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REVIEW ARTICLE

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The relationship between obstructive sleep apnea syndrome and obesity: A new perspective on the pathogenesis in terms of organ crosstalk

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Abstract

Introduction: Obstructive sleep apnea syndrome (OSAS) is a common disorder that has a major impact on public health. The connection between OSAS and obesity is very complex and likely represents an interaction between biological and lifestyle factors. Oxidative stress, inflammation and metabolic dysregulation are both actors involved in the pathogenesis of OSAS and obesity. Also, the current evidence suggests that gut microbiota plays a significant role in the emergence and progression of some metabolic disorders. When the relationship between OSAS and obesity is evaluated extensively, it is understood that they show mutual causality with each other, and that metabolic challenges such as impaired microbiota affect this bidirectional organ interaction, and by ensuing organ injury.

Objectives: The aim of this study is to investigate the association between OSAS and obesity, and the effect of "organ crosstalk" on the pathogenesis of the relationship and to contribute to the diagnosis and treatment options in the light of current data.

Data Source: We performed an electronic database search including PubMed, EMBASE and Web of Science. We used the following search terms: OSAS, obesity, inflammation, metabolic dysregulation and gut microbiota.

Conclusion: Obesity and OSAS adversely affect many organs and systems. Besides the factors affecting the diagnosis of the OSAS-obesity relationship, mutual organ interactions among the respiratory system, adipose tissue and intestines should not be ignored for prevention and treatment of OSAS and obesity. Comprehensive clinical trials addressing the efficacy and efficiency of current or potential treatments on therapeutic applications in the OSAS-obesity relationship are needed.

KEYWORDS

gut microbiota, inflammation, metabolic dysregulation, obesity, obstructive sleep apnoea, organ cross-talk

1 | INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is caused by upper airway collapse during sleep. These episodes are associated with recurrent oxyhemoglobin desaturations and arousals, which lead to disruption of the sleep pattern and cognitive deterioration.[1] They are known to be some risk factors for OSAS development, including obesity, hypertension, diabetes, male sex, tobacco and alcohol consumption, chronic nasal congestion and asthma. While recent studies show that around half

the people with OSAS are obese, there is prevalence of sleep apnoea in approximately 40% of the moderately overweight (male and female) population. Also, it is estimated that in severe obesity, the prevalence of sleep apnoea was estimated to vary between 40% and 90%.[2,3] By the way, it should be noted that the prevalence of OSAS varies significantly based on the population being studied and how OSAS is defined (eg, apnoea -hypopnea index threshold, scoring criteria used and testing methodology).[4] Polysomnography is the reference method for the diagnosis of OSAS, but conventional measures of OSAS severity, such as the apnoea -hypopnea index, may not be correlated well with the severity of clinical symptoms.[3,4] Various conditions closely related to obesity, such as oxidative stress, systemic inflammation, visceral fat accumulation, dyslipidemia and insulin resistance (IR) may also occur as OSAS-associated manifestations.[5,6] Data from epidemiological studies and randomized clinical trials strongly suggest that OSAS is a common and treatable risk factor for the development of hypertension, heart failure and stroke, especially in men.[7] According to several reports, OSAS and obesity are not only important risk factors for metabolic disorder but also can act synergistically.[4,6] Moreover, in recent years, the gut microbiota has emerged as one of the key factors regulating early events triggering inflammation associated with obesity and metabolic dysfunction.[6,7] Also, some metabolic disorders such as obesity and IR with microbiota composition of the host are thought to be associated. In recent studies, it is accepted that gut microbiota plays a causal role in human metabolism and in the development of metabolic disorders such as obesity and OSAS-induced hypertension.[8,9] Therefore, it is suggested that Firmicutes/Bacteroidetes ratio and as well as the production of LPS decrease with different treatment methods.[10] On the other hand, structural and functional dysfunctions in target or other end organs due to pathological changes and circulating metabolites in a damaged organ are defined as "organ crosstalk", and there are increasing publications on this subject (Figure 1). For instance, many researchers work on understanding of the mechanisms of organ crosstalk in diseases such as obesity, and nonalcoholic fatty liver disease (NAFLD).[11,12] In addition to obesity, adipose tissue, liver and intestines have been suggested to play essential roles in organ interactions related to mechanisms involved in the pathogenesis of OSAS. Therefore, this review aims to explore the relationship between obesity and OSAS, describe the complex, interleaved vicious cycles that connect the two diseases, and reveal the secret and potential effects of organ crosstalk.

2 | THE INTERACTIONS BETWEEN OSAS AND OBESITY

In the last quarter of the century, besides research on OSAS-obesity interaction and pathophysiology, several review studies are also being published.[5] Although obesity is the main

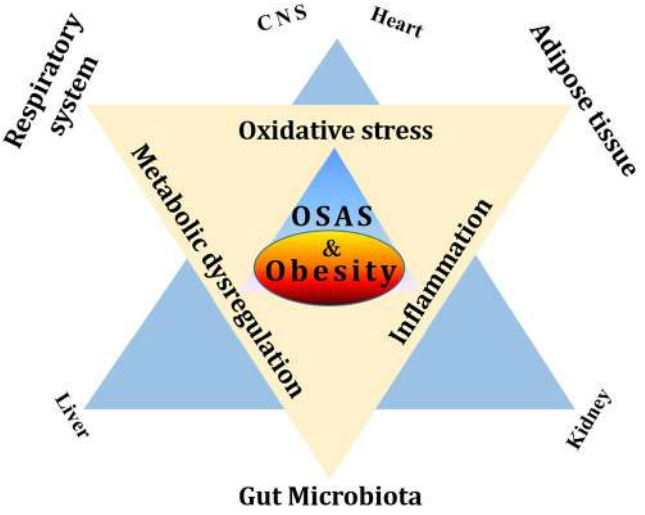

FIGURE 1 Simple presentation of primary or secondary organs and systems that play an important role in the pathogenesis of the relationship OSAS and obesity. (CNS, central nervous system)

risk factor for the development of OSAS, some authors have suggested that OSAS can cause weight gain and therefore, obesity.[13,14] There are different causal factors including reduced physical activity, IR and increased ghrelin levels in this process.[15] Likewise, obesity can result in upper airway collapsibility by increasing fat deposit in upper airway lumen and muscles, thus leading to susceptibility to OSAS.[14] Javaheri et al[16] claim that there are many potential mechanistic factors, including increased sympathetic nerve activity, vascular endothelial dysfunction, intermittent hypoxia, inflammation, oxidative stress and metabolic dysregulation in linking obesity with OSAS as well as the upper airway dysfunction and respiratory control instability. Not all individuals with OSAS are overweight, but the majority of OSAS patients are obese. Moreover, both obesity and OSAS are associated with similar adverse cardiovascular, metabolic and neurocognitive outcomes.

