recent study explored the interplay of sleep fragmentation, glycolipid metabolism, and melatonin administration by exposing one group of adult male C57BL/6 mice to sleep fragmentation with melatonin treatment and the other group to sleep fragmentation without melatonin compared to control. The study showed that the weight gain, glucose dysregulation, and inflammation induced by sleep fragmentation were reduced in the group given melatonin [77]. These effects were attributed to the antioxidant properties of melatonin as well as the ability of melatonin to support pathways and enzymes such as AMPK that are necessary for energy balance, fatty acid oxidation, glucose uptake, and mitochondrial capacity [77].

Another study examined the effects of melatonin on insulin resistance, arteriolar vasodilation, capillary perfusion, nitrite/nitrate generation, ROS generation, and hypertension in the setting of CIH [78]. The study utilized male Syrian hamsters divided into four groups of eight exposed to either normoxic or hypoxic conditions and either given or not given melatonin. The elevation of various parameters, including mean arterial pressure (MAP), hematocrit, plasma insulin, and plasma blood glucose, coupled with reductions in arteriolar diameter and capillary perfusion, among the groups exposed to IH without melatonin, emphasized the effects of CIH. In contrast, there were lower levels of blood pressure, blood glucose, and ROS and nitrite/nitrate levels, and higher capillary perfusion and vasodilation seen in the group exposed to IH treated with melatonin. Compared to the IH-group given melatonin, the glucose infusion rate was lower in the IH-group in the last 30 minutes of a test controlling blood glucose and insulin levels. This suggests more favorable insulin sensitivity in the IH-group given melatonin. The researchers stated that elevated ROS generation, disrupted NO formation, and consequent increased sympathetic discharge in the setting of CIH may lead to microvascular smooth muscle dysfunction associated with reduced capillary perfusion, increased arteriolar vasoconstriction, and elevated MAP. Endothelial damage secondary to oxidative stress may also be associated with impaired sensitivity to insulin. The ensuing hyperglycemia further exacerbates ROS and reactive nitrogen species generation. In this context, the capacity of melatonin and its metabolites to scavenge free radicals plays a crucial role in mitigating microvascular dysfunction, which, in turn, sustains arteriolar vasodilation and enhances capillary perfusion. Ultimately, this heightened blood flow facilitates improved glucose utilization, thus complementing the function of insulin [69]. The study thus concludes that melatonin may mitigate reductions in arteriolar vasodilation, capillary perfusion, and insulin sensitivity brought about by CIH [69].

Melatonin administration has been shown to limit TG accumulation in adipose tissue, modulate TC levels and cholesterol absorption, decrease activity of lipogenic enzymes, alter lipoprotein profile and metabolism, and reduce incorporation and deposition of visceral fat in animal models and in humans [42,79-84]. One study investigated the interaction between melatonin and CIH on the progression of steatohepatitis and fatty liver sensitivity to CIH injury. In this study, high-fat diet (FD)-induced obesity mouse models were exposed to agents that simulated IH/normoxia events for 8 hours a day with or without melatonin supplementation. As stated in the study, autophagy plays an important role in lipid homeostasis as it facilitates the degradation of cytoplasmic lipid droplets along with damaged organelles [85,86]. The results of this study revealed that melatonin can enhance autophagy by increasing the expression of autoph-

agy-related genes and proteins such as Beclin-1 and Atg12-5 conjugate [85]. This supports not only the possible role of melatonin in ameliorating lipid metabolism dysregulation but also on its protective effect in the pathogenesis of nonalcoholic steatohepatitis (NASH) and FD/CIH-induced liver injury. The association between OSA and lipid metabolism dysregulation suggests a promising therapeutic role for melatonin administration. However, further research is needed to understand the effects of melatonin on lipid metabolism abnormalities in the setting of OSA.

