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REVIEW

Sleep and Metabolic Health

Obstructive sleep apnea and metabolic syndrome

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Abstract

Metabolic syndrome (MS) is a heterogeneous condition associated with increased cardiovascular risk. There is growing evidence from experimental, translational, and clinical investigations that has suggested that obstructive sleep apnea (OSA) is associated with prevalent and incident components of MS and MS itself. The biological plausibility is supportive, primarily related to one of the main features of OSA, namely intermittent hypoxia: increased sympathetic activation with hemodynamic repercussions, increased hepatic glucose output, insulin resistance through adipose tissue inflammation, pancreatic β-cell dysfunction, hyperlipidemia through the worsening of fasting lipid profiles, and the reduced clearance of triglyceride-rich lipoproteins. Although there are multiple related pathways, the clinical evidence relies mainly on cross-sectional data preventing any causality assumptions. The overlapping presence of visceral obesity or other confounders such as medications challenges the ability to understand the independent contribution of OSA on MS. In this review, we revisit the evidence on how OSA/intermittent hypoxia could mediate adverse effects of MS parameters independent of adiposity. Particular attention is devoted to discussing recent evidence from interventional studies. This review describes the research gaps, the challenges in the field, perspectives, and the need for additional high-quality data from interventional studies addressing the impact of not only established but promising therapies for OSA/obesity.

INTRODUCTION

Metabolic syndrome (MS) is a cluster of risk factors that includes increased waist circumference, blood glucose levels, triglycerides, and blood pressure and lower high-density lipoprotein (HDL) cholesterol [1]. It has been estimated that 34.7% of the American population has MS [2]. Despite significant debate questioning the real value of defining MS or focusing only on the individual components, a meta-analysis reported that MS is associated with increased cardiovascular risk [3]. Supporting the potential cardiovascular role of MS, a 2019 cohort showed that MS recovery was associated with 15% fewer cardiovascular events compared with patients who retained the MS diagnosis [4]. Therefore, continuous efforts to identify MS and related comorbidities may pave the way for proposing comprehensive treatments aiming at the reduction of cardiovascular end points.

Among the comorbidities associated with MS, obstructive sleep apnea (OSA) has gained growing interest in the literature. This sleep-disordered breathing is characterized by recurrent episodes of upper airway obstructions leading to increased negative intrathoracic pressure, intermittent hypoxia (IH), and sleep fragmentation [5]. Both the reported prevalence of OSA in patients with MS and the prevalence of MS in patients with OSA are quite high (ranging from 60%-70%) [6–8]. MS is six to nine times more likely to be present in individuals with OSA compared with the general population [9, 10]. MS and OSA share various pathophysiological mechanisms of cardiometabolic complications, highlighting the impact of obesity and related adipose tissue inflammation as the common etiological factor of both conditions [11, 12]. Evidence has shown that adipose tissue inflammation mediated mainly by IH, common to OSA and/or obesity, is the main pathway for the various changes in glucose and lipid

metabolism and, consequently, cardiovascular disease development [12]. In this sense, it would be of great relevance to our understanding of how these complex conditions interact. Is OSA a mere epiphenomenon of obesity/MS, or may OSA amplify the metabolic deregulation observed in these conditions? What would be the best strategy for treating patients with OSA and MS—weight loss strategies only (including diet, exercise, medications, bariatric surgery), OSA treatments (such as continuous positive airway pressure [CPAP]) only, or combined therapies?

In this paper, we provide an updated review on the theme that includes the following: 1) experimental and translational evidence; 2) clinical evidence; 3) evidence from interventional studies; 4) perspectives; and 5) the potential new therapies for obesity, diabetes, and OSA.

Study Importance

What is already known?

- Obstructive sleep apnea (OSA) and its components (highlighting the role of intermittent hypoxia [IH]) seem to exacerbate one or more components of metabolic syndrome (MS); until recently, most of the evidence was based on cross-sectional data.

What does this review add?

- We provide an updated review addressing experimental, translational, and clinical evidence on how OSA/IH could worsen metabolic parameters in MS independent of adiposity. Particular attention is devoted to discussing recent evidence from interventional studies.

How might these results change the direction of research?

- This review supports the potential role of OSA in MS, highlighting the importance of new mechanistic data addressing the complex interactions between adiposity and OSA and the crucial role of IH in triggering impairments on "omics" and microbiota, as well as the relative importance of metabolic derangements in the cardiovascular events mediated by OSA.

EXPERIMENTAL AND TRANSLATIONAL EVIDENCE

IH, a cardinal feature of OSA, seems to be the main OSA component triggering metabolic dysfunction [13]. Evidence from animal models demonstrated that IH promoted sympathetic activation, thereby promoting blood pressure surges, elevating circulating inflammatory products, and increasing the production of reactive oxygen species, important pathways linking OSA/IH with MS [14]. IH promotes hyperlipidemia in both lean and obese animal models through the worsening of fasting lipid profiles (by upregulation of pathways of triglyceride and phospholipid biosynthesis and inhibition of pathways of cholesterol uptake in the liver) and reduced clearance of triglyceride-rich lipoproteins [15–17]. Specifically, IH promotes inhibition of lipoprotein lipase (LpL) in the adipose tissue [17]. LpL is a key enzyme of lipoprotein clearance mediated by hypoxia-inducible factor-1 transcriptionally, activating a lipoprotein lipase inhibitor, angiopoietin-like 4 (Angptl4) [17]. This pathway seems to contribute to the progression of atherosclerosis induced by IH in a murine model [18]. Indeed, Angptl4 depletion using neutralizing antibodies abolished IH-induced decreases in adipose LpL activity and increases in plasma very low-density lipoprotein cholesterol and triglyceride levels, ultimately contributing to reducing the size of atherosclerotic plaques in the model [18]. Translational approaches provided supportive information: 1) In patients with obesity undergoing bariatric surgery, the severity of nocturnal hypoxemia predicted Angptl4 levels in subcutaneous adipose tissue [18]; and 2) injection of a triglyceride-rich chylomicron-like emulsion, labeled with [14C] cholesteryl oleate and [3H] triolein to determine the fractional clearance rate (FCR) of the radiolabeled lipids, revealed a significant delay in both cholesteryl ester FCR and triglyceride FCR in patients with severe OSA compared with age-, body mass index (BMI)-, and waist circumference-matched volunteers without OSA [19]. Moreover, in a subgroup of patients with OSA treated with CPAP for 3 months, triglyceride FCR increased fivefold [19].

