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REVIEW ARTICLE

Metabolic dysfunction in OSA: Is there something new under the sun?

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Summary

The growing number of patients with obstructive sleep apnea is challenging healthcare systems worldwide. Obstructive sleep apnea is characterized by chronic intermittent hypoxaemia, episodes of apnea and hypopnea, and fragmented sleep. Cardiovascular and metabolic diseases are common in obstructive sleep apnea, also in lean patients. Further, comorbidity burden is not unambiguously linked to the severity of obstructive sleep apnea. There is a growing body of evidence revealing diverse functions beyond the conventional tasks of different organs such as carotid body and gut microbiota. Chronic intermittent hypoxia and sleep loss due to sleep fragmentation are associated with insulin resistance. Indeed, carotid body is a multi-sensor organ not sensoring only hypoxia and hypercapnia but also acting as a metabolic sensor. The emerging evidence shows that obstructive sleep apnea and particularly chronic intermittent hypoxia is associated with non-alcoholic fatty liver disease. Gut dysbiosis seems to be an important factor in the pathophysiology of obstructive sleep apnea and its consequences. The impact of sleep fragmentation and intermittent hypoxia on the development of metabolic syndrome may be mediated via altered gut microbiota. Circadian misalignment seems to have an impact on the cardiometabolic risk in obstructive sleep apnea. Dysfunction of cerebral metabolism is also related to hypoxia and sleep fragmentation. Therefore, obstructive sleep apnea may alter cerebral metabolism and predispose to neurocognitive impairment. Moreover, recent data show that obstructive sleep apnea independently predicts impaired lipid levels. This mini-review will provide novel insights into the mechanisms of metabolic dysfunction in obstructive sleep apnea combining recent evidence from basic, translational and clinical research, and discuss the impact of positive airway pressure treatment on metabolic disorders.

KEYWORDS
carotid body, dyslipidaemia, dysmetabolism, gut microbiota, metabolic diseases, obstructive sleep apnea, sleep

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1 | INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent sleep disorder, characterized by partial or complete upper airway collapses leading to apneic events during sleep, sleep fragmentation (SF) and chronic intermittent hypoxia (CIH). A recent European study based on polysomnographic findings in the general population gave an estimated prevalence of 30% in men and 13% in women for moderate–severe OSA (Fietze et al., 2019). Obesity is the major risk factor for OSA, and a shared risk factor for its several comorbidities. However, the comorbidity burden is high also in non-obese OSA patients (Akahoshi et al., 2010; Gunduz et al., 2018).

Chronic intermittent hypoxia and sleep loss due to SF are associated with insulin resistance (Tasali et al., 2008) and metabolic dysfunction (Olea et al., 2014; Ryan et al., 2019; Sacramento et al., 2016; Shin et al., 2014). Recently, adipose tissue dysfunction has been suggested to play a key role in dysmetabolism in OSA (Ryan et al., 2019). There is a growing body of evidence that OSA and particularly CIH is associated with non-alcoholic fatty liver disease (NAFLD; Aron-Wisnewsky et al., 2016; Aron-Wisnewsky & Pepin, 2015; Mirrakhimov & Polotsky, 2012). Carotid body (CB) is a multisensor organ not sensoring only hypoxia and hypercapnia but also insulin resistance and glucose metabolism (Conde et al., 2014, 2017). OSA may alter cerebral metabolism and thereby predispose to neurocognitive impairment (Liguori et al., 2021).

In healthy people, the gut microbiota consist mostly of beneficial bacteria. An imbalance in gut microbiota composition has been suggested to contribute to a variety of disorders. Sleep loss, SF and CIH have been linked with gut dysbiosis (Benedict et al., 2016; Lucking et al., 2018; Poroyko et al., 2016). Recently, alterations in gut microbiota have been associated with obesity, diabetes, dyslipidaemia, cardiorespiratory control, hypertension and coronary heart disease – all of those common comorbidities of OSA (Liu et al., 2020; O'Connor et al., 2020).

This mini-review will provide novel insights into the mechanisms of metabolic dysfunction in OSA combining recent evidence from basic, translational and clinical research, and paving the way to new research questions, treatment options and precision medicine for OSA.

2 | METABOLIC COMORBIDITIES ASSOCIATED WITH OSA

The relationship between OSA and metabolic disease is unequivocal. If on one hand, sleep apnea results in intermittent hypoxia (IH) and SF leading to and exacerbating obesity, metabolic syndrome and type 2 diabetes (T2D; Bonsignore et al., 2013; Conde et al., 2014) and NAFLD (Jin et al.,2018); on the other hand, obesity is considered a major risk factor for the development and progression of OSA (Bonsignore et al., 2013; Conde et al., 2014).

2.1 | Metabolic syndrome and T2D

Obstructive sleep apnea is independently associated with metabolic syndrome or its core components that incorporate visceral obesity, hypertension, insulin resistance, glucose intolerance and dyslipidaemia (Bonsignore et al., 2013; Conde et al., 2014). While the link between OSA and some of the pathological features of metabolic syndrome, such as daytime hypertension, was highly cemented, the link with insulin resistance and dysmetabolism emerged more recently. Several clinical studies showed that in patients with OSA, the apnea–hypopnea index (AHI) and OSA severity, independently of obesity and fat mass, contributed to insulin resistance (Ip et al., 2002; Punjabi & Beamer, 2009) and to pancreatic β-cell dysfunction (Punjabi & Beamer, 2009), to elevated fasting glucose and to impaired oral glucose tolerance (Punjabi et al., 2004). As anticipated by the link between OSA and insulin resistance and glucose intolerance, OSA is a risk factor for the development of T2D. It was seen in several observational studies that OSA and its severity is positively associated with the incidence of T2D, independent of adiposity, body mass index (BMI) and age (Muraki et al., 2018; Nagayoshi et al., 2016; Reichmuth et al., 2005). It was also corroborated in a retrospective study that investigated the relationship between OSA and incident T2D in 1,206 Chinese adults in Hong Kong from 2006 and 2013, where the authors found that OSA severity independently predicted incident diabetes and that there were no interactions between OSA and obesity (Xu et al., 2019). Also, in a cross-sectional analysis of 5,294 participants of the multi-national European Sleep Apnoea Cohort (European Sleep Apnoea Database, ESADA), it was found that OSA severity independently predicts glycaemic health in non-diabetic subjects (Kent et al., 2014). Supporting the link between OSA and glycaemic dysmetabolism, snoring, which is known to be a surrogate marker of OSA, is associated with a higher risk for T2D (Al-Delaimy et al., 2002; Elmasry et al., 2000). The link between OSA and dysmetabolism was also supported by the effect of continuous positive airway pressure (CPAP) on the pathophysiological variables that characterize metabolic disease. CPAP therapy in T2D patients with OSA decreased postprandial glucose levels and glycated haemoglobin (Babu et al., 2005; Malik et al., 2017), and increased insulin sensitivity (Harsch et al., 2004). Also, regular long-term CPAP use in moderate-to-severe OSA was associated with reduced risk of incident T2D, after adjustment for various baseline metabolic risk factors and subsequent body weight change (Xu et al., 2019). However, these beneficial effects of CPAP on glucose metabolism and insulin resistance in patients with OSA are not consensual. CPAP treatment for 3 or 6 months did not improve fasting glucose or insulin plasma levels (Ip et al., 2000). In agreement, a more recent study in a population of 888 participants from the Sleep Apnea Cardiovascular Endpoints (SAVE) trial, with OSA and stable cardiovascular disease, and in where patients were followed for HbA1c at baseline and at 2 and 4 years, found that CPAP therapy did not affect glycaemic control in those with diabetes or prediabetes or diabetes risk over standard-of-care treatment (Loffler et al., 2020). However, this