Although not all individuals with OSAS are overweight, the vast majority of patients with OSAS are obese. Moreover, both obesity and OSAS are associated with similar adverse cardiovascular, metabolic and neurocognitive outcomes. Many reports have concluded that sleep deprivation, OSAS and obesity may be interrelated, and both conditions increase the severity and effects of the other.[14,17] apnoea -mediated nocturnal intermittent hypoxia, increased sympathetic tonus, OS, inflammation and endothelial dysfunction are among the pathophysiological mechanisms for OSAS-Obesity relationship. Increased BMI and increased weight-related metabolic syndrome have been reported in obese OSAS patients compared to obese individuals without sleep apnoea.[18] Additionally, the evidence suggests that the association of OSAS and obesity promotes weight gain, obesity and, type 2 diabetes in a variety of ways creating multiple complex vicious cycles.[14,19] The complex pathophysiologic interrelationships

between obesity and OSAS often defy clear assignment of cause and effect. However, we know more clearly that OSAS contributes to weight gain and obesity in various ways, or vice versa. Therefore, approaching the relationship between OSAS and obesity in terms of the effect of mutual organ interaction on the pathogenesis of OSAS and obesity will help elucidate this complex relationship.[19]

3 | THE ROLE OF THE LUNG IN THE ORGAN CROSSTALK

Emerging clinical and experimental evidence supports the hypothesis of multidirectional organ crosstalk between lungs and distal organs. The lung influenced by the environment is a highly immunologic organ, representing a gateway to out of the body. The lungs have critical pathophysiological connections with the heart and kidneys, especially in the cases of failure of these organs.[20,21] Also, there is increasing evidence that acute lung injury (ALI) directly contributes to organ dysfunction in the brain, liver, kidney, heart and other organs, especially in critically ill patients.[22] Rutten et al[23] proposed that the increased metabolic demands that are associated with the physical activities of patients with chronic obstructive pulmonary disease (COPD) result in a reduction in the intestinal perfusion causing ischemia in these tissues. In patients with ALI, oxygen supply also decreases due to renal hypoxia. Moreover, ALI not only can cause renal injury, but also worsen COPD and OSAS.[24] Recurrent obstructive apnoeas expose both the heart and the coronary vessels to the cascade of harmful stimuli and lead to initiate progression of the cardiovascular disorder over time.[7] Of course, the bidirectional interaction of the lungs with other organs (heart, liver or kidneys) cannot be ignored in terms of OSAS-related samples such as hypertension and heart failure. Since metabolic dysfunction and inflammation are common components of the three also interactions, lung-adipose tissue, gut-lung and adipose tissue-gut interactions are particularly discussed in this review article (Figure 2).

3.1 | Lung-Adipose tissue interaction and Lung-the other remote organ crosstalks

In general, excess fat in the body accumulates in three different areas: subcutaneous, internal organs (abdominal cavity) and ectopic fat (heart and pharyngeal pads). Especially pharyngeal pad is associated with OSAS, and these patients have very low sleep quality and high risk of cardiovascular disease.[25] Obesity is a strong risk factor for OSAS, a disease characterized by periodic upper airway occlusion during sleep. In obese patients, changing respiratory physiology partly explains the increase in the frequency of OSAS in obesity.[5] In addition to anatomical and physiological changes affecting the face, neck, pharynx, chest wall and lungs in obese patients, it is also observed that excessive visceral fat increases the abdominal pressure.[26] Obesity manifests as increased abdominal adiposity and low-grade inflammation, which can be accompanied by a range of health problems, including IR, type 2 diabetes, dyslipidemia, NAFLD and cardiovascular diseases.[27,28] The majority of patients with obesity have an impaired adipose tissue function which leads

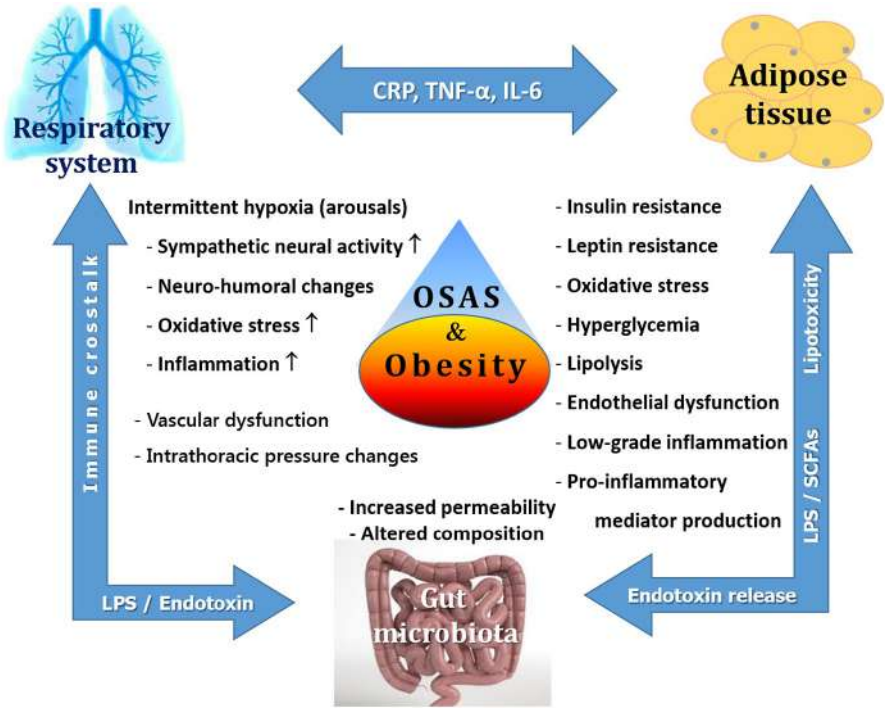

FIGURE 2 The "cross-talk" among respiratory system, adipose tissue and intestine and mechanistic actors and mediators associated with main mechanistic component in the pathogenesis of the relationship OSAS and obesity. (LPS, lipopolysaccharides; SCFAs, short-chain fatty acids)

to adipocyte hypertrophy, hypoxia, a variety of stresses and inflammatory processes within adipose tissue.[29] Also, many of the inflammatory pathways releaved to be activated by intermittent hypoxia in OSAS are activated in adipose tissue.[11] Visceral obesity emerged as a consequence of adipose tissue dysfunction, which is further characterized by changes in the cellular composition, increased lipid storage and impaired insulin sensitivity in adipocytes as well as increased secretion of proinflammatory cytokines.[27,29]