Regarding glucose metabolism, IH induces insulin resistance through β-cell dysfunction [20–23] and adipose tissue inflammation [24–26]. In particular, IH induces a proinflammatory phenotype of the visceral adipose tissue (VAT) with polarization of adipose tissue macrophages toward an M1–proinflammatory subtype, upregulation and secretion of numerous proinflammatory adipokines, and subsequent impairment of the insulin-signaling pathway [24]. IH also increases hepatic glucose output [21, 22], worsens glucose metabolism, and induces nonalcoholic fatty liver disease [27]. Increased blood pressure, another feature of MS, is tightly related to IH-induced sympathetic activation [28, 29]. Beyond the direct effects of IH on key tissues related to metabolic dysfunction, a considerable amount of evidence has shown that the sympatho-excitation evoked through the carotid body may contribute to the pathogenesis of MS, inducing systemic hypertension and insulin resistance as well [30–32].

Finally, sleep fragmentation (another feature of OSA) may play a role in the cardiometabolic risk in OSA. Although less consistent than the impact of IH and the degree of hypoxemia [33, 34], the arousals required to terminate obstructive respiratory events in OSA lead to sleep fragmentation that was shown to induce metabolic dysfunction in healthy patients and elevate sympathetic output [35].

EVIDENCE IN HUMANS

Cross-sectional studies

Overall, previous evidence has consistently shown that OSA is associated with higher levels of one or more components of MS, as well as surrogate markers of cardiovascular risk. Coughlin and colleagues conducted one of the first studies to address the association between OSA and MS and its components [9]. The authors observed, from a sample of 104 patients (61 with moderate-to-severe OSA and 43 control patients), that OSA was associated with a significant increase in systolic, diastolic, and mean arterial blood pressure, fasting insulin, and triglyceride concentration; a reduction in HDL cholesterol; and an increase in the cholesterol/HDL cholesterol ratio, after adjusting for obesity. As expected, they observed an increase in the prevalence of MS in these patients with OSA. Drager and colleagues [6] examined the prevalence of unrecognized OSA in 152 consecutive patients with MS. They found a 60.5% prevalence of moderate-to-severe OSA in this population. Furthermore, this larger study showed that OSA was independently associated with biomarkers of metabolic dysfunction and systemic inflammation. Specifically, OSA was independently associated with two MS criteria, i.e., triglycerides and glucose, and with three non-MS cardiovascular risk factors, i.e., cholesterol/HDL cholesterol ratio, uric acid, and C-reactive protein. It is worth mentioning that these associations were not influenced by the excessive daytime sleepiness status. Furthermore, we explored the associations of OSA with surrogate markers of atherosclerosis and arterial stiffness in consecutive patients with MS. Patients with MS with comorbid OSA had an increase of carotid intima-media thickness, carotid-femoral pulse wave velocity, and carotid diameter in comparison with patients with MS without OSA [7]. Of note, almost 20% of patients with MS and OSA had carotid plaques. Again, all of these parameters of vascular impairment observed were similar in patients with MS and OSA with or without excessive daytime sleepiness. These findings underscore that OSA is not only common but, even in the absence of daytime symptoms, might have cardiometabolic health care consequences.

Longitudinal studies

To the best of our knowledge, only one prospective longitudinal study has been conducted to evaluate the incidence of MS in patients with OSA. This investigation combined data from two cohorts: Episono (Brazil) and HypnoLaus (Switzerland) [36]. After a mean follow-up of 6 years, the incidence of MS in patients with moderate-to-severe OSA was 17.2%, representing a 2.5-fold increased risk of developing MS in comparison with the control group (no OSA). A detailed analysis showed that this result was driven by an increase in waist circumference mediated by nocturnal IH (Figure 1) [36].

Conversely, a nationwide Korean population-based study assessed the incidence of OSA, in which 10,113,560 individuals were enrolled in 2009 and followed up until 2018 [37]. The incidence rate of OSA was higher in patients with MS than those without MS (1.16 vs. 0.82, respectively). Patients with MS had a hazard ratio of 1.50 for OSA, which increased as the number of MS criteria increased, even after adjusting for confounders. Among the MS criteria, abdominal obesity (measured using waist circumference) and high triglyceride level showed the strongest correlation with OSA [37].

Taken together, cross-sectional and longitudinal studies provide epidemiological evidence supporting the hypothesis that OSA may contribute to metabolic dysregulation and MS predisposition/progression.

Interventional studies (non-randomized and randomized)

As recommended in all research areas, cause-effect inferences require interventional studies, in this case addressing the effects of OSA treatment in the prevention of MS and in reversing MS (generally defined by patients who demonstrated fewer than three MS criteria at the end of the follow-up). So far, there is no evidence, to our knowledge, that treating patients with OSA may prevent new cases of MS. Available evidence is focused on patients who already have several components of MS (or MS per se); significant heterogeneity of methodologies in terms of design, sample size, follow-up, and adherence to CPAP treatment have been observed among the related studies.