study was not primarily dedicated to evaluate the impact of CPAP on metabolic outcomes (insulin sensitivity or glucose tolerance), and therefore the authors cannot infer about the effect of CPAP on these. The interaction between gender and CPAP for fasting glycaemia in participants with pre-existing diabetes was also interesting, with women with OSA and diabetes responding more favourably to CPAP in terms of glycaemic control in comparison with women allocated to usual care that showed a deterioration in glycaemic control during follow-up (Loffler et al., 2020). This clearly points towards the existence of sex differences in the link between OSA and dysmetabolism that deserves further clarification.

Multiple factors may contribute to the heterogeneity of the results on the effect of CPAP on metabolic pathological characteristics and disease, and on the link between OSA and dysmetabolism, including different levels of CPAP adherence, background glycaemic control, the use of anti-diabetic drugs, disease progression and the presence of confounding factors, such as obesity, among others. These discrepancies among studies clearly indicate that more research on the effects of CPAP and on the link between OSA and dysmetabolism are needed to elucidate pathophysiological mechanisms. Research in animal models of CIH, that mimic OSA - particularly in rodents, has allowed the knowledge on the mechanisms behind the association between OSA and metabolic diseases to deepen. CIH and sleep loss due to SF are two pathological characteristics of OSA, and both are associated with insulin resistance (Tasali et al., 2008) and metabolic dysfunction (Olea et al., 2014; Ryan et al., 2019; Sacramento et al., 2016; Shin et al., 2014). Whereas the effects of CIH on insulin sensitivity are consensual with several authors showing that CIH induces alterations in insulin secretion (Sacramento et al., 2016; Wang et al., 2013) and insulin resistance (Olea et al., 2014; Sacramento et al., 2016; Wang et al., 2013) in mice and rats, the effects of CIH on glucose homeostasis are controversial. Olea et al. (2014) found that rats submitted to 15 days of CIH exhibit insulin resistance without alterations in fasting glycaemia and glucose tolerance, and Shin et al. (2014) showed that mice exposed to CIH during 4/6 weeks increased fasting blood glucose, baseline hepatic glucose output but not insulin sensitivity (Shin et al., 2014). These differences in the pathophysiological features that characterize dysmetabolism might be explained by the distinct species studied, and by the exposure to CIH paradigms of different severity and duration. Another factor contributing to and aggravating metabolic dysfunction in patients with OSA is obesity, where it is estimated that 40% of obese individuals have OSA and approximately 70% of individuals with OSA are obese (Daltro et al., 2007; Vgontzas et al., 2000). However, metabolic dysfunction is known to be present in lean OSA subjects (Pamidi et al., 2012), and in CIH rodent models without the obesity component (Carreras et al., 2012; Fenik et al., 2012; Sacramento et al., 2016; Shin et al., 2014; Wang et al., 2013) and without alterations in the fat depots (Olea et al., 2014; Sacramento et al., 2016). Therefore, we can conclude that in OSA, obesity is not the only factor contributing to metabolic dysfunction and, in fact, obesity has been a confounding factor in unveiling the mechanisms behind the link between OSA and dysmetabolism.

Diverse mechanisms have been proposed to explain the dysmetabolic phenotype in OSA: increased sympathetic activation, deregulation of the hypothalamus–pituitary axis, generation of reactive oxygen species (ROS; Tasali et al., 2008), alteration in adipokine levels (Olea et al., 2014; Reinke et al., 2011) and inflammation of the adipose tissue (Almendros et al., 2015; Murphy et al., 2017; Reinke et al., 2011; Thorn et al., 2017). In fact, more recently the hypothesis that adipose tissue dysfunction is a major contributor for dysmetabolism in OSA has gained attention (Ryan et al., 2019). Adipose tissue inflammation, characterized by infiltration of macrophages and increased secretion of pro-inflammatory cytokines, was observed in lean CIH rodent models (Almendros et al., 2015; Murphy et al., 2017; Reinke et al., 2011) and in isolated human adipocytes (Murphy et al., 2017; Taylor et al., 2014). Apart from inflammation, hypoxia was also suggested to be involved in adipose tissue dysfunction; however, the data are not consensual. Whereas some authors found that lean mice exposed to CIH exhibit visceral adipose tissue dysfunction via activation of hypoxia-inducible factor (HIF; Gozal et al., 2017) and that increased expression of HIF-1α in this tissue is associated with decreased insulin signalling and sensitivity (Thomas et al., 2017), others found that CIH induced whole-body insulin resistance with a decrease in visceral adipose tissue insulin signalling but with no alterations in HIF-1α and 2α (Sacramento et al., 2016). These last results were sustained by the work of Thorn et al. (2017), showing that although OSA patients exhibit adipose tissue dysfunction, characterized by a low degree of chronic inflammation and increased expression of peroxisome proliferator-activated receptor-gamma, this tissue was not more hypoxic than in BMI-matched controls despite lower mean daytime arterial oxygen saturation. Another contributor within the adipose tissue that could also be involved in dysmetabolism is the altered secretion of adipokines, leptin and adiponectin (Olea et al., 2014; Pierard et al., 2019; Thorn et al., 2017). CIH is associated with increased leptin levels (Olea et al., 2014; Pierard et al., 2019). Knowing that leptin is a potent sympathetic activator (Gauda et al., 2020), acting also at the CB (Caballero-Eraso et al., 2019; Ribeiro et al., 2018), that hyperleptinaemia and leptin resistance are associated with metabolic diseases, and that sympathetic activation runs with CIH and OSA, it is possible to postulate that the altered secretion of leptin contributes to CIH/OSA-induced metabolic dysfunction (Gauda et al., 2020; Figure 1). Adiponectin, an insulin-sensitizer, is also decreased in patients with OSA (Thorn et al., 2017), and recently it was observed that CIH in mice modifies adiponectin oligomerization as well as the expression of adiponectin receptors in insulin-sensitive tissues, such as the skeletal muscle and heart, suggesting that these alterations might contribute to the link between CIH and dysmetabolism (Pierard et al., 2019). Finally, the oxidative status can also contribute to deregulation of adipose tissue as well as to whole-body dysmetabolism (Berger & Polotsky, 2018; Gileles-Hillel et al., 2017; Olea et al., 2014). CIH in rats induces a whole-body oxidative status manifested by an increase in lipid peroxides and diminished