As it is known, metabolic homeostasis emerges from the complex, multidirectional crosstalk between key metabolic tissues, including liver, adipose tissues and skeletal muscle.[11] OSAS-associated intermittent hypoxia interacts with systemic inflammation, while at the same time modifying white adipose tissue inflammatory cytokine production. In the liver, although CRP is mainly synthesized under the control of IL-6, hepatic CRP mRNA expression is also stimulated by IL-1 and TNF-α.[11,30] Similarly, it is claimed that intermittent hypoxia induces activation of endothelial NF-κB and leads to irregular adipokine production by activating NF-κB in the adipose tissue.[30] On the other hand, most of the pathological signalling functions originate from or are associated with the communication between organs. For instance, changes in the alveolar-capillary barrier can induce oxidative stress in the pulmonary microcirculation as well as in the inflammatory cascade. Both changes in the barrier and oxidative stress predisposes alveolar wall injury and leads to progressive lung damage cycles.[20] Also, many circulating factors after kidney and liver ischemia-reperfusion injury play a role in the pathogenesis of pulmonary inflammation.[31,32]

3.2 | The lung-gut axis

The gut microbial community has several enzymatic functions to assimilate various dietary nutrients leading to the release of metabolites having multiple functions in the host.[33] Dysbiosis in gut microbiota is associated with lung disorders and respiratory tract infections.[21] It has been suggested that the bacterial fragments and metabolites can modulate the immune response in the lung and gut along the bidirectional gut-lung axis.[31] Recent studies findings support that the lungs and gut are intricately linked organs that influence each others' homeostasis.[33,34] Furthermore, human intestinal microbiota plays a role in the development of both obesity and obesity-related complications such as NAFLD and OSAS.[12,35] Since both the lung and the intestines are part of the mucosal immune system, an inflammatory response in one of these organs causes the other to be affected.[36] OSAS, characterized by intermittent hypoxia and sleep fragmentation, has effects on gut microbiota and it is suggested that such changes lead to the emergence of systemic inflammatory processes that promote cardiovascular and metabolic morbidities.[35] Several clinical studies suggest that OSAS alters the gut epithelial barrier, which can lead to inflammation and metabolic dysfunction.[37,38] According to Nobili et al, OSAS may promote liver damage by both weakening intestinal barrier function and promoting endotoxemia and sensitizing the liver to endotoxin and proinflammatory stimuli.[39] So, these pathways may mediate OSAS-associated liver injury in NAFLD.

Intestinal changes accompanied by microbial composition and function change and changes in respiratory immune responses have also been associated with the development of lung diseases such as asthma and COPD.[33] Increased evidence suggests an intimate relationship between the intestinal tract and the respiratory tract, while increased intestinal permeability and systemic endotoxemia are claimed to mediate mechanisms that serve the association of dietary fat content, microbiota and obesity.[40,41] Also, the evidence is now emerging that gut dysbiosis plays a causal role in the development of OSAS-induced hypertension.[9] OSAS often does not exist alone, people with apnoea usually suffer from some other organ system diseases such as obesity, or diabetes. As OSAS and obesity are associated with low-grade inflammation and altered composition of the gut microbiota, a bacterial compound might act as a triggering factor in the development of obesity, OSAS and inflammation induced by a high-fat diet.[9,42]

4 | The RELATIONSHIP AMONG OBESITY, OSAS AND GUT MICROBIOTA

Many studies confirm that pharyngeal fat deposits in the upper airway cause respiratory distress during sleep, leading to OSAS in obese individuals. It is also known that the risk of metabolic syndrome is higher in both obesity and OSAS patients.[43,44] Overall, there is a strong link between high fat-induced alterations in gut microbiota, an increase in harmful gut bacteria, local and low-grade systemic inflammation observed in obesity.[45] Gut microbiota has emerged as one of the key factors regulating early events triggering inflammation associated with obesity and metabolic dysfunction (Figure 2). This effect seems to be related to diet- and obesity-associated changes in gut microbiota composition, and to increased variation of immunogenic bacterial products, which activate innate and adaptive immunity in the gut and beyond, contributing to an increase in inflammatory tone. Innate immune receptors, like Toll-like receptors, are known to be up-regulated in the tissue affected by most inflammatory disorders and activated by both specific microbial components and dietary lipids.[46] Indeed, most OSAS patients are obese, and in approximately half of the patients, metabolic syndrome is concurrently present.[47] The intestinal microbiota changes, caused by episodic exchanges in blood oxygen

content may also be due to the association of microbiota-modulated metabolic alterations (obesity and metabolic syndrome) with OSAS.[48,49] Interestingly, newly available data also support the notion that OSAS per se may feed back into mechanisms resulting in the development or reinforcement of obesity.[50] However, sleep deprivation can cause impairment of the gut barrier function. A few days of sleep deprivation in rats resulted in translocation of gut bacteria and septicemia, culminating in fatal bloodstream infection.[51] Also, it is reported that fragmented sleep activated neutrophils and caused their migration to the visceral organs in rats.[52] It is assumed that the gut microbiota is actively communicating with the host and extraintestinal organs like that in the inter-organ interaction. Therefore, the gut microbiota has been associated with many diseases, including obesity and inflammatory diseases.[53] Additionally, the gut microbiota is an attractive suspect for involvement in the metabolic and inflammatory complications of disordered sleep because altered gut microbiota has been convincingly associated with obesity, metabolic syndrome and intestinal inflammation.[54,55]

5 | THE KNOWN BASIC ACTORS OF ORGAN INTERACTIONS IN THE PATHOGENESIS OF OSAS AND OBESITY

Obstructive sleep apnoea adversely affects multiple organs and systems, and several conditions associated with OSAS, such as IR, hypertension, systemic inflammation, visceral fat deposition and dyslipidemia, are also present in other conditions closely related to OSAS, such as obesity and reduced sleep duration. These close interactions between obesity and OSAS share the common pathophysiologic feature of metabolic dysregulation.[5]