An observational study demonstrated that CPAP treatment for 8 weeks was associated with an improvement in markers of cardiovascular risk in patients with severe OSA and MS. This result was associated with a reduction in blood pressure and total cholesterol levels. Furthermore, it was found that these patients exhibited decreased insulin resistance, tumor necrosis factor α (TNF-α) levels, and oxidative stress markers. However, it is worth noting that these benefits were observed only in the group of patients who showed high adherence to CPAP (≥4 hours of use per night of sleep) and those who used continuous medication [38]. Of note, MS reversibility was not reported in this investigation. In 2013, Hoyos and colleagues [39] evaluated the impact of CPAP treatment for 3 months on MS reversal based on a retrospective analysis of a randomized trial [40]. This study included 65 patients with moderate-to-severe OSA without a previous history of diabetes but who had cardiometabolic comorbidities and were using antihypertensive and lipid-lowering drugs. Of this total number of patients, 52 completed the 3-month follow-up, from which 28 were randomized to the CPAP group, whose treatment adherence was 3.6 hours of sleep per night. From the 18 patients with MS prior to treatment with CPAP, only 3 reversed this condition after 3 months of active intervention. This finding was observed in only one of the fourteen patients randomized to sham CPAP (p = nonsignificant). A further systematic review (not addressing MS itself but cardiometabolic markers), concluded that CPAP treatment does not significantly improve lipid profiles, insulin resistance, inflammatory markers, or the proportion of patients with MS. However, the authors highlight the robust effect of CPAP in reducing sympathetic activity, being considered one of the main mechanisms of blood pressure reduction [41].

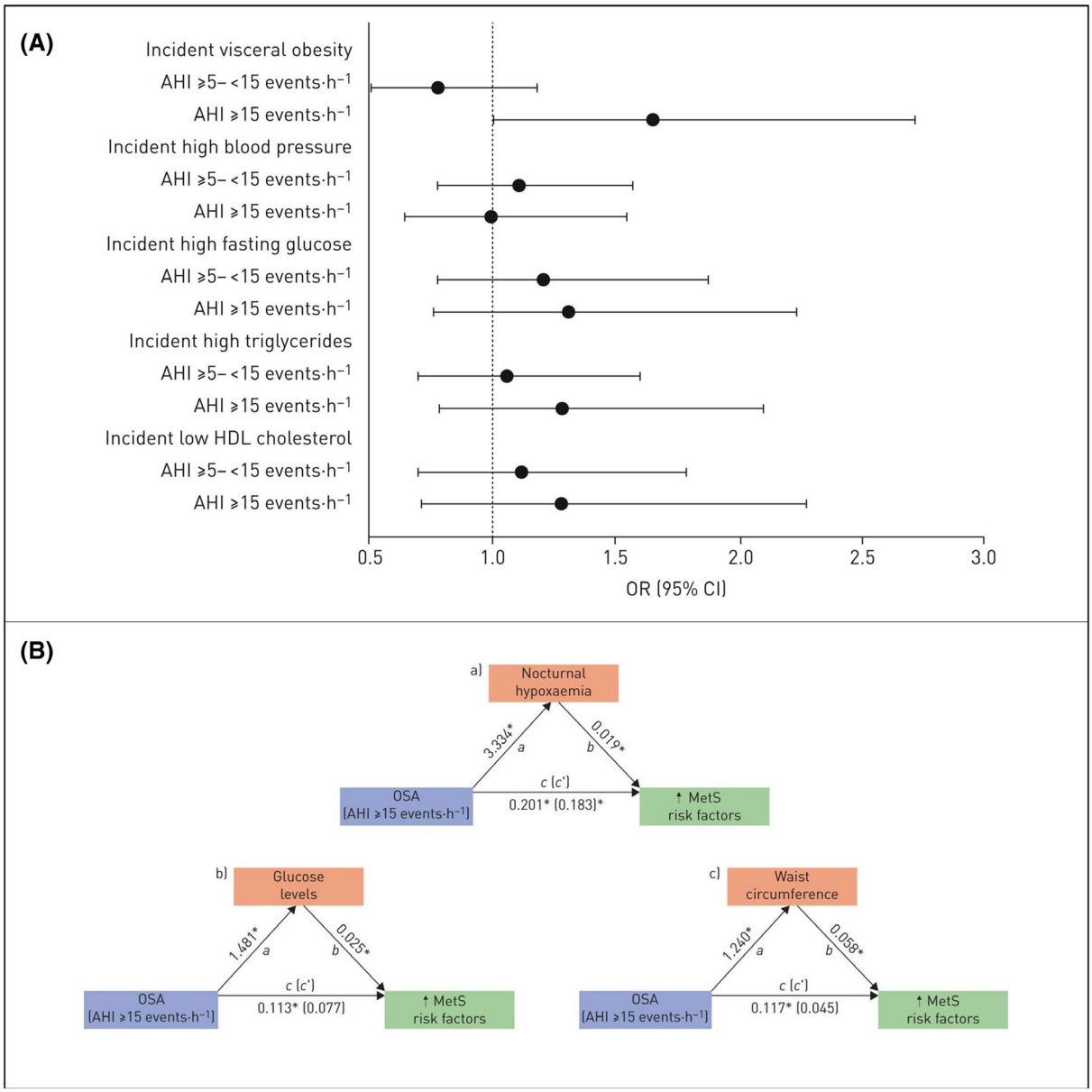

FIGURE 1 Impact of OSA on incident MS. (A) Impact of OSA severity on the incidence of each individual component of MS. (B) OSA and the mediator factors for increasing MS. Reproduced with permission of ©ERS [36]. AHI, apnea-hypopnea index; HDL, high-density lipoprotein; OR, odds ratio; OSA, obstructive sleep apnea; MS and MetS, metabolic syndrome. *p<0.05 [Color figure can be viewed at wileyonlinelibrary.com]