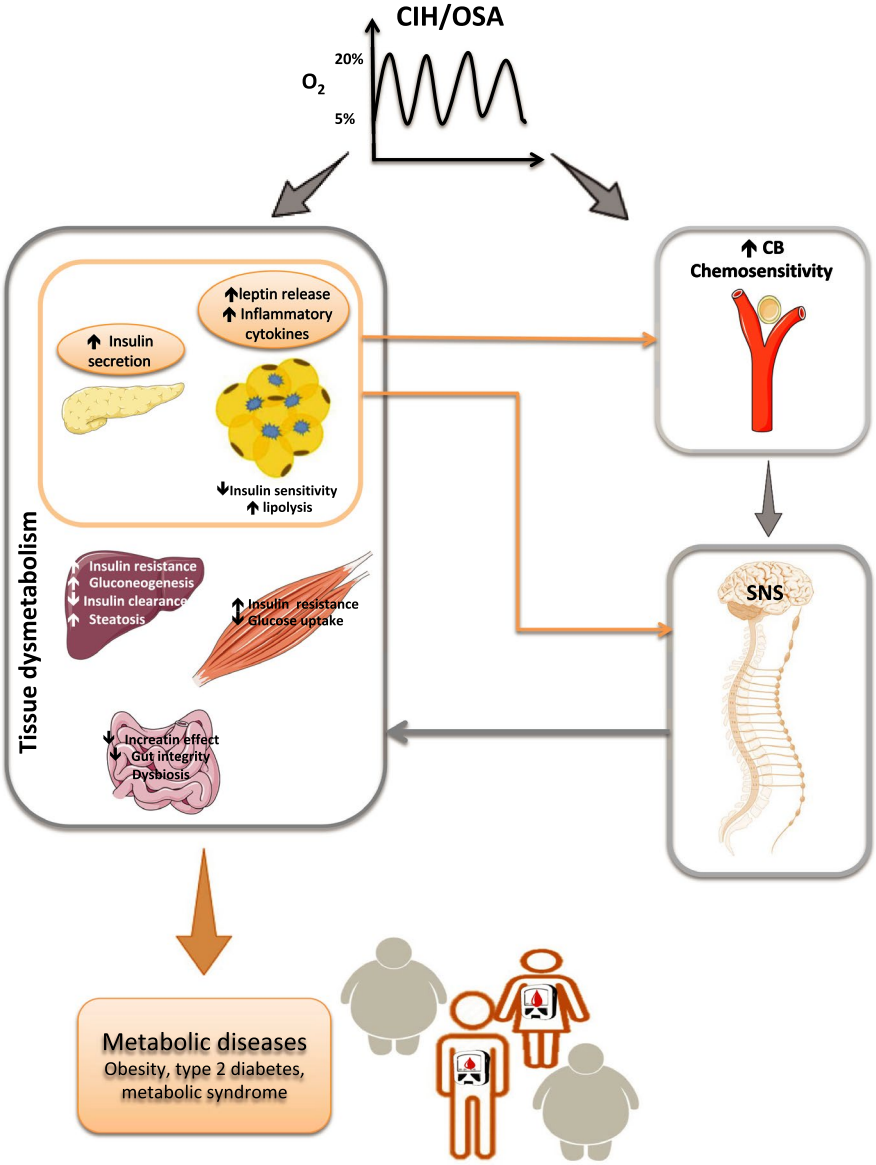

FIGURE 1 Postulated mechanisms supporting the involvement of carotid body (CB) in the link between obstructive sleep apnea (OSA) and chronic intermittent hypoxia (CIH) and metabolic diseases. CIH, one of the pathological features characterizing OSA, can act directly on CB to induce its overactivation, or indirectly at the pancreas and in the adipose tissue to promote a hyperinsulinaemia and hyperleptinaemia and inflammation, respectively, that will act on the CB to promote its dysfunction. CB signals to the sympathetic nervous system (SNS) promoting a sustained SNS activation that leads to and aggravates metabolic dysfunction in insulin-sensitive tissues, such as the liver, skeletal muscle, intestine, gut, adipose tissue and the pancreas. This generates a vicious cycle CIH–CB–SNS–metabolic dysfunction that leads to metabolic diseases such as obesity, type 2 diabetes (T2D) and metabolic syndrome

activities of superoxide dismutase (Olea et al., 2014) and, in the visceral adipose tissue, CIH–metabolic dysfunction is associated with increased ROS production and alterations in the electron transport chain (Gileles-Hillel et al., 2017). Altogether, we can conclude that adipose tissue dysfunction plays a role in the link between CIH and dysmetabolism, but is probably not the only or the main trigger initiating a dysmetabolic state. For example, pancreatic β-cells are particularly sensitive to hypoxia (Pallayova et al., 2011), and mice exposed to CIH exhibited pancreatic β-cell dysfunction, manifested by impaired glucose-stimulated insulin secretion and augmented mitochondrial ROS (Wang et al., 2013). Moreover, the CBs, classically defined as hypoxic sensors, activity increased during CIH (Peng et al., 2009; Prabhakar et al., 2007; Rey et al., 2004), leading to augmented sympathetic activity that can contribute to metabolic dysfunction (Conde et al., 2014, 2017). Therefore, we can say that more studies in this field are needed to provide a better understanding of the mechanisms involved in the link between OSA and metabolic diseases.

2.2 | Non-alcoholic fatty liver diseases

Non-alcoholic fatty liver diseases is now the most common liver disease in the world, accounting for 25% of the worldwide population. The prevalence of the disease parallels the epidemic of metabolic diseases, namely obesity and T2D, hence the mechanisms underlying the dysmetabolism, insulin resistance and obesity seem to be important in the development of both hepatic steatosis and non-alcoholic steatohepatitis, two stages of NAFLD progression (Harrison et al., 2003; Montesi et al., 2013). OSA, and particularly CIH, as described in the previous section, are also known to be independently associated with the different pathological features associated with NAFLD, such as visceral obesity, insulin resistance and abnormal lipid metabolism (Bonsignore et al., 2013; Conde et al., 2014), and therefore a role for OSA and CIH on the exacerbation of NAFLD could be postulated. In fact, there is a growing body of evidence that OSA and particularly CIH is associated with NAFLD (Aron-Wisnewsky et al., 2016; Aron-Wisnewsky & Pepin, 2015; Mirrakhimov & Polotsky,