## POTENTIAL OF MELATONIN ON COGNITIVE IMPAIRMENT IN THE SETTING OF OSA

Several studies have documented the negative effects of OSA on cognitive function with deficits in attention, memory, visuospatial abilities, language function, psychological functioning, and executive function [87-93]. It may also affect brain structure with deleterious consequences on white matter integrity and gray matter volume [94]. It has thus been associated with various neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease [95]. The mechanism underlying cognitive decline in the setting of OSA involves an interplay between alterations in sleep architecture and effects of CIH on the brain. Altered sleep architecture impairs optimal cognitive functioning by precluding sleep continuity and by decreasing slow-wave sleep, rapid-eye movement sleep, K-complexes, and sleep spindles, which are necessary to facilitate neurogenesis, synaptic plasticity, alertness, and memory formation and consolidation [96-104]. This is aggravated by hypoxia, oxidative stress, chronic inflammation, small vessel damage, and local ischemia associated with OSA [103,105,106]. The structural changes brought about by this disease process include: 1) reduced gray matter concentration in the amygdalo-hippocampal formation, insular, thalamus, cingulate gyri, frontoparietal cortices, temporal lobes, and cerebellum; 2) reduced axonal integrity in the internal capsule, ventral lateral thalamus, hippocampus, amygdala, cerebral peduncles, cerebellar nuclei, cingulate cortex, corpus callosum, ventral medial prefrontal cortex, and other areas of frontal cortex possibly due to demyelination, shrinkage of axons, and axonal loss; cerebrovascular pathology in the form of microinfarcts, angiopathy, arteriolosclerosis, and atherosclerosis, and; increased deposition of misfolded proteins such as amyloid plaques and tau proteins possibly due to glymphatic dysfunction [103,106-109]. The chronic inflammation and subsequent cell death in certain areas of the brain lead to functional consequences such as affective and cognitive impairment, executive dysfunction, cardiovascular disturbances, and dysregulation of respiratory control [107].

Given the detrimental effects of chronic inflammation and cellular damage in the brain, potential therapeutic strategies to mitigate these consequences have been explored. Research has shown the ability of melatonin to scavenge free radicals combat oxidative stress, contributing to its neuroprotective properties in ischemic conditions affecting the brain [110]. One study investigated the neuroprotective effect of melatonin against CIH-induced damage. In this study, thirty 8-week-old Wistar rats were divided into three groups of ten: a control group, a vehicle-treated CIH group, and a melatonin-treated CIH group. The rats were exposed to either IH or air-air cycling at 30 cycles/hour, 8 hours/day for 4 weeks. Tissue sections of the hippocampi were examined for apoptosis via the terminal-deoxynucleotidyl-transferase-mediated dUTP-biotin nick end-labeling (TUNEL) method while oxidative stress was measured with SOD kits and 3,4-methylenedioxyamphetamine (MDA) kits. Analysis of the tissue sections revealed attenuated neuronal apoptosis in the hippocampi of the group given melatonin through decreased expression of pro-apoptotic enzymes and proteins such as MDA and BAX in addition to upregulated expression of antioxidant enzymes and anti-apoptotic proteins such as SOD and BCL-2 [111]. Neuronal morphological changes characteristic of apoptosis such as cellular shrinkage and chromatin condensation were thus less seen in the group treated with melatonin [111]. To support the possible neuroprotective effects of melatonin, the study thus concluded that melatonin, in addition to its ability to decrease ROS and scavenge free radicals, may abrogate CIH-induced oxidative stress injury by influencing MDA content, SOD activity, BCL-2 expression, and BAX expression in relation to apoptosis [111].