Recently, we conducted a randomized placebo-controlled trial to specifically answer the question of whether OSA treatment with CPAP per se promotes MS reversal. Moreover, we explored the effect of CPAP treatment on each MS criterion, metabolic and inflammatory profiles, abdominal fat, and endothelial function [42]. We recruited patients with moderate-to-severe OSA with a recent diagnosis of MS under no medication, diet, or regular exercise. These patients were randomly assigned to receive therapeutic CPAP or nasal dilator strips (placebo group) for 6 months. After the follow-up period, we observed that CPAP therapy promoted a fivefold increase in the chance of reversing MS compared with placebo (18% vs. 4%; $p = 0.04$). No single MS criterion drove this response for patients whose MS diagnosis was reversed. Moreover, a recent subanalysis from this trial revealed that 6-month CPAP therapy prevented atrial remodeling and increased the chance of diastolic dysfunction reversibility [43]. However, most patients kept the MS diagnosis, possibly explained by the absence of effects on adiposity biomarkers and depots (Figure 2). At first glance, our results indicating that most patients maintained the diagnosis of MS despite good adherence to CPAP [42] may minimize the importance of OSA in this scenario. Of note, the impact of CPAP treatment on the reversal of MS does not seem so modest compared with other single therapies (Table 1). A large, multicenter randomized controlled trial evaluated the effects on MS reversal of two high-fat Mediterranean diets, one supplemented with extra-virgin olive oil and another supplemented with mixed nuts. After a 1-year intervention, the MS reversion rate was 21% in the Mediterranean diet with extra-

virgin olive oil group and 25.3% in the Mediterranean diet with mixed nuts group. This last was significantly different from the control group (low-fat diet) and, consequently, was suggested as a possible strategy for the management of MS [44]. Following 4.8 years, this same cohort was assessed to determine the long-term effects of the Mediterranean diets on MS reversibility. Out of a total of 3392 participants with MS at baseline, the reversion occurred only in 958 (28.2%). Both Mediterranean diets were more effective to revert MS compared with the control diet [45].

Stewart and colleagues [46] conducted a randomized controlled trial that evaluated the impact of exercise training in older people on risk factors associated with MS and whether these are mediated by changes in fitness or body composition. The exercise training was performed three times per week for 6 months and was composed of resistance and aerobic exercise. Following this period, the authors showed that the improvement in risk factors associated with MS was associated with changes in body composition (reductions in total and abdominal fat) and not with changes in fitness. At baseline, 42.3% of participants had MS. At 6 months, nine exercisers (17.7%) and eight controls (15.1%) no longer had MS, whereas four controls (7.6%) and no exercisers developed it. Group differences for the change in MS classification fell just short of statistical significance ($p = 0.06$) [46].

Regarding combined therapy, Jeejeebhoy and colleagues [47], in a prospective, longitudinal, before-after feasibility study, assessed the effects of personalized diet and exercise training for 12 months on MS reversal. At 12 months, 19% of patients showed reversal of MS. This percentage of improvement was achieved within 6 months, remaining stable for up to 1 year.

Strategies that connect mind and body, such as yoga, were also investigated in the context of MS. A randomized controlled, parallel, open-label trial with 182 participants with MS examined the impact of 1 year of yoga exercise on MS status. The change of the number of MS components after the 1-year experimental period was significantly associated with the yoga intervention ($p = 0.026$) but with a nonsignificant increase in the rate of MS remission (44% in the yoga group compared with 35% in the control group, $p = 0.150$) [48]. This result meets previous studies that have shown the favorable effects of yoga exercise on body weight and body composition and, consequently, modification of cardiovascular risk factors [49, 50].

Unlike the observed proportion of patients who reverted MS in the aforementioned studies, a randomized controlled trial with Korean older adults aged ≥60 years showed a 61.9% reversal rate of MS versus 47.6% of the control group in response to a lifestyle modification program based on the transtheoretical model for 6 months [51]. This program involved health counseling, education classes, a self-management handbook, newsletters, and a health diary, and the patients were not taking medication. The authors pointed out that it is possible to incorporate lifestyle changes in elderly patients, although they are known to have behavioral beliefs that are difficult to change [51].

In general, interventions that lead to weight loss are considered the cornerstone for the management of MS. This is due to the fact that weight reduction is probably the starting point for underlying mechanisms that finally result in the improvement of the MS components [52]. In the context of OSA, strategies aimed at weight loss should also be recommended, either together with other therapies or as the sole initial treatment for asymptomatic patients. Weight loss is associated with improved OSA severity, and there is no established threshold for this; major benefits are observed with greater weight loss [53, 54].

PERSPECTIVES AND RESEARCH AGENDA

The evidence summarized in the previous topics provides biological relevance for presuming that OSA is not a mere epiphenomenon of obesity/MS but that it may contribute to adding cardiometabolic risk for these conditions. Figure 3 provides a summary of the potential pathways and the results of CPAP intervention.