2012). Enormous evidences have come from studies in animals where it was shown that CIH causes triglyceride accumulation in the liver and liver injury as well as hepatic inflammation in mice, and therefore contributes to the progression of NAFLD (for review, see Aron-Wisnewsky et al., 2016; Mirrakhimov & Polotsky, 2012). Also, several authors have found that OSA is associated with liver injury in obese (Aron-Wisnewsky et al., 2012; Ng et al., 2021 Polotsky et al., 2009) and non-obese patients (Qi et al., 2015), and that CIH is implicated in steatohepatitis, in the exacerbation of NAFLD during obesity, and contributes to the progression to non-alcoholic steatohepatitis and liver fibrosis (Aron-Wisnewsky et al., 2012; Polotsky et al., 2009; Qi et al., 2015). The link between OSA and NAFLD, apart from being present in adults, was also found to be present in obese children (Alkhouri et al., 2015; Nobili et al., 2015), and associated with OSA severity (Nobili et al., 2015). Similar to the relationship between CPAP and OSA and T2D, the effect of CPAP on NAFLD is not consensual, with some authors showing beneficial effects of CPAP on fatty liver (Kim et al., 2018; Toyama et al., 2014) while others do not (Jullian-Desayes et al., 2016; Kohler & Stradling, 2016; Ng et al., 2021). In fact, Toyama et al. found in male patients with OSA who developed fatty liver at baseline, that liver fat accumulation decreased after CPAP therapy in spite of stable BMI, visceral and subcutaneous fat accumulation, and other metabolic conditions (Toyama et al., 2014). Also, Kim et al. showed that OSA treatment with CPAP was associated with significant biochemical improvement and reduction in NAFLD-related fibrosis after adjusting for obesity class and severity of OSA (Kim et al., 2018). Altogether these results suggest that long-term CPAP could contribute to improvement in NAFLD and its progression in OSA patients with abdominal obesity. However, on the other hand, several authors have found no effect of CPAP on liver injury (Jullian-Desayes et al., 2016; Kohler & Stradling, 2016) and, more recently, a randomized clinical study showed that despite significant correlations between hepatic steatosis and markers of severity of OSA, CPAP alone did not improve hepatic steatosis and fibrosis (Ng et al., 2021). These controversial data highlight that more studies are needed to clearly define the impact of CPAP on NAFLD and its progression as well as the population/disease stage that could benefit from therapeutic interventions.

Based on rodent and human studies, several pathophysiological mechanisms have been proposed to explain the link between liver injury and OSA/CIH, with some sharing characteristics with those proposed for the link between OSA and T2D. Namely, it is known that OSA generates metabolic dysfunction (see previous section), contributing to the development of obesity and insulin resistance, which are pathological features associated with NAFLD (Bonsignore et al., 2013; Conde et al., 2014). Additionally, other mechanisms, such as the increased expression of genes involved in lipogenesis via the HIF-1α pathway; the increased expression of lysyl oxidase enzyme, a protein involved in the rigidity of extracellular matrix; an increased oxidative stress and lipid peroxidation; the increased mitochondrial dysfunction; the increased liver sympathetic nervous system activity; and the increased intestinal permeability and disruption of the gut–liver axis (Aron-Wisnewsky et al., 2016; Mirrakhimov & Polotsky, 2012) might be involved in liver injury and progression to more severe disease states.

3 | SLEEP AND MICROBIOTA

Although Hippocrates had already suggested the association between diseases and sleep, the first systematic studies of the effects of a bacterial infection on sleep were not done until about 30 years ago (Toth & Krueger, 1988, 1989). They demonstrated that bacterial infection initially increases non-rapid eye movement (NREM) sleep followed by an inhibition in NREM sleep. Rapid eye movement (REM) sleep is inhibited during infections. Further, depletion of gut microbiota by antibiotic treatment alters sleep architecture in mice (Ogawa et al., 2020).

In a randomized within-subject crossover study utilizing a standardized in-lab protocol in healthy men, after 2 days of partial sleep deprivation (PSD) versus after 2 days of normal sleep (NS), individuals exhibited an increased Firmicutes:Bacteroidetes ratio, higher abundances of the families Coriobacteriaceae and Erysipelotrichaceae, and lower abundance of Tenericutes, previously all associated with metabolic perturbations in animal or human models (Benedict et al., 2016). Fasting and postprandial insulin sensitivity decreased after PSD versus NS (Benedict et al., 2016). Chronic SF in mice particularly promoted the growth of Lachnospiracae and Ruminococcacae families, with contrasting decreases in Lactobasiaceae and Bifidobacteriaceae families that consist of many beneficial species (Poroyko et al., 2016). Indeed, the impact of SF on the development of metabolic syndrome may be mediated by altered gut microbiota (Poroyko et al., 2016). These findings suggest that metabolic dysfunction associated with sleep loss may in fact be mediated through the overgrowth of specific gut bacteria.

Recently, gut microbiota composition has been reported to be associated with sleep disorders such as narcolepsy (Lecomte et al., 2020), insomnia disorder and OSA. The gut microbiota of patients with insomnia compared with healthy controls were characterized by lower microbial richness and diversity, depletion of anaerobes, and short-chain fatty acid-producing bacteria (Li et al., 2020). Lachnospira and Bacteroides were signature bacteria in patients with acute insomnia, while Faecalibacterium and Blautia were signature bacteria for distinguishing chronic insomnia patients from healthy controls. These signature bacteria were also associated with patients' self-reported sleep quality and plasma IL-1β (Li et al., 2020). CIH, a characteristic of OSA, leads to disrupted gut microbiota in mice (Moreno-Indias et al., 2015). In guinea pigs, exposure to CIH alters gut microbiota richness and composition, brainstem neurochemistry, and autonomic control of heart rate, independent of CB sensitization, suggesting modulation of breathing and autonomic homeostasis via the microbiota–gut–brainstem axis (Lucking et al., 2018).

It would be appealing to improve sleep quality by modifying gut microbiota with probiotics. The data addressing this issue are still scarce. In a study of 32 students, the administration of the probiotic

Lactobacillus gasseri CP2305 markedly improved sleep quality measured by the Pittsburgh Sleep Quality Index (PSQI; Nishida et al., 2017). Concomitantly, the relative abundance of 15 gut microbial species differed between the control and probiotic groups, including decreases in Bact. Vulgatus and increases in Dorea Longicatena following probiotic use. Another double-blind randomized controlled trial found that daily use of a probiotic mixture (containing Lactobacillus fermentum LF16, Lactobacillus rhamnosus LR06, Lactobacillus plantarum LP01 and Bifidobacterium longum BL04) in young healthy participants led to improvement in PSQI score over time, although PSQI scores did not differ from those of controls (Marotta et al., 2019).

4 | CIRCADIAN MISALIGNMENT, OBESITY AND MICROBIOTA

Circadian rhythm is the rhythm that is driven internally (i.e. by the endocrine system) and controlled by the central clock located in the suprachiasmatic nucleus. When this rhythm is entrained by environmental factors (e.g. time zeitgebers), it is called the diurnal rhythm. The two rhythms are interrelated, and circadian rhythms are usually synchronized to environmental cues. There is some evidence that bacterial cells have their clocks that oscillate in a determined rhythm based on specific factors, whether related to the host or the surrounding environmental factors (Mashaqi & Gozal, 2020).

The role of circadian misalignment in OSA is unclear. However, both SF (Poroyko et al., 2016) and short sleep duration (Benedict et al., 2016) are associated with gut dysbiosis, which may be due to activation of the hypothalamic–pituitary–adrenal (HPA)-axis. Metabolic disturbances associated with sleep loss may in fact be mediated through the overgrowth of specific gut bacteria (Benedict et al., 2016). Reciprocally, the end-products of bacterial species that grow in response to sleep loss are able to induce fatigue (Zielinski et al., 2013). Inter-tissue circadian misalignment occurs also with IH (Manella et al., 2020), a typical feature of OSA. This means that there is a bidirectional relationship between the gut microbiota and the host clock. Circadian misalignment, for example due to shift work, may therefore impact this bidirectional relationship. Recently, it has been suggested that shift-work-induced circadian misalignment may potentiate the cardiometabolic risk of patients with OSA (Santos et al., 2020).