Another study explored the potential of melatonin as an agent against β-amyloid plaque deposition in the setting of CIH brought about by OSA [112]. The study utilized adult rats either exposed to atmospheric air or hypoxic conditions for 3 days or for 7 days. Results revealed that the group exposed to hypoxic conditions for 3 days expressed higher levels of β-amyloid compared to the control group; however, this disparity was not seen in the group exposed to hypoxic conditions for 7 days [112]. This rise in β-amyloid was determined to be independent of increased amyloid precursor protein (APP) expression. Further analysis revealed elevated mRNA and protein levels of BACE1 and PSEN1, key regulators of β-amyloid production, in the group exposed to 3 days of hypoxia, accompanied by an increase in HIF-1α protein levels in the same group. To evaluate the effect of free radical scavenger melatonin, adult rats were either kept under atmospheric air or treated with hypoxia for 3 days with daily injection of either vehicle or melatonin [112]. Although no differences were observed in PSEN1 and HIF-1α protein levels, the melatonin-treated group exhibited decreased PSEN1 protein and mRNA levels, along with reduced APP processing [112]. The study thus concluded that melatonin supports its neuroprotective effect by attenuating the expression of BACE and PSEN1, reducing ROS linked to oxidative stress, and consequently decreasing B-amyloid generation [112].

## CONCLUSION AND FUTURE DIRECTIONS

This review evaluated the potential of melatonin as an adjunctive therapy for OSA by mitigating oxidative stress, inflammation, cardiovascular and metabolic dysfunction, and neurocognitive impairment. It discussed findings from various animal studies demonstrating melatonin's cardioprotective, glycemic, and lipid-regulating effects, as well as its role in enhancing cognitive function. Although preclinical studies provide compelling evidence for melatonin's potential benefits in OSA, clinical data remain limited.

Some studies have explored melatonin as part of a personalized combination therapy approach for OSA, emphasizing its potential to complement CPAP by improving sleep efficiency and reducing oxidative stress. The antioxidant properties of melatonin may reduce loop gain and apnea-hypopnea index (AHI) by limiting the formation of ROS and subsequent IH-induced ventilatory neuroplasticity, which impairs chemoreflex control of ventilation [113].

These findings suggest that melatonin supplementation could be tailored based on individual chronotypes and disease severity, paving the way for precision medicine in OSA management [113]. The combination of therapies—such as positive airway pressure, surgery, pharmacologic agents, and hypoglossal nerve stimulation—targeting various physiological traits of OSA (e.g., pharyngeal critical closing pressure, loop gain, arousal threshold, and upper airway recruitment) may theoretically enhance treatment efficacy. Clinical trials have demonstrated improvements in AHI with combination therapy [113], underscoring the need for further research to determine optimal dosing, long-term safety, and the effects of melatonin alongside CPAP and other treatment modalities.

In summary, melatonin shows promise as a therapeutic adjunct for mitigating the consequences of CIH associated with OSA. Its antioxidant and anti-inflammatory properties offer protective effects against CIH-induced cardiovascular, metabolic, and neurological complications. Emerging evidence underscores melatonin's capacity to reduce oxidative stress and inflammation, supporting its potential role in addressing OSA-related comorbidities. Despite encouraging preclinical and early clinical findings, further large-scale studies are needed to establish optimal dosing, long-term safety, and efficacy. Integrating melatonin into OSA management could expand the therapeutic options, particularly for patients with poor adherence to standard treatments such as CPAP. Ongoing clinical trials aim to evaluate the effectiveness of melatonin in alleviating OSA-related complications and symptoms.

### Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

### Author Contributions

Conceptualization: Jose Javier Lasala, Don Eliseo III Lucero-Prisno. Data curation: Jose Javier Lasala. Formal analysis: Jose Javier Lasala. Investigation: Jose Javier Lasala. Methodology: Jose Javier Lasala. Project administration: Jose Javier Lasala. Resources: Don Eliseo III Lucero-Prisno. Supervision: Don Eliseo III Lucero-Prisno. Validation: Jose Javier Lasala. Visualization: Jose Javier Lasala. Writing—original draft: Jose Javier Lasala. Writing—review & editing: Jose Javier Lasala, Don Eliseo III Lucero-Prisno.

### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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