Having put these advances in context, there is a significant amount of work for improving our ability to comprehend the real magnitude of OSA and its components in the obesity/MS scenario. We

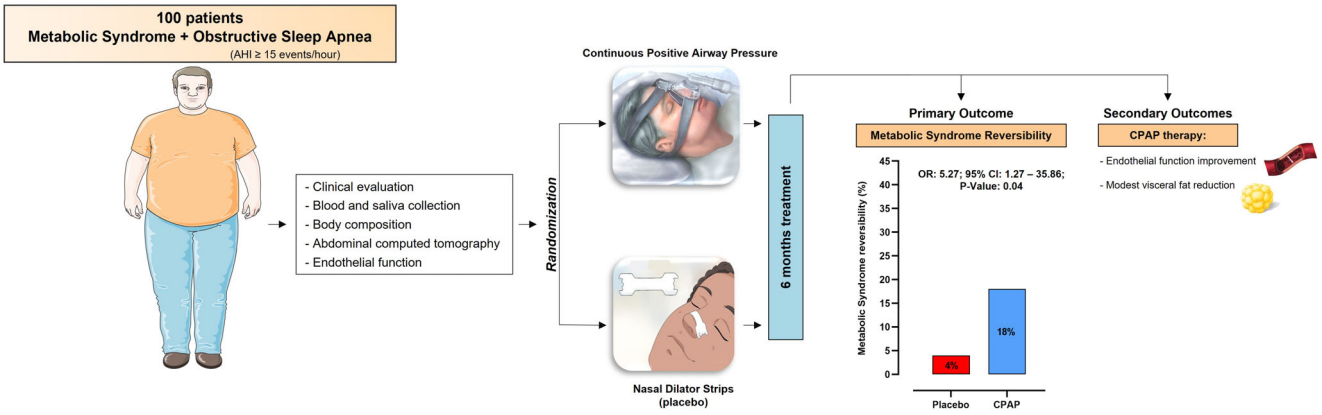

FIGURE 2 Effects of CPAP therapy on metabolic syndrome reversibility in the TREATOSA-MS trial. CPAP, continuous positive airway pressure; TREATOSA-MS, Impact of Obstructive Sleep Apnea Treatment in Patients With Metabolic Syndrome [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Impact of several interventions on MS reversibility

Intervention	First author, year	Studied groups	Follow-up (mo)	Mean age	% Male individuals	Baseline BMI	Design (no RCT/RCT)	Rate of MS reversibility success (%)
Diet	Salas-Salvadó et al., 2008 [44]	MedDiet + VOO	12	67.2 ± 5.9	45.2	29.2 ± 3.1	RCT	21.0
		MedDiet + Nuts		67.2 ± 5.7	50.9	29.3 ± 3.2		25.3
		Control		67.9 ± 6.2	42.6	29.5 ± 3.5		16.4
Exercise	Stewart et al., 2005 [46]	Exercise	6	63.0 (61.5-64.5)	49.0	29.4 (28.3-30.4)	RCT	17.7
		Control		64.1 (62.4-65.8)	49.0	29.7 (28.3-31.0)		15.1
Diet + Exercise	Jeejeeboy et al., 2017 [47]	Diet + Exercise	12	60.3 ± 9.0	48.0	31.7 ± 3.4	No RCT	19.0
Yoga	Siu et al., 2015 [48]	Yoga	12	56.3 ± 8.8	28.5	-	RCT	44
		Control		55.7 ± 9.4	23.4	-		35
Lifestyle modification program	Yoo S et al., 2012 [51]	Transtheoretical model	6	65.68 ± 3.38	40.7	25.87 ± 2.36	RCT	61.9
		Control		65.73 ± 4.07	35.4	26.12 ± 2.36		47.6
CPAP to OSA in MS	Giampá et al., 2022 [42]	CPAP	6	48 ± 9	76	33.1 (29.4-35.7)	RCT	18.0
		Control		49 ± 10	82	32.0 (29.8-35.0)		4.0

Abbreviations: CPAP, continuous positive airway pressure; MS, metabolic syndrome; OSA, obstructive sleep apnea; RCT, randomized controlled trial; VOO, virgin olive oil.

provide some insights in the following sections, covering more recent evidence from preliminary data.

Omics/microbiome

Important efforts have been undertaken to decode the precise molecular mechanisms and pathways by which OSA predisposes cardiometabolic consequences. Metabolomic and microbiome biomarkers have gained notoriety in this setting, which may facilitate early diagnosis and treatment [55].

In the OSA context, urine samples of mice exposed to IH revealed increased levels of lactate and trans-aconitate and decreased levels of pyruvate, citrate, succinate, and acetoacetate, indicating that the predominance of the energy metabolism pathway of these animals was changed to anaerobic metabolism [56]. Thus, oxidative stress resulting from IH may be the major cause of this change because an increase in the levels of oxidation products was observed [56]. Male Wistar rats subjected to chronic sleep fragmentation showed a decrease in metabolites related to excitatory neurotransmitters such as glutamate and aspartate in the hippocampus. In addition, acetylcholine precursors were observed to be below normal levels. Such findings allow us to speculate why sleep fragmentation can impair memory and learning ability [57].

Clinical studies revealed, from the analysis of urine samples from patients with OSA, an increase in most fatty acids and fatty acid-related compounds, which are associated with lipolysis induced by IH. Glycolytic intermediates involved in the production of adenosine triphosphate and branched-chain amino acids associated with mitochondrial dysfunction that act as biomarkers of insulin resistance were also elevated in patients with OSA compared with controls [58]. A pilot metabolomics study pointed to three urinary metabolites that could be used as predictive biomarkers of OSA-induced cardiovascular diseases. Long-chain acylcarnitine (C14:1), biogenic amines of symmetric dimethylarginine, and sphingomyelin (C18:1) are involved in lipid metabolism, nitric oxide metabolism, and association with lipoprotein formation, respectively [59].