A meta-analysis of shift work showed an increased risk of obesity both in cross-sectional and follow-up cohort studies, especially in developing abdominal obesity (Sun et al., 2018). Not only the food content but also the timing of food intake is crucial for gut microbiota and host metabolism. When the feeding of mice was restricted either to dark-cycle or light-cycle (both 12 hr), the dark-fed group (i.e. fed during their normal activity phase) gained less weight than the light-fed group (Arble et al., 2009). Further, time-restricted feeding without reducing caloric intake prevented metabolic diseases in mice fed with a high-fat diet (Hatori et al., 2012). Every-other-day fasting reduced weight gain and increased energy expenditure through non-shivering thermogenesis (Li et al., 2017).

5 | OSA AND MICROBIOTA

Research in both animal models and humans has provided solid evidence that the microbiota is involved in OSA development and in its consequences. In fact, there are two main challenges that potentially affect the gut microbiota, and result in dysbiosis and health consequences in the host caused by OSA, IH and SF. Recent studies have shown that IH and SF could promote alterations in intestinal lumen, inducing variations in microbial diversity, pro-inflammatory mediators and bacterial translocation. At mid-term, these alterations could result in gut epithelial barrier dysfunction triggering both local and systemic inflammatory responses. Thus, all tissues and organs of the host could be affected, promoting cognitive/mood alterations and cardiovascular or metabolic diseases.

Regarding IH, a recent work carried out in rats has described that application of IH similar to that experienced in patients with OSA is translated into the gut lumen (Moreno-Indias et al., 2015). Specifically, the oxygenation was locally measured using an oxygen microelectrode. These measurements revealed that IH, although progressively attenuated in amplitude, is translated further into the lumen, at least until 200 μm. Furthermore, animals exposed to IH showed a different gut microbiota composition in comparison to controls (Moreno-Indias et al., 2015). Interestingly, the IH-induced alterations are quite persistent: after a 6-week period of recovery by normal breathing, the differences in microbiota composition remained in a principal component analysis (Moreno-Indias et al., 2016). More recent data also show that IH-induced changes in gut microbiota are able to elicit sleep alterations (Badran et al., 2020). This finding was revealed by measuring sleep recording in the faecally transplanted mice. The animals receiving faecal samples from IH-exposed mice experienced a reduction in total wake time, mainly caused by reductions in the dark phase, indicating increased abnormal somnolence.

In terms of SF, the information is still scarce. In a recent experimental study, mice were subjected to a realistic paradigm of SF mimicking OSA (Poroyko et al., 2016). The authors found that this challenge can modify the gut microbiota resulting in adipose tissue inflammation and metabolic alterations. Animals subjected to SF exhibited an increased visceral fat mass after 4 weeks of exposure, and returned to normal levels after 2 weeks of recovery. The insulin sensitivity assessed ex vivo in visceral white adipose tissue adipocytes revealed a reduction of phospho-AKT/AKT ratio in mice exposed to SF when compared with control sleep mice. As in visceral fat mass, insulin sensitivity was recovered after 2 weeks of SF cessation. More interestingly, the insulin response in control sleep mice was similar to SF-exposed mice when the animals were transplanted with faecal samples from SF-exposed mice. These findings indicate that the changes that SF induce in the microbiota can be translated to important metabolic features.

Very limited information is available from clinical studies to date. In a recent work, the authors found significant differences at the general level microbiota, particularly when comparing controls and severe OSA (Ko et al., 2019). The differences were more evident when looking at specific microbe type, for instance Prevotella. In another study, carried out on an animal model based on upper airway obstructions, application of OSA significantly increased systolic blood pressure at 7 and 14 days (Ganesh et al., 2018). The main novelty of this study was that such hypertensive alteration can be abolished by the probiotic Clostridium butyricum or the prebiotic Hylon VII. Therefore, solid experimental data and preliminary clinical results are available on the role that the gut microbiota plays in OSA. Figure 2 depicts how gut microbiota alterations induced by OSA components could mediate cardiovascular and metabolic consequences. Our current knowledge on the topic clearly deserves further basic and clinical research.

6 | CEREBRAL METABOLISM AND OSA

The harmful effect of disturbed sleep on brain health is particularly evident in patients with OSA. Both IH and SF due to OSA conditions may concur altering brain homeostasis and producing cerebral inflammation, cognitive deterioration, neuropsychological disturbances and cerebrovascular dysfunction. There is growing evidence that brain functional state and energetics are mutually related (Shulman, 2011); it is remarkable that glutamate and ATP, as well as glucose, lactate and other metabolites, are molecules involved in cerebral cellular metabolism, but also have signalling functions in the brain (DiNuzzo, 2016). In particular, glucose and glycogen catabolism, though aerobic glycolysis, features wakefulness; whereas lactate brain levels decrease, characterizing the transition to sleep; moreover, lower lactate levels during sleep represent the effect of decreased glucose production and increased glymphatic clearance (Aalling et al., 2018). Accordingly, mouse model studies suggested that extracellular lactate concentrations may be a reliable

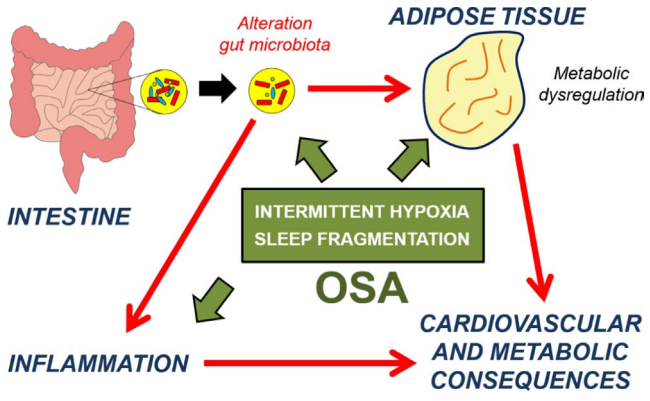

FIGURE 2 Gut microbiota alterations induced by obstructive sleep apnea (OSA) components could mediate some of its associated cardiovascular and metabolic consequences

sleep–wake biomarker. This evidence was reached by observing that persistent and sustained decreases in brain lactate levels were documented in mice during sleep, whereas elevated lactate levels were present from awakening and maintained throughout prolonged wake (Naylor et al., 2012).