5.1 | Oxidative stress

There is widespread consensus that OSAS is an oxidative stress disorder. Similarly, oxidative stress plays an important role in the development, progression and complications of obesity.[56,57] Because of the important role of oxidative stress and hypoxia in the pathophysiology of obesity, attention has been shifted to possible interactions with OSAS, particularly the activation of mechanisms common to both diseases.[6] Apnoea produces a decline in oxygen levels, followed by reoxygenation when breathing resumes. The cyclical episodes of hypoxia-reoxygenation, analogous to cardiac ischemia/reoxygenation injury cause ATP depletion and xanthine oxidase activation, and increase the generation of oxygen-derived free radicals.[58] Intermittent hypoxemia causes anoxia and reoxygenation in OSAS patients, which contributes to the production of oxygen radicals and elicits local and systemic inflammation.[59] Moreover, it is known that increased oxidative stress and inflammation in obesity also enhance OSAS processes (Table 1).[60] Although adipose tissue is considered an independent factor for the generation of systemic oxidative stress, there are several mechanisms by which obesity produces oxidative stress, such as mitochondrial and peroxisomal oxidation of fatty acids, and overconsumption of oxygen in the mitochondrial respiratory chain.[61]

TABLE 1 The known basic mechanistic actors of organ interactions in the pathogenesis of the relationship of OSAS and obesity. The interactions between OSAS-obesity or OSAS-the other metabolic dysfunctions both involve similar signalling pathways and sharing of changes in the pathological process

Related component	Known indicators and evidences
Oxidative stress	Increase of hydrogen peroxide levels; excessive NADPH oxidase activity; enhanced release of superoxide from leukocytes; increased oxidation of lipids, proteins and DNA; changes of antioxidant defence system; reduced blood antioxidant capacity; increased expression of eNOS; reduced bioavailability of nitric oxide; lipid peroxidation (TBARS ↑); exhaled 8-isoprostane ↑; urinary 8-OhdG ↑
Inflammation	Local and/or systemic inflammatory responses; activation of inflammatory cells; activation of NF-κB; increased expression of TNF-α; enhanced production of inflammatory cytokines (IL-1β, -6 and -8); increased in proinflammatory vascular mediators; elevated inflammatory biomarkers (CRP/hsCRP, fibrinogen, pentraxin-3); the other cytokines involved in the inflammatory process (leptin and other adipocytokines)
Metabolic disease or dysfunction	Some mechanistic pathways associated with these metabolic dysregulation or disorders
Metabolic syndrome, insulin resistance, type 2 diabetes, hyperlipidemia, hypertension, endothelial dysfunction, atherosclerosis, increased cardio-metabolic risk	Local or systemic inflammation; increased oxidative strees; central adiposity; hypoxemia; sleep apnoea or sleep deficiency; decreased β-cell function; abnormal glucose metabolism; increased fat deposition; chronic low-grade inflammation; hepatic insulin resistance; fatty liver; changes in gut microbiota; signals from the gut microbiota to distant organs; increased sympathetic activity; low baroreceptor sensitivity; neurohormonal changes; adipokines (leptin) dysregulation; macrophage infiltration in adipose tissue;altered lipid metabolism; atherogenic dyslipidemia; vascular dysfunction, impaired cardiovascular variability

The fat accumulation increases Nox activity and ER stress in adipocytes lead to increased ROS production. Additionally, abnormal postprandial ROS production, hyperleptinemia, chronic inflammation, tissue dysfunction and low antioxidant defence are other factors contributing to oxidative stress in obesity.[62]

5.2 | Inflammation

Many local and circulating inflammatory biomarkers are also elevated in obesity, and disentangling obesity from OSAS-related effects is a challenge, especially given the high correlation between the apnoea -hypopnea index and body mass index. Obesity may magnify the effects of OSAS because macrophages in fat are likely the target cells for the effects of chronic intermittent hypoxia, leading to increases in inflammatory biomarkers; thus, OSAS and obesity may have synergistic effects.[16] Obese patients affected by OSAS display neutrophilic airway inflammation. In a previous study results, it is suggested that airway inflammation may be the consequence of the mechanical stress on the mucosa because of the intermittent obstruction of the upper airways typical of the OSAS.[63] It is widely accepted that the role of OSAS in the progression of endothelial damage is mediated by inflammation. Indeed both obesity and OSAS are associated with vascular endothelial inflammaition, and increased risk for cardiovascular diseases. However, OSAS is thought to be responsible for vascular endothelial dysfunction, inflammation and increased oxidative stress in obese patients (Table 1).[64]

In a study, it has been suggested that NF-κB appears to play a key role in mediating the inflammatory and cardiovascular consequences of OSAS, and may regulate inflammatory signalling in the adipose tissue of OSAS patients.[31] In addition to factors such as genetic, environmental and lifestyle, it is assumed that interactions between OSAS and obesity cause systemic inflammation by activating pathophysiological pathways at increased levels of TNF-α and IL-6. According to a meta-analysis study, it is noteworthy, that in 27 of the 37 studies published so far adult patients with OSAS, showed higher circulating TNF-α levels than the controls did.[65] The association between OSAS and obesity is known to cause intermittent hypoxia and sleep fragmentation.[5,14] In this togetherness process, disruption of both OS and microbiota leads to increased gut permeability through activation of cellular immune pathways and consequently to increased inflammatory mediators such as TNF-α and IL-6.

5.3 | Metabolic dysregulation

OSAS and obesity are important risk factors for metabolic dysregulation and they may act synergistically. In previous years, it has been noted that OSAS and obesity share similar pathophysiologic mechanisms, potentially leading to cardiovascular disorders.[16,17] OSAS adversely affects multiple organs and systems, with particular relevance to cardiovascular disease. Several cardiometabolic alterations have been associated with OSAS, independently of obesity and other potential confounders.[5] Among the most important are glucose intolerance and IR, which are risk factors for the development of diabetes and cardiovascular disease.[66] IR, liver dysfunction and atherogenic dyslipidemia, which are common metabolic disorders associated with OSAS, are important pathogenic factors in both obesity and OSAS (Figures 1, 2, and Table 1).[6] The relationship between metabolic disorders and OSAS is multidirectional. Moreover, OSAS alters glucose metabolism, promotes IR, and is associated with development of metabolic syndrome, type 2 diabetes and NAFLD.[67] OSAS or sleep deprivation would elevate the risk of developing IR, while diabetes would worsen the quality of sleep.[15] Pamidi and Tasali suggested that there is a mutual causal relationship between OSAS and type 2 diabetes, and particularly visceral adiposity was claimed to be a preparative and confounding factor in this interaction.[68] In a more recent study highlighting the interconnectedness and pathophysiology of OSAS and diabetes, it has also been emphasized that OSAS may increase the risk of complications related to diabetes.[69]