One of the studies that used blood-derived biofluids (plasma and serum) to characterize the metabolomic profiles of patients with OSA observed 14 significant metabolic alterations (highlighting those belonging to the porphyrins and glycerophospholipids group) in individuals with more- versus less-severe OSA [60]. The former is related to protection against oxidative stress, whereas the latter could impact the production of inflammatory mediators and platelet aggregation. However, it is worth mentioning that the study has some limitations such as the lack of a control group (no OSA) and adjustments for confounding factors. Another study that evaluated plasma samples from patients with moderate-to-severe OSA without a medical history of diabetes demonstrated the alteration of the expression of six metabolites, four of which are related to glucose and inflammation, compared with an age-, gender-, and fat-composition-matched volunteers without OSA [61]. Overall, disturbances in the metabolism of carbohydrates, fatty acids, and amino acids have been described in patients with OSA

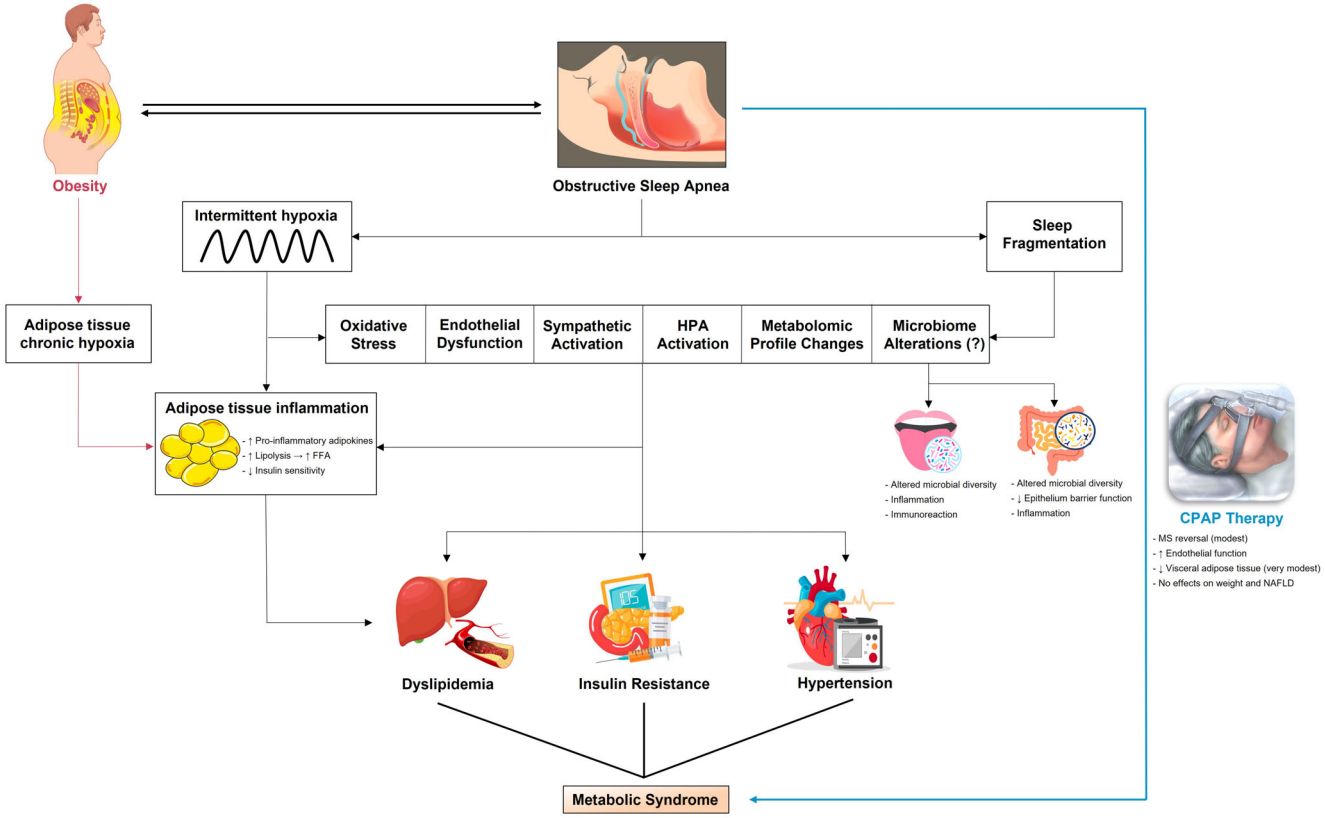

FIGURE 3 Putative mechanisms connecting OSA, obesity, and MS. OSA and obesity exert synergistic effects on MS. The intermittent hypoxia and sleep fragmentation observed in OSA play a pivotal role in MS pathogenesis from activation of the sympathetic nervous system, HPA axis, oxidative stress, endothelial dysfunction, metabolomic profile changes, and alterations in the microbiome (oral and gut). In general, these mechanisms, single or together, impair metabolic homeostasis, leading to adipose tissue inflammation, dyslipidemia, insulin resistance, and hypertension, which configure the criteria that define MS. In parallel, the IH-induced adipose tissue dysfunction is observed in obesity per se. The same seems to apply to OSA. Therefore, if OSA and obesity coexist, it is possible that this negative metabolic response may be exacerbating. The CPAP therapy, in turn, can be considered as a coadjutant therapy for MS reversal in patients with OSA and MS. CPAP, continuous positive airway pressure; FFA, free fatty acid; HPA, hypothalamic-pituitary-adrenal; IH, intermittent hypoxia; MS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; OSA, obstructive sleep apnea [Color figure can be viewed at wileyonlinelibrary.com]

and rodent models [56, 58, 59, 61]. These alterations are related to IH and, consequently, to oxidative stress. Although these studies are innovative and they allow us to reflect on the pathophysiological status of OSA and its association with metabolic dysfunction, it is necessary to be careful in extrapolation from data given the existing methodological limitations. Therefore, more studies are necessary for this research area.