The measurement of cerebrospinal fluid (CSF) lactate levels can reflect the brain glucose metabolism (in combination with pyruvate levels), which can also be measured by the 2-deoxy-2-(18F)-fluoro -D-glucose positron emission tomography ([18F]FDG PET; Liguori et al., 2016). Patients with OSA present with high CSF lactate levels, possibly owing to two different and concomitant mechanisms: (i) brain energetic metabolism damage; (ii) neurodegenerative processes (Liguori et al., 2015, 2017). This cerebral glucose metabolism malfunction in patients with OSA can be related to both hypoxia and SF, as high neuronal activity due to increased night-time wakefulness and hypoxic conditions promotes mitochondrial dysfunction and oxidative stress. On the other hand, OSA can promote neurodegenerative processes due to the privation of the positive effects of sleep quality and continuity on brain health. In particular, the beneficial effect of sleep related to glymphatic system activity can be suppressed by OSA with the accumulation of brain catabolic products interfering with neuronal functioning (Figure 3). Moreover, hypoxia can trigger neurodegenerative processes by inducing β-amyloid plaque formation and neuronal damage (Shiota et al., 2013).

Cortical brain glucose consumption can be measured by [18F] FDG PET (Liguori et al., 2016), a widely diffuse tool to evaluate and monitor cerebral metabolism in both a clinical setting and research (Attwell & Laughlin, 2001; Liguori, Ruffini, et al., 2019). Consistently, the use of PET tracers became a valuable instrument to investigate brain function and activity (Liguori et al., 2021). Few [18F]FDG PET studies have been performed in patients with OSA and documented that this clinical condition may alter cerebral metabolism in eloquent brain areas for neurodegeneration, first of all the precuneus (Yaouhi et al., 2009). Brain metabolism dysfunction has been confirmed in further studies including asymptomatic patients with OSA recruited from the community; moreover, this brain glucose metabolism malfunction corresponded to β-amyloid plaque deposition (André et al., 2020). These findings reinforce the evidence that OSA can promote and accelerate neurodegenerative processes in adults and the elderly (Liguori, Mercuri, et al., 2019; Liguori & Placidi, 2018). Notably, OSA can be treated with complete resolution of clinical signs and symptoms thanks to CPAP treatment. One of the main hypotheses in the literature is that CPAP can restore brain metabolism dysfunction, thus possibly reverting or slowing neurodegenerative processes (Bubu et al., 2020; Lajoie et al., 2020; Liguori, Mercuri, et al., 2019; Liguori & Placidi, 2018). In agreement with this suggestion, short-term CPAP treatment induces modest changes in cerebral glucose metabolism in patients with OSA; briefly, it has been demonstrated that glucose metabolism dysfunction in bilateral frontal and temporal lobes improved after CPAP treatment, although did not reach the level of functioning of controls (Ju et al., 2012). Further longer longitudinal studies performed in larger samples of patients, coupling the [18F]FDG PET results to cognitive performance evaluations, should

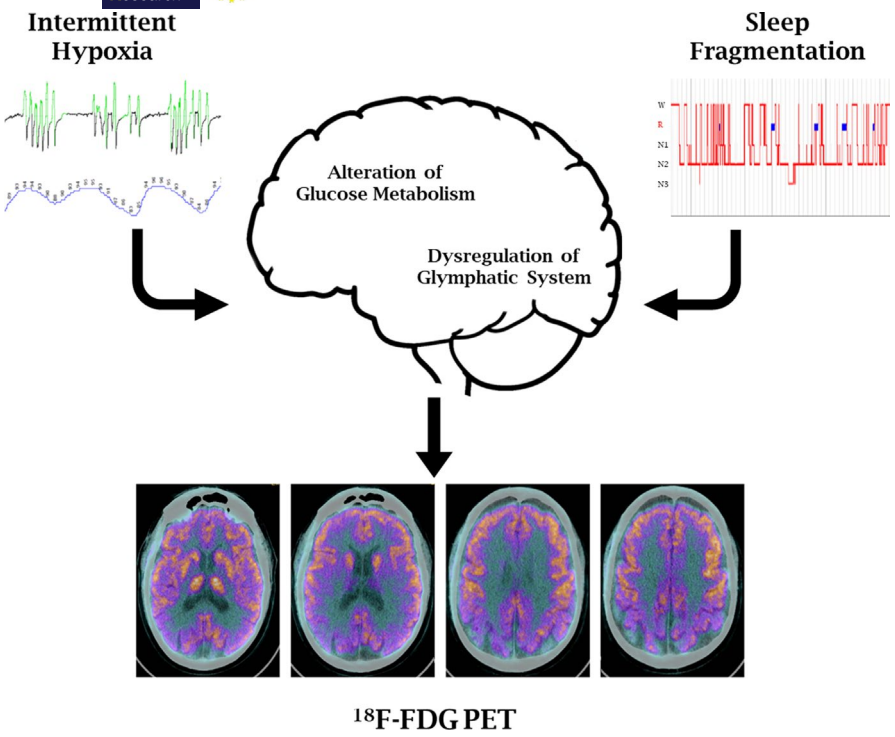

FIGURE 3 Intermittent hypoxia (IH) and sleep fragmentation (SF) can negatively influence brain glucose metabolism and induce glymphatic system malfunction in patients with obstructive sleep apnea (OSA); as a result, brain 2-deoxy-2-(18F)-fluoro-D-glucose positron emission tomography ([18F]FDG PET) shows the reduction of cerebral glucose metabolism indicative of a preclinical neurodegenerative process resembling Alzheimer's disease pathology. R, REM sleep; N1, stage 1 of non-REM sleep; N3, stage 3 of non-REM sleep; W, wake; [18F]FDG PET, 2-deoxy-2-(18F)-fluoro-D-glucose positron emission tomography

be planned in the future in order to better investigate brain metabolism in patients with OSA and the possibly beneficial role of CPAP treatment.

Hence, OSA clearly affects brain metabolism, by altering glucose consumption, promoting inflammation, and inducing neurodegenerative processes. Hypoxia and SF are the two main detrimental factors involved in this relation. CPAP can represent a reliable treatment for ensuring the physiological brain metabolism in patients with OSA, although novel and clear evidence should be achieved to reinforce this suggestion.

7 | CB, IH AND METABOLISM

The CBs are arterial chemoreceptors that classically sense and respond to changes in arterial blood O_2, CO_2 and pH levels. Besides their role in the control of ventilation, the CBs have been described as metabolic sensors involved in energy homeostasis (Conde et al., 2017, 2018). In OSA, it is consensual that the CBs mediate the reflex increase in sympathetic activity and blood pressure due to CIH (Fletcher et al., 1992b; Narkiewicz et al., 1999; Peng et al., 2003), an effect mediated by an increase in CB chemosensitivity (Peng et al., 2009; Prabhakar et al., 2007; Rey et al., 2004), and abolished by CB and carotid sinus nerve (CSN) denervation (Fletcher et al., 1992a; Prabhakar et al., 2005). More recently, the CB has been also proposed to be one of the links between CIH and metabolic dysfunction. Supporting this link, CB denervation prevented CIH-induced fasting hyperglycaemia and hepatic glucose output (Shin et al., 2014). Additionally, the Conde group has described that the CB is primordial in controlling peripheral insulin sensitivity and glucose homeostasis, as the denervation and/or modulation of the CSN, the CB-sensitive nerve, prevents and reverts the pathological dysmetabolic features – insulin resistance, glucose intolerance and impaired glucose uptake in insulin-sensitive tissue – induced by the hypercaloric diets in rats (Ribeiro et al., 2013; Sacramento et al., 2017, 2018). Also, they found that abolishment of CB activity normalized the heightened sympathetic activity observed in these animal models (Cracchiolo et al., 2019; Sacramento et al., 2017), meaning that the neural-circuitry by which the CB is involved in the control of metabolism involves the sympathetic nervous system. In agreement, the same group found that CB activity is increased in metabolic syndrome, prediabetes and T2D animal models (Dos Santos et al., 2018; Ribeiro et al., 2013; Sacramento et al., 2017) and patients (Cunha-Guimaraes et al., 2020), and postulated that insulin, leptin and inflammatory cytokines, which are known to act on the CB and whose levels are deregulated in OSA and metabolic disease, contribute to the vicious cycle of CIH–CB activation–metabolic disease (Conde et al., 2017, 2018; Sacramento et al., 2020). Therefore, it could be postulated that CIH, by acting on the CB directly or indirectly via altering insulin secretion by the pancreas or the increasing leptin and inflammation in the adipose tissue, lead to an increase in CB chemosensitivity that promotes metabolic dysfunction (Figure 1).