On the other hand, leptin, a peptide hormone produced primarily in white adipose tissue, regulates energy homeostasis, metabolism, inflammation and sympathetic nerve activity. Many human studies using single leptin measurements have shown that blood leptin levels increase in patients with OSAS as compared to the controls.[70] In a study on whether blood and leptin levels are correlated with the severity of sleep apnoea, Öztürk et al[71] reported a positive correlation between plasma leptin levels and OSAS severity regardless of age and BMI. Also, leptin plays an important role in both obesity-induced oxidative stress and inflammation as multiple regulatory mechanisms. It is suggested that OS and hyperleptinemia play an important role in the pathogenesis of OSAS, intermittent hypoxia-related cardiovascular and metabolic disorders and may increase mortality in OSAS and obesity.[72] In recent studies, researchers have provided convincing evidence that insufficient sleep is a risk factor for obesity, IR and type 2 diabetes.[73,74] Since the repair of damaged tissues and organs occurs during sleep, the risk of diabetes, hypertension, heart and kidney diseases increases in case of sleep deficiency.[73] This increased risk of end-organ diseases is another evidence of inter-organ interaction in the association of OSAS and obesity. It is known that sleep apnoea results in sleep fragmentation and intermittent hypoxia, which lead to and exacerbate obesity and type 2 diabetes by increasing sympathetic activity, oxidative stress, inflammation and lipolysis.[72,73] Consequently, obesity and OSAS appear to contribute to the initiation and progression of each

other, possibly through their shared effects on the recruitment and potentiation of inflammatory pathways.[75]

Previous studies have shown that the alterations of gut microbiota, and its metabolic products regarded as key players in the pathogenesis of many diseases.[76,77] It has been realized that impaired gut microbiota not only contributes to metabolic diseases, including obesity, diabetes and IR but also is inextricably linked to cardiovascular diseases and even central nervous system.[77] Interestingly, some authors suggest that altered sleep and oxygenation patterns, as seen in OSAS, will promote specific alterations in the gut microbiota that in turn, will elicit the immunologic alterations that lead to OSAS-induced end-organ morbidities.[35] Chronic intermittent hypoxia is accompanied by considerable and reproducible changes in gut microbial communities. Interestingly, an animal model of OSA demonstrated that induced intermittent hypoxia in mice caused alterations in microbiota composition and diversity, and especially enhanced the Firmicutes/Bacteroidetes ratio as compared to the controls.[78] In another mice study, it has been reported that chronic sleep disruption leads to changes in microbiota by increasing intestinal permeability, and an increase in fat mass as well.[79] According to these study results, faecal microbiota composition and diversity are altered as a result of intermittent hypoxia realistically mimicking OSAS, suggesting the possibility that physiological interplays between host and gut microbiota could be deregulated in OSAS. Moreover, a new clinical study support that changes in the gut microbiota have a pathophysiological role in OSAS, and to be associated with the pathophysiology of metabolic comorbidities in patients with OSAS.[80]

6 | THE METABOLIC CHANGES RELATED TO SOME TREATMENT APPLICATIONS

OSAS is a complex condition, and treatment cannot be limited to any single symptom or feature of the disease.[6,81] Lifestyle changes and weight loss are cornerstones of OSAS therapy. Some authors support the claim that weight loss may lead to an improvement in the severity of OSAS and may even lead to a resolution.[82] Additionally, exercise and the Mediterranean diet have positive effects on the severity of OSAS, independently of weight loss.[81] Naturally, polysomnography represents the gold standard to confirm the clinical suspicion of OSAS, to assess its severity and to guide therapeutic choices. Also, behavioural,[83] medical and surgical options are available for treatment.[2,4] According to another group of authors, the mainstay of treatment for OSAS is continuous positive airway pressure (CPAP) therapy in adults and adenotonsillectomy in children. Even though these therapies are effective in resolving the sleep-disordered breathing component of OSAS, they do not always produce helpful effects on metabolic function.[84] Although CPAP represents the preferred treatment for most patients, a multidisciplinary and integrated strategy is required to achieve effective and long-term therapeutic success.[3] Weight loss, especially through bariatric surgery, has been shown to reduce the severity and symptoms of OSAS and, sometimes though not always, result in its complete resolution.[85]

There is growing evidence that treatment with CPAP can reduce inflammation and oxidative stress. For example, our study group demonstrated a decrease in inflammation and oxidative stress levels in the respiratory tract of patients with OSAS with CPAP treatment.[86] This treatment also helped decrease systemic oxidative stress levels in the serum. Also, the results of a meta-analysis study suggest that OSAS is significantly associated with airway inflammation and elevated fractional exhaled nitric oxide levels can be modified by long-term CPAP therapy.[87] Although insulin sensitivity, and control of hyperglycemia in obese patients with OSAS, are among the therapeutic targets, the conclusions on the efficacy of CPAP therapy in IR, metabolic syndrome or diabetes are controversial. It is found that the CPAP treatment significantly improved IR, and indicated that treating OSAS could positively impact the symptoms of type 2 diabetes.[88] However, in a meta-analysis study evaluating evidence for the efficacy of CPAP in patients with type 2 diabetes and OSAS, CPAP therapy that did not affect HbA1c levels was reported not to improve glycemic control.[89] Additionally, another meta-analysis study showed that CPAP could significantly reduce leptin levels in OSAS patients without concomitant weight loss.[90] Interestingly, obesity-related changes in the gut microbiota, such as increased intestinal permeability, LPS translocation, and low-grade systemic inflammation, as well as glucose tolerance and hyperphagic behavior, have been reversed by probiotics. Also, probiotics have been reported to cause an improvement in hypothalamic insulin and leptin resistance.[91] A healthy diet and appropriate lifestyle modifications towards better control of metabolic function are equally important as CPAP treatment in the holistic management of OSAS. In other words, a multidisciplinary treatment plan should be applied, considering inter-organ interaction in the treatment of both OSAS and obesity.

7 | CONCLUSION

According to the existing literature data, OSAS and obesity adversely affect many organs and systems. In general, the communication network associated with OSAS and obesity is affected by the lung, adipose tissue and gut microbiota. Given the known pathophysiological triggers of intermittent hypoxia and sleep fragmentation in OSAS, the potential mechanisms of OSAS-obesity and other dysfunction

interactions involve sympathetic activation, oxidative stress, inflammation and metabolic dysregulation changes. Recently, the gut microbiota is accepted to be interrelated in the pathogenesis of OSAS and obesity, and therefore, may be a potential factor responsible for OSAS-obesity coexistence. When the relation between OSAS and obesity has been extensively evaluated, it is implicated that it has shown bidirectional causality with each other, and that it may have mutual interaction with the other metabolic dysregulations.