The microbiome represents a complex and dynamic ecosystem that contributes essential functions to its host, playing a key role in health-disease control. Alterations in the gut microbiome (GM) are associated with a variety of immunological and cardiometabolic diseases, but it is still poorly understood how these processes are regulated [62]. The GM acts as a "common player" for OSA and cardiometabolic diseases. In other words, GM changes are related to OSA and, at the same time, they seem to play a critical role in the development of cardiometabolic diseases [63]. Sleep fragmentation per se can also affect GM. Fecal analysis of the microbiota of mice exposed to sleep fragmentation for 4 weeks revealed an increase in members of Lachnospiraceae and *Ruminococcaceae* bacterial families in contrast to a significant decrease in Lactobacillaceae and Bifidobactericeae, which are integrated by many beneficial species. In parallel, high levels of interleukin-6 (IL-6), lipopolysaccharide-binding protein, and neutrophil gelatinase-associated lipocalin were also observed. Collectively, such changes resulted in systemic and visceral white adipose tissue inflammation, in addition to altered insulin sensitivity, possibly mediated by the disruption of the colonic epithelium barrier [64]. Reduced epithelial barrier integrity was shown to be associated with translocation of microbially produced substances into the bloodstream, causing systemic inflammation [65].

IH has also appeared to affect GM. Moreno-Indias and colleagues [66] showed, in mice submitted to a pattern of chronic IH (20 seconds at 5% oxygen and 40 seconds at room air for 6 h/d) for 6 weeks, that oscillations in the partial pressure of oxygen were also observed at various depths within the intestinal lumen. In view of this, there were significant changes in the composition and diversity of the intestinal microbiota, including higher abundance of Firmicutes and a smaller abundance of Bacteroidetes phyla. The Firmicutes/Bacteroidetes

proportion is of paramount importance, as a high proportion may be associated with obesity [67].

Understanding how changes in GM can promote disease states encourages the development of therapeutic approaches aimed at altering the composition and function of the human gut microbiota with the purpose of reversing the disease process of interest. For example, transplantation of lean donor fecal microbiota into male individuals with obesity and MS resulted in improvements in insulin sensitivity [68]. From another perspective, fecal microbiota transplantation from mice subjected to IH for 6 weeks to naive mice provoked insulin resistance (i.e., increases in homeostatic model assessment of insulin resistance) and induced insulin resistance on naive adipocytes through plasma exosomes. Therefore, it was suggested that chronic IH leads to significant changes in an intercellular communication pathway (exosomal pathway) that involves GM and adipose tissue, resulting in metabolic dysfunction [69]. In view of the findings, there is no denying the existence of GM signatures of OSA. However, this signature can be shared with those observed in MS considering the overlap of its risk factors and manifestations [55].

Visceral imaging and inflammation

As described in the earlier sections, VAT inflammation appears to be the cornerstone of cardiometabolic outcomes associated with OSA [12]. Among the anthropometric indices used to assess adipose tissue and, consequently, obesity, BMI and waist circumference stand out. Although the anthropometric parameters are largely incorporated into clinical practice, they are not ideal for capturing local adiposity, including the visceral fat distribution [70]. In view of this limitation, studies using other methodological analyses to evaluate VAT have been carried out. Computed tomography has shown an increase in visceral fat in men with OSA, with and without obesity, even after adjusting for age and BMI [71, 72]. OSA treatment with CPAP for 6 months showed a very small decrease in VAT compared with the placebo group, highlighting no relevant effects of OSA in modulating the amount of VAT but the properties of this adipose tissue [42]. To address this very relevant topic, some studies have focused on evaluating the VAT-specific metabolic or inflammatory activity [25]. The hybrid ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET)/magnetic resonance method can be used for this purpose. ^{18}F-FDG is a glucose analogue radiotracer that accumulates in metabolically active cells, mainly in inflammatory foci. Thus, ^{18}F-FDG is injected into the patient and, subsequently, PET/magnetic resonance imaging is performed, enabling one to assess the volume and metabolic activity of VAT. From this method, it is also possible to identify specific imaging biomarkers to quantify the inflammatory burden in adipose tissue [25, 73]. Kundel and colleagues [25] conducted a pilot study using hybrid ^{18}F-FDG PET/magnetic resonance for volumetric and metabolic assessment of VAT in patients with OSA (respiratory disturbance index ≥ 5 events/h), before and after 3 to 4 months of CPAP treatment. The authors demonstrated a positive association between OSA severity and VAT metabolic activity, which was higher in patients with moderate-to-severe OSA compared with mild OSA, even after adjusting for confounding factors. Interestingly, it was also observed that VAT volume was inversely correlated with CPAP adherence. This last finding contrasts with previous studies that did not observe significant effects in subcutaneous adipose tissue after the use of CPAP [74].

Overall, there is a strong need for more studies to explore new possibilities aimed at elucidating the real role of OSA-adipose tissue interactions and propose specific and useful biomarkers to stratify risk and predict susceptible patients to improve cardiometabolic profiles with OSA treatment.

Ongoing trials

Like GM, the oropharyngeal microbiome has gained notoriety in the OSA setting [75–77]. The dramatic reduction in the airflow due to airway pressure changes affects the moisture and oxygen content in the upper respiratory tract, which could explain the oropharyngeal flora disorder observed in patients with moderate-to-severe OSA [75]. Concurrently, oral bacteria seem to be involved in the cardiovascular disease pathogenesis [78].

In patients with OSA and hypertension, alterations in the oral microbiota were observed, especially for the *Aggregatibacter* and *Porphyromonas* genera, accompanied by high levels of proinflammatory cytokines, which could affect the probability of cardiovascular events through inflammatory mediators [76]. Therefore, it is speculated that oral microbiota changes in patients with OSA are accompanied by immune, inflammatory, and oxidative stress responses. CPAP treatment, in turn, seems to have a positive impact on the oral microbiome. A pilot study subjected patients with severe OSA to overnight CPAP therapy and observed a reduction in *Gemella* and an increase in *Staphylococcus* genera [77]. The *Gemella* genus appears to be an important factor for the development of hypertension because of its role in atherosclerotic plaque formation [79]. *Staphylococcus* improves endothelial cells and reduce blood pressure from the production of nitric oxide via the NO_3-NO_2-NO pathway [77, 80]. Although these studies are preliminary, they already demonstrated oral microbiota signatures of OSA, showing new possibilities for diagnosis and treatment.