8 | DYSLIPIDAEMIA AND OSA

Patients with sleep apnea are more likely to develop cardiovascular and metabolic disorders, in particular systemic hypertension, heart failure, coronary heart disease, stroke, diabetes mellitus, insulin resistance and also dyslipidaemia (Drager et al., 2013). Dyslipidaemia, defined as abnormally elevated total cholesterol or triglycerides with or without a corresponding significantly reduced high-density

lipoprotein (HDL) level, is associated with progressive atherosclerosis. There is an increased risk of cardiovascular morbidity and mortality in patients with sleep apnea with high lipid levels, and especially in the ones with other risk factors like obesity, diabetes, physical inactivity, and a high-cholesterol diet (Seetho et al., 2014).

The role of OSA in the development of dyslipidaemia has been investigated in animal models and clinical studies for evaluation of an independent relationship beyond the effects of obesity. Although a clear causal relationship of OSA and dyslipidaemia is yet to be demonstrated, there is increasing evidence that CIH causes upregulation of lipid biosynthesis in the liver, an increase in adipose tissue lipolysis, and also an inhibition of lipoprotein clearance, mechanisms that may promote dyslipidaemia (Adedayo et al., 2014; Barros & García-Río, 2019). Evidence from animal models of OSA has shown that CIH induces fasting dyslipidaemia even in lean mice (Li et al., 2005), and mice exposed to CIH and a high-cholesterol diet developed atherosclerotic lesions in the aorta, and progression of dyslipidaemia (Savransky et al., 2007). The clinical evidence supporting the impact of OSA on lipid metabolism is mostly based on cross-sectional studies. Even so, OSA has been shown to be independently associated with dyslipidaemia diagnosis in clinical studies, and the link is strong with the severity of OSA, especially measured by IH (Figure 4; Gunduz et al., 2019; Trzepizur et al., 2013). Although OSA could worsen the lipid metabolism in non-obese patients (Karkinski et al., 2017), lipid levels are higher in particular in OSA patients with central obesity, as shown in the large multicentre ESADA cohort (Gunduz et al., 2018). A meta-regression analysis including 18,116 patients demonstrated that OSA is associated with higher total cholesterol, triglyceride and low-density lipoprotein (LDL), and lower HDL concentrations, with a correlation between AHI and lipid profile. Therefore, dyslipidaemia may be the mechanism of atherosclerosis in patients with OSA (Nadeem et al., 2014).

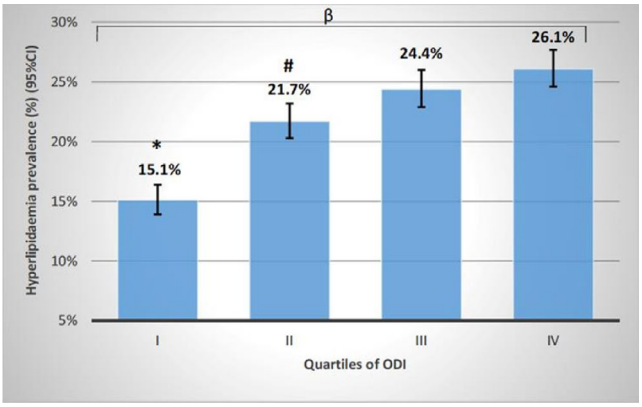

FIGURE 4 Hyperlipidaemia prevalence rates (95% confidence interval [CI]) in obstructive sleep apnea (OSA) increases across quartiles of oxygen desaturation index (15.1%, 21.7%, 24.4% and 26.1%, respectively; $p < .001$, between groups). Significant differences in prevalence between groups were reported for quartile I versus quartiles II–IV, and for quartile II versus quartile IV ($p < .05$ both, within groups). 95% CIs were demonstrated by bars. β$p < .001$ between groups I–IV. *$p < .05$ within groups I versus II, III and IV. #$p < .05$ within groups II versus IV (Gunduz et al., 2019)

Continuous positive airway pressure is the first-line treatment for OSA, but it is unclear whether CPAP treatment can improve dyslipidaemia and reduce cardiovascular morbidities in patients with OSA. In a meta-regression analysis (Nadeem et al., 2014), it was shown that CPAP treatment improves dyslipidaemia by decreasing total and LDL-cholesterol, and increasing HDL-cholesterol levels. However, another meta-analysis (Xu et al., 2014) included only randomized controlled trials comparing CPAP therapy with sham CPAP or control groups, and demonstrated that CPAP treatment significantly decreases only total cholesterol (especially in patients of younger age, more obese, and treated with long-term CPAP), but not LDL- and HDL-cholesterol or triglyceride levels. Overall, trials evaluating the effects of CPAP on lipid metabolism present inconclusive results, probably due to the observational design, small sample size, short-term follow-up or potentially not fully controlling confounding factors on top of CPAP treatment. Chirinos et al. (2014) randomly assigned 146 patients with obesity and moderate-to-severe OSA to CPAP treatment, weight-loss, or CPAP plus weight-loss intervention for 24 weeks, and triglyceride levels were significantly reduced in the weight-loss and combined-intervention groups, but not in the CPAP-alone group. The effect of long-term CPAP therapy on dyslipidaemia was evaluated in a recent study, and total and LDL-cholesterol levels decreased significantly following both short- and long-term CPAP therapy, but triglyceride or HDL-cholesterol did not change (Simon et al., 2020). Similarly, we investigated the long-term effect of CPAP therapy on lipid profile in the ESADA cohort, and all lipid levels improved following CPAP treatment in the unadjusted analysis (Gunduz et al., 2020). However, after adjustment for age, sex, lipid-lowering medication, change in weight, CPAP compliance and duration, only total cholesterol levels decreased significantly during follow-up (Figure 5), and duration of CPAP therapy was the only independent predictor for cholesterol reduction. Besides, coronary heart disease risk assessed by Framingham risk score decreased with CPAP therapy in both male and female OSA patients (Figure 6).