In the diagnostic approach to the relationship between OSAS and obesity, organ interactions among the lungs, adipose tissue and gut should be especially noted. Also, effective treatment options in these cases should be managed well. Although CPAP is a standard treatment for OSAS, dietary and lifestyle changes are also crucial for the overall management of the OSAS-obesity relationship. Based on the current data, the gut microbiota may be a potential therapeutic target for both OSAS and obesity. However, comprehensive clinical trials addressing the efficacy and efficiency of current or potential treatments on therapeutic applications in the OSAS-obesity relationship are needed.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

AUTHOR CONTRIBUTIONS

Topic suggestion: Kuvat
Study design: Armutcu
Data acquisition and/or analysis: Kuvat, Tanriverdi, Armutcu
Revision and final approval: Kuvat, Tanriverdi, Armutcu

ETHICS

This study is in accordance with the Declaration of Helsinki.

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REFERENCES

1. Mannarino MR, Di Filippo F, Pirro M. Obstructive sleep apnea syndrome. *Eur J Intern Med*. 2012;23:586-593.
2. Schwartz AR, Patil SP, Laffan AM, Polotsky V, Schneider H, Smith PL. Obesity and obstructive sleep apnea: pathogenic mechanisms and therapeutic approaches. *Proc Am Thorac Soc*. 2008;5(2):185-192.
3. Laratta CR, Ayas NT, Povitz M, Pendharkar SR. Diagnosis and treatment of obstructive sleep apnea in adults. *CMAJ*. 2017;189(48):E1481-E1488.
4. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American academy of sleep medicine clinical practice guideline. *J Clin Sleep Med*. 2017;13(3):479-504.
5. Romero-Corral A, Caples SM, Lopez-Jimenez F, Somers VK. Interactions between obesity and obstructive sleep apnea. *Chest*. 2010;137:711-719.
6. Bonsignore MR, McNicholas WT, Montserrat JM, Eckel J. Adipose tissue in obesity and obstructive sleep apnoea. *Eur Respir J*. 2012;39:746-767.
7. Kasai T, Floras JS, Bradley TD. Sleep apnea and cardiovascular disease: a bidirectional relationship. *Circulation*. 2012;126:1495-1510.
8. Tarantino G. Gut microbiome, obesity-related comorbidities, and low-grade chronic inflammation. *J Clin Endocrinol Metab*. 2014;99:2343-2346.
9. Durgan DJ, Ganesh BP, Cope JL, et al. Role of the gut microbiome in obstructive sleep apnea-induced hypertension. *Hypertension*. 2016;67:469-474.
10. Moreno-Indias I, Cardona F, Tinahones FJ, Queipo-OrtuÃ±o MI. Impact of the gut microbiota on the development of obesity and type 2 diabetes mellitus. *Front Microbiol*. 2014;5:190. https://doi.org/10.3389/fmicb.2014.00190.
11. Bleau C, Karelis AD, St-Pierre DH, Lamontagne L. Crosstalk between intestinal microbiota, adipose tissue and skeletal muscle as an early event in systemic low grade inflammation and the development of obesity and diabetes. *Diabetes Metab Res Rev*. 2015;31(6):545-561.
12. Zhang X, Ji X, Wang Q, Li JZ. New insight into inter-organ crosstalk contributing to the pathogenesis of non-alcoholic fatty liver disease (NAFLD). *Protein Cell*. 2018;9(2):164-177.
13. Unnikrishnan D, Jun J, Polotsky V. Inflammation in sleep apnea: an update. *Rev Endocr Metab Disord*. 2015;16:25-34.
14. Pillar G, Shehadeh N. Abdominal fat and sleep apnea the chicken or the egg? *Diabetes Care*. 2008;31(suppl 2):S303-S309.
15. Rasche K, Keller T, Hader C, Leidag M, Prinz C. Impact of obstructive sleep apnoea on type 2 diabetes and vice versa. *Eur Endocrinol*. 2013;9(2):107-109.
16. Javaheri S, Barbe F, Campos-Rodriguez F, et al. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. *Am J Cardiol*. 2017;69:841-858.
17. Arens R, Muzumdar H. Obesity and obstructive sleep apnoea syndrome in children. *J Appl Physiol*. 2010;108:436-444.
18. Basoglu OK, Sarac F, Sarac S, Uluer H, Yilmaz C. Metabolic syndrome, insulin resistance, fibrinogen, homocysteine, leptin, and C-reactive protein in obese patients with obstructive sleep apnea syndrome. *Ann Thorac Med*. 2011;6:120-125.
19. Carter R, Watenpaugh DE. Obesity and obstructive sleep apnea: or is it OSA and obesity? *Pathophysiology*. 2008;15:71-77.
20. Husain-Syed F, McCullough PA, Birk H-W, et al. Cardiopulmonary-renal interactions: a multidisciplinary approach. *J Am Coll Cardiol*. 2015;65(22):2433-2448.
21. Armutcu F. Organ crosstalk: the potent roles of inflammation and fibrotic changes in the course of organ interactions. *Inflamm Res*. 2019;68(10):825-839.
22. Quílez ME, López-Aguilar J, Blanch L. Organ crosstalk during acute lung injury, acute respiratory distress syndrome, and mechanical ventilation. *Curr Opin Crit Care*. 2012;18(1):23-28.
23. Rutten EPA, Lenaerts K, Buurman WA, Wouters EFM. Disturbed intestinal integrity in patients with COPD: effects of activities of daily living. *Chest*. 2014;145:245-252.
24. Domenech P, Perez T, Saldarini A, Uad P, Musso CG. Kidney-lung pathophysiological crosstalk: its characteristics and importance. *Int Urol Nephrol*. 2017;49(7):1211-1215.