In addition to innovative microbiome-related studies, large randomized controlled trials are being conducted to fill existing gaps related to the impact of CPAP treatment on metabolic health. Among these studies, the Hyperglycemic Profiles in Obstructive Sleep Apnea (HYPNOS) randomized clinical trial stands out, the aim of which is to verify whether positive airway pressure (PAP) therapy in patients with OSA and type 2 diabetes for 3 months improves glycemic measures and glycemic control. In parallel, the objective and subjective analysis of sleep will also be carried out through actigraphy and questionnaires, respectively. Secondary outcomes include anthropometric measurements, blood, and urine collection; 24-hour blood pressure monitoring; and endothelial function. The expected outcome from this study is to provide a more relevant clinical contribution to the effects of CPAP therapy on glucose metabolism to be considered in the therapeutic arsenal for type 2 diabetes [81].

TABLE 2 Summary of the trials designed to evaluate potential new therapies for obesity, diabetes, and OSA

Registration/trial name	Sample size/ follow-up	Comparator	Primary end point
ISRCTN16250774. EUDRACT No. 2014–000988-41. UTN U1111-1139-0677/ROMANCE trial	132/26 weeks	Four arms: Liraglutide (1.8 mg once per day) alone Liraglutide 1.8 mg once per day with CPAP CPAP alone (conventional care) No treatment (control)	Change in AHI
NCT04186494/not available	30/28 days	Three arms: Liraglutide (0.6 mg increments to 3.0 mg) Standard CPAP Liraglutide + CPAP	Improvement in insulin resistance defined by HOMA-IR
NCT05412004/SURMOUNT-OSA	412/52 weeks	Tirzepatide versus placebo (independent analysis for patients with and without CPAP)	Percent change from baseline in AHI

Abbreviations: AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; HOMA-IR, homeostatic model assessment of insulin resistance; OSA, obstructive sleep apnea.

Potential new therapies for obesity, diabetes, and OSA

It is well known that mechanical (CPAP) and/or lifestyle-based metabolic interventions such as diet and/or weight loss provide numerous benefits in the OSA-MS scenario. However, the long-term adherence to multiple interventions may not be ideal. Considering this, new studies have been addressed to search for new therapies for the metabolic dysfunction associated with OSA (Table 2).

Recently, Sprung and colleagues [82] published the study protocol titled Randomised, cOntrolled Multicentre trial of 26 weeks subcutaneous liraglutide (a glucagon-like peptide-1 receptor Agonist), with or without contiNuous positive airway pressure (CPAP), in patients with type 2 diabetes mellitus (T2DM) and obstructive sleep apnoEa (OSA) (ROMANCE), designed to assess the impact of liraglutide, either as a stand-alone treatment or as an adjunct to CPAP. Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist used to reduce glycemic values as well as treat obesity. Thus, the primary outcome of the study is to verify the change in apnea-hypopnea index (AHI), whereas the secondary outcomes include the assessment of the change in glycated hemoglobin, weight loss, daytime sleepiness, and quality of life. Other measures such as physical activity analysis, distribution of fat volume and skeletal mass, cardiac function, arterial function, and structure constitute the exploratory outcomes. The results of this study may provide promising information on the impact of pharmacological treatment in this setting, helping to determine new practices for the comprehensive care of patients with OSA and metabolic dysfunction.

Assuming the same rationale as aforementioned, another randomized trial under recruitment (ClinicalTrials.gov NCT04186494) with an exploratory proof-of-concept feature is evaluating the effect of liraglutide-based weight loss versus CPAP treatment or a combination of both for 6 months on the improvement of insulin resistance characterized by homeostatic model assessment of insulin resistance. As secondary outcomes, body weight, glucose intolerance, OSA severity, changes in 24-hour blood pressure, endothelial function, coronary artery calcification, and vascular inflammation are planned. Another pharmacological treatment has been investigated in the setting of OSA and metabolic dysfunction. Tirzepatide is an agonist receptor at both glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 [83]. The combined effects of GIP and GLP-1 potentiate weight loss independent of insulin sensitivity and lipid metabolism. In view of this, a randomized, double-blind, placebo-controlled trial is being conducted (Obstructive Sleep Apnea Master Protocol GPIF: A Study of Tirzepatide (LY3298176) in Participants With Obstructive Sleep Apnea [SURMOUNT-OSA]; ClinicalTrials.gov NCT05412004), which aims to investigate the efficacy and safety of tirzepatide in patients with OSA and obesity who refuse or cannot use PAP therapy or those who are on PAP therapy. The primary outcome is characterized by the percent change in AHI. The secondary outcomes include the percentage of participants who reduced AHI, the comparison of Functional Outcomes of Sleep Questionnaire (FOSQ) score, and change in body weight, systolic blood pressure, C-reactive protein, and sleep apnea-specific hypoxic load.

In conclusion, OSA is a potential modifiable risk factor for MS. This comprehensive review provides a current update summarizing basic, translational, and clinical evidence. Despite significant advances in this important research area, future investigations will face significant challenges to address pathways, potential biomarkers of risk, and susceptible patients to the cardiometabolic impact of OSA [84].O

AUTHOR CONTRIBUTIONS

Sara Q.C. Giampá and Luciano F. Drager wrote the first draft; and Geraldo Lorenzi-Filho made critical review and significant contribution. All authors revised the manuscript.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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