In conclusion, patients with OSA may exhibit higher rates of IH-induced dyslipidaemia, a risk factor for cardiovascular and cerebrovascular disorders, and the severity of OSA is correlated to the level of dyslipidaemia. CPAP therapy may have a beneficial effect on lipid profile but, along with CPAP device, lifestyle modifications like diet, physical activity and weight reduction are also important in patients with sleep apnea. Future studies are needed to explore the correlation between dyslipidaemia and OSA. Also, long-term randomized controlled trials with large sample size and after controlling confounding factors should be performed to determine the effect of CPAP therapy on lipid levels.

9 | CONCLUSIONS

Obstructive sleep apnea is a highly prevalent disorder with major cardiovascular and metabolic consequences. The relationship

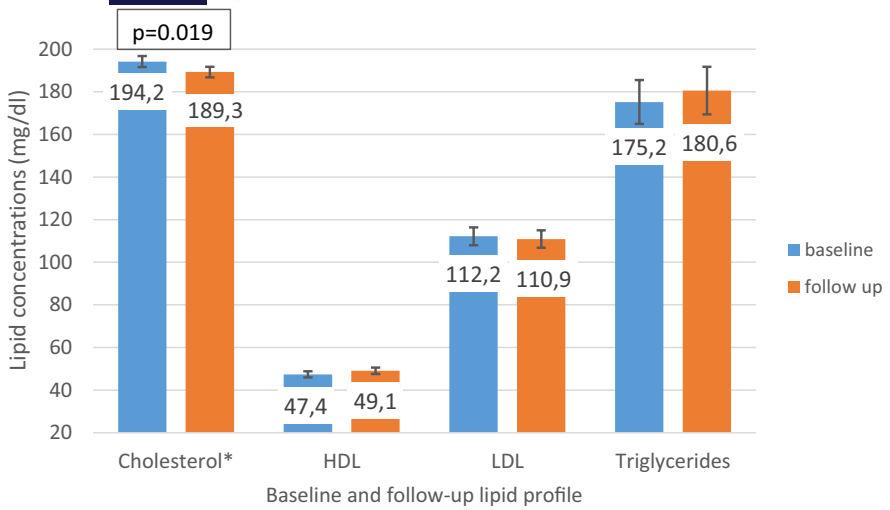

FIGURE 5 Pairwise comparisons in lipid profile in regression model adjusted for age, sex, lipid-lowering medication, change in weight, continuous positive airway pressure (CPAP) compliance, and duration. *Parameters with $p < .05$, **all values expressed as mean ± SD (mg dl^{-1}) (Gunduz et al., 2020)

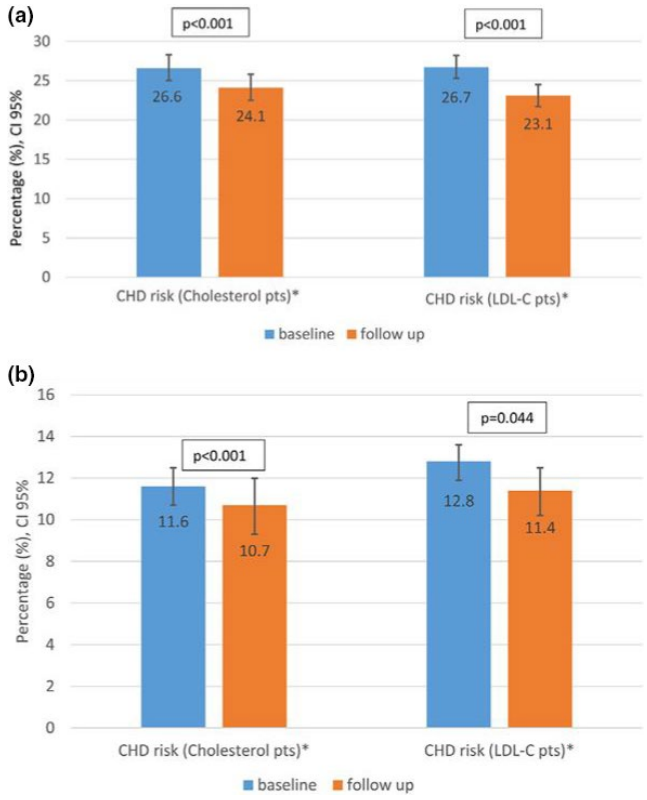

FIGURE 6 Comparison of baseline and follow-up coronary heart disease (CHD) risk scores** in male (a) and female (b) patients adjusted for continuous positive airway pressure (CPAP) duration, lipid-lowering medication, and change in weight. *Parameters with *p*-value < .05. **Framingham CHD risk has been calculated in terms of total cholesterol and low-density lipoprotein (LDL)-cholesterol points. *Parameters with *p*-value < .05. **Framingham CHD risk has been calculated in terms of total and LDL-cholesterol (Gunduz et al., 2020)

between OSA and metabolic comorbidities is bidirectional. OSA-induced IH and SF may result in decreased insulin sensitivity, sympathetic excitation, and systemic inflammation that eventually lead to metabolic consequences. Sleep apnea is a risk factor for T2D, and the prevalence of diabetes increases with the severity of OSA. Besides, the relationship between the two conditions is independent of obesity. OSA is also associated with metabolic syndrome and its components, including visceral obesity, hypertension, insulin resistance, glucose intolerance and dyslipidaemia. Additionally, there is an association between OSA and NAFLD.

Circadian misalignment may increase the risk of obesity. As well as the food content, the timing of the food intake is important for gut microbiota and host metabolism. The gut microbiota composition has been reported to associate with sleep disorders such as narcolepsy, insomnia and OSA. In OSA, IH and SF affect the gut microbiota, and result in dysbiosis and health consequences. Both IH and SF due to OSA may also concur altering brain homeostasis and producing cerebral inflammation, cognitive deterioration, neuropsychological disturbances and cerebrovascular dysfunction. There is also increasing evidence that IH causes upregulation of lipid biosynthesis in the liver, an increase in adipose tissue lipolysis and also an inhibition of lipoprotein clearance, mechanisms that may promote dyslipidaemia. Patients with OSA may exhibit higher rates of dyslipidaemia, and the severity of OSA is correlated to the level of dyslipidaemia.

The underlying mechanisms of metabolic dysfunction in OSA require further exploration using animal models and clinical data. Additionally, CPAP is the first-line treatment for OSA, but it is unclear whether CPAP treatment can improve metabolic disorders. Preliminary results of probiotic administration to improve sleep quality in healthy volunteers are promising, but no data are available in patients with OSA. Therefore, further studies are needed.

CONFLICT OF INTEREST

I.A., Ö.K.B., S.V.C., C.L. and T.S. have nothing to disclose.

AUTHOR CONTRIBUTIONS

I.A. wrote the section on OSA and microbiota; Ö.K.B. the sections on Dyslipidaemia and OSA and Conclusions; S.V.C. the sections on Metabolic comorbidities associated with OSA and CB, IH and metabolism; C.L. the section on Cerebral metabolism and OSA; and T.S. the Abstract, the sections on Introduction, Sleep and microbiota,

and Circadian misalignment, obesity and microbiota. All authors critically reviewed and accepted the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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