25. Schafer H, Pauleit D, Sudhop T, Gouni-Berthold I, Ewig S, Berthold HK. Body fat distribution, serum leptin, and cardiovascular risk factors in men with obstructive sleep apnea. *Chest*. 2002;122(3):829-839.
26. Zammit C, Liddicoat H, Moonsie I, Makker H. Obesity and respiratory diseases. *Int J Gen Med*. 2010;3:335-343.
27. Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006;444:860-867.
28. Alkhouri N, Gornicka A, Berk MP, et al. Adipocyte apoptosis, a link between obesity, insulin resistance, and hepatic steatosis. *J Biol Chem*. 2010;285:3428-3438.
29. Blüher M. Adipose tissue dysfunction in obesity. *Exp Clin Endocrinol Diabetes*. 2009;117(6):241-250.
30. Garvey JF, Taylor CT, McNicholas WT. Cardiovascular disease in obstructive sleep apnoea syndrome: the role of intermittent hypoxia and inflammation. *Eur Respir J*. 2009;33:1195-1205.
31. Grams ME, Rabb H. The distant organ effects of acute kidney injury. *Kidney Int*. 2012;81:942-948.
32. Nastos C, Kalimeris K, Papoutsidakis N, et al. Global consequences of liver ischemia/reperfusion injury. *Oxid Med Cell Longev*. 2014;2014:906965.
33. Budden KF, Gellatly SL, Wood DLA, et al. Emerging pathogenic links between microbiota and the gut-lung axis. *Nat Rev Microbiol*. 2017;15(1):55–63.
34. Anand S, Mande SS. Diet, microbiota and gut-lung connection. *Front Microbiol*. 2018;9:2147. https://doi.org/10.3389/fmicb.2018.02147.
35. Farre N, Farre R, Gozal D. Sleep apnea morbidity: a consequence of microbial-immune cross-talk? *Chest*. 2018;154(4):754-759.
36. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. *Cell*. 2014;157(1):121-141.
37. Gileles-Hillel A, Alonso-Álvarez ML, Kheirandish-Gozal L, et al. Inflammatory markers and obstructive sleep apnea in obese children: the NANOS study. *Mediators Inflamm*. 2014;2014:605280.
38. Barceló A, Esquinas C, Robles J, et al. Gut epithelial barrier markers in patients with obstructive sleep apnea. *Sleep Med*. 2016;26:12-15.
39. Nobili V, Alisi A, Cutrera R, et al. Altered gut-liver axis and hepatic adiponectin expression in OSAS: novel mediators of liver injury in paediatric non-alcoholic fatty liver. *Thorax*. 2015;70(8):769-781.
40. He Y, Wen Q, Yao F, Xu D, Huang Y, Wang J. Gut-lung axis: the microbial contributions and clinical implications. *Crit Rev Microbiol*. 2017;43(1):81-95.
41. Cândido FG, Valente FX, Grześkowiak ŁM, Moreira APB, Rocha DMUP, Alfenas RdCG. Impact of dietary fat on gut microbiota and low-grade systemic inflammation: mechanisms and clinical implications on obesity. *Int J Food Sci Nutr*. 2018;69(2):125-143.
42. Delzenne NM, Neyrinck AM, Bäckhed F, Cani PD. Targeting gut microbiota in obesity: effects of prebiotics and probiotics. *Nat Rev Endocrinol*. 2011;7:639-646.
43. Glicksman A, Hadjiyannakis S, Barrowman N, Walker S, Hoey L, Katz SL. Body fat distribution ratios and obstructive sleep apnea severity in youth with obesity. *J Clin Sleep Med*. 2017;13(4):545-550.
44. Patinkin ZW, Feinn R, Santos M. Metabolic consequences of obstructive sleep apnea in adolescents with obesity: a systematic literature review and meta-analysis. *Child Obesity*. 2017;13(2):102-110.
45. Jehan S, Pandi-Perumal SR, Wall S, et al. Obstructive sleep apnea and obesity: implications for public health. *Sleep Med Disord*. 2017;1(4):pii:00019.
46. Sanz Y, Moya-Pérez A. Microbiota, inflammation and obesity. *Adv Exp Med Biol*. 2014;817:291-317.
47. Bonsignore MR, Esquinas C, Barceló A, et al. Metabolic syndrome, insulin resistance and sleepiness in real-life obstructive sleep apnoea. *Eur Respir J*. 2012;39:1136-1143.
48. Le Chatelier E, Nielsen T, Qin J, et al. Richness of human gut microbiome correlates with metabolic markers. *Nature*. 2013;500:541-546.
49. Moreno-Indias I, Cardona F, Tinahones FJ, Queipo-Ortuño MI. Impact of the gut microbiota on the development of obesity and type 2 diabetes mellitus. *Front Microbiol*. 2014;5:190. https://doi.org/10.3389/fmicb.2014.00190.
50. Ong CW, O'Driscoll DM, Truby H, Naughton MT, Hamilton GS. The reciprocal interaction between obesity and obstructive sleep apnoea. *Sleep Med Rev*. 2013;17:123-131.
51. Everson CA, Toth LA. Systemic bacterial invasion induced by sleep deprivation. *Am J Physiol Regul Integr Comp Physiol*. 2000;278:R905-R916. https://doi.org/10.1152/ajpregu.2000.278.4.R905.
52. Everson CA, Thalacker CD, Hogg N. Phagocyte migration and cellular stress induced in liver, lung, and intestine during sleep loss and sleep recovery. *Am J Physiol Regul Integr Comp Physiol*. 2008;295:R2067-R2074. https://doi.org/10.1152/ajpregu.90623.2008.
53. Schroeder BO, Backhed F. Signals from the gut microbiota to distant organs in physiology and disease. *Nat Med*. 2016;22(10):1079-1089.
54. Vijay-Kumar M, Aitken JD, Carvalho FA, et al. Metabolic syndrome and altered gut microbiota in mice lacking toll-like receptor 5. *Science*. 2010;328:228-231.
55. Burcelin R, Serino M, Chabo C, Blasco-Baque V, Amar J. Gut microbiota and diabetes: from pathogenesis to therapeutic perspective. *Acta Diabetol*. 2011;48:257-273.
56. Lavie L. Obstructive sleep apnoea syndrome: an oxidative stress disorder. *Sleep Med Rev*. 2003;7:35-51.
57. Manna P, Jain SK. Obesity, oxidative stress, adipose tissue dysfunction, and the associated health risks: causes and therapeutic strategies. *Metab Syndr Relat Disord*. 2015;13:423-444.
58. Eisele HJ, Markart P, Schulz R. Obstructive sleep apnea, oxidative stress, and cardiovascular disease: evidence from human studies. *Oxid Med Cell Longev*. 2015;2015:608438. https://doi.org/10.1155/2015/608438.
59. Uygur F, Tanriverdi H, Can M, et al. The impact of obstructive sleep apnoea and nasal continuous positive airway pressure on circulating ischaemia-modified albumin concentrations. *Mediators Inflamm*. 2016;2016:8907314. https://doi.org/10.1155/2016/8907314.
60. Salerno FG, Carpagnano E, Guido P, et al. Airway inflammation in patients affected by obstructive sleep apnea syndrome. *Respir Med*. 2004;98:25-28.
61. Lee SD, Ju G, Choi JA, Kim JW, Yoon IY. The association of oxidative stress with central obesity in obstructive sleep apnea. *Sleep Breath*. 2012;16:511-517.
62. Crujeiras AB, Díaz-Lagares A, Carreira MC, Amil M, Casanueva FF. Oxidative stress associated to dysfunctional adipose tissue: a potential link between obesity, type 2 diabetes mellitus and breast cancer. *Free Radic Res*. 2013;47:243-256.
63. Damiani MF, Carratù P, Quaranta VN, Resta O. Influence of obstructive sleep apnea on endothelial function in obese patients. *Chest*. 2012;141:1639-1640.

64. Htoo AK, Greenberg H, Tongia S. Activation of nuclear factor kappaB in obstructive sleep apnea: a pathway leading to systemic inflammation. *Sleep Breath*. 2006;10:43-50.
65. Kheirandish-Gozal L, Gozal D. Obstructive sleep apnea and inflammation: proof of concept based on two illustrative cytokines. *Int J Mol Sci*. 2019;20(3):pii:E459.
66. Wolk R, Somers VK. Obesity-related cardiovascular disease: implications of obstructive sleep apnea. *Diabetes Obes Metab*. 2006;8:250-260.
67. Doumit J, Prasad B. Sleep apnea in type 2 diabetes. *Diabetes Spectr*. 2016;29:14-19.
68. Pamidi S, Tasali E. Obstructive sleep apnea and type 2 diabetes: is there a link? *Front Neurol*. 2012;3:126. https://doi.org/10.3389/fneur.2012.00126.
69. Chattu V, Chattu S, Burman D, Spence D, Pandi-Perumal S. The interlinked rising epidemic of insufficient sleep and diabetes mellitus. *Healthcare (Basel)*. 2019;7(1):pii:E37. https://doi.org/10.3390/healthcare7010037.
70. Imayama I, Prasad B. Role of leptin in obstructive sleep apnea. *Ann Am Thorac Soc*. 2017;14(11):1607-1621.
71. Ozturk L, Unal M, Tamer L, Celikoglu F. The association of the severity of obstructive sleep apnea with plasma leptin levels. *Arch Otolaryngol Head Neck Surg*. 2003;129(5):538-540.
72. Berger S, Polotsky VY. Leptin and leptin resistance in the pathogenesis of obstructive sleep apnea: a possible link to oxidative stress and cardiovascular complications. *Oxid Med Cell Longev*. 2018;2018:5137947. https://doi.org/10.1155/2018/5137947.
73. Reutrakul S, Van Cauter E. Sleep influences on obesity, insulin resistance, and risk of type 2 diabetes. *Metabolism*. 2018;84:56-66.
74. Framnes SN, Arble DM. The bidirectional relationship between obstructive sleep apnea and metabolic disease. *Front Endocrinol*. 2018;9:440. https://doi.org/10.3389/fendo.2018.00440.
75. Hakim F, Kheirandish-Gozal L, Gozal D. Obesity and altered sleep: a pathway to metabolic derangements in children? *Semin Pediatr Neurol*. 2015;22(2):77-85.
76. Zhao L. The gut microbiota and obesity: from correlation to causality. *Nat Rev Microbiol*. 2013;11:639-647.
77. Lin L, Zhang J. Role of intestinal microbiota and metabolites on gut homeostasis and human diseases. *BMC Immunol*. 2017;18(1):2. https://doi.org/10.1186/s12865-016-0187-3.
78. Moreno-Indias I, Torres M, Montserrat JM, et al. Intermittent hypoxia alters gut microbiota diversity in a mouse model of sleep apnoea. *Eur Respir J*. 2015;45(4):1055-1065.
79. Poroyko VA, Carreras A, Khalyfa A, et al. Chronic sleep disruption alters gut microbiota, induces systemic and adipose tissue inflammation and insulin resistance in mice. *Sci Rep*. 2016;6:35405. https://doi.org/10.1038/srep35405.
80. Ko C-Y, Liu Q-Q, Su H-Z, et al. Gut microbiota in obstructive sleep apnea-hypopnea syndrome: disease-related dysbiosis and metabolic comorbidities. *Clin Sci (Lond)*. 2019;133(7):905-917.
81. Cowan DC, Livingston E. Obstructive sleep apnoea syndrome and weight loss: review. *Sleep Disord*. 2012;2012:163296. https://doi.org/10.1155/2012/163296.
82. Dobrosielski DA, Papandreou C, Patil SP, Salas-Salvadó J. Diet and exercise in the management of obstructive sleep apnoea and cardiovascular disease risk. *Eur Respir Rev*. 2017;26(144):160110. https://doi.org/10.1183/16000617.0110-2016.
83. Johnson-Taylor WL, Fisher RA, Hubbard VS, Starke-Reed P, Eggers PS. The change in weight perception of weight status among the overweight: comparison of NHANES III (1988-1994) and 1999-2004 NHANES. *Int J Behav Nutr Phys Act*. 2008;5:9. https://doi.org/10.1186/1479-5868-5-9.
84. Gileles-Hillel A, Kheirandish-Gozal L, Gozal D. Biological plausibility linking sleep apnoea and metabolic dysfunction. *Nat Rev Endocrinol*. 2016;12(5):290-298.
85. Fritscher LG, Mottin CC, Canani S, Chatkin JM. Obesity and obstructive sleep apnea-hypopnea syndrome: the impact of bariatric surgery. *Obes Surg*. 2007;17:95-99.
86. Karamanlı H, Özol D, Ugur KS, et al. Influence of CPAP treatment on airway and systemic inflammation in OSAS patients. *Sleep Breath*. 2014;18:251-256.
87. Zhang D, Luo J, Qiao Y, Xiao YI, Huang R, Zhong XU. Measurement of exhaled nitric oxide concentration in patients with obstructive sleep apnea: a meta-analysis. *Medicine (Baltimore)*. 2017;96(12):e6429.
88. Chen L, Pei JH, Chen HM. Effects of continuous positive airway pressure treatment on glycaemic control and insulin sensitivity in patients with obstructive sleep apnoea and type 2 diabetes: a meta-analysis. *Arch Med Sci*. 2014;10(4):637-642.
89. Labarca G, Reyes T, Jorquera J, Dreyse J, Drake L. CPAP in patients with obstructive sleep apnea and type 2 diabetes mellitus: systematic review and meta-analysis. *Clin Respir J*. 2018;12(8):2361-2368.
90. Chen X, Niu X, Xiao Y, Dong J, Lu M, Kong W. Effect of continuous positive airway pressure on leptin levels in patients with obstructive sleep apnea: a meta-analysis. *Otolaryngol Head Neck Surg*. 2015;152(4):610-618.
91. Bagarolli RA, Tobar N, Oliveira AG, et al. Probiotics modulate gut microbiota and improve insulin sensitivity in DIO mice. *J Nutr Biochem*. 2017;50:16-25.

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