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METABOLISM (M DALAMAGA, SECTION EDITOR)

Sleep Apnea, Obesity, and Disturbed Glucose Homeostasis: Epidemiologic Evidence, Biologic Insights, and Therapeutic Strategies

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Abstract

Purpose of Review Obstructive sleep apnea (OSA), obesity, and disturbed glucose homeostasis are usually considered distinct clinical condition, although they are tightly related to each other. The aim of our manuscript is to provide an overview of the current evidence on OSA, obesity, and disturbed glucose homeostasis providing epidemiologic evidence, biological insights, and therapeutic strategies.

Recent Findings The mechanisms hypothesized to be involved in this complex interplay are the following: (1) "direct weight-dependent" mechanisms, according to which fat excess compromises respiratory mechanics, and (2) "indirect weight-dependent" mechanisms such as hyperglycemia, insulin resistance and secondary hyperinsulinemia, leptin resistance and other hormonal dysregulations frequently found in subjects with obesity, type 2 diabetes, and/or sleep disorders. Moreover, the treatment of each of these clinical conditions, through weight loss induced by diet or bariatric surgery, the use of anti-obesity or antidiabetic drugs, and continuous positive airway pressure (CPAP), seems to positively influence the others.

Summary These recent data suggest not only that there are multiple connections among these diseases but also that treating one of them may result in an improvement of the others.

Keywords Obesity · Obstructive sleep apnea · Type 2 diabetes mellitus · Metabolic syndrome

Introduction

Obstructive sleep apnea (OSA) is a sleep disorder characterized by recurrent apneic events, with increased upper airway resistance in the presence of respiratory effort, which leads to intermittent hypoxia (IH) and sleep fragmentation [1]. OSA is diagnosed through polysomnography, which measures the following: (1) apnea events that are defined as episodes of cessation of breathing of at least 10 s with or without oxygen desaturation, (2) hypopnea events characterized by a reduction of respiration of at least 30% of the nasal pressure signal, (3) the respiratory effort-related arousal (RERA) events that correspond to any respiratory disturbance of at least 10 s not entered in the previous categories [2], and [3] the apnea-hypopnea index (AHI) which is obtained from the sum of apnea and hypopnea events and serves to classify the OSA syndrome in mild, moderate, or severe, if AHI is included between 5 and 15, 15–30, or if it is > 30, respectively [2]. The obstruction that determines OSA syndrome can be caused by an abnormal anatomy (narrow airways, enlarged tonsils) [4], by a reduction in muscle tone, and more frequently by an obese anatomy due to fat accumulation in the neck and in pharyngeal tissue [3, 5]; in fact, OSA is most frequently found in obese middle-aged men [6]. The main adverse effects of OSA are oxygen desaturation, IH, and sleep fragmentation; however, numerous evidence also suggest a destabilization of sleep homeostasis and unfavorable repercussions on metabolic parameters, insulin sensitivity, and the cardiovascular system [7, 8, 9••, 10, 11], thus creating an interesting connection between sleep disorders and metabolic pathologies such as obesity, diabetes mellitus, and metabolic syndrome.

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OSA has a prevalence of 17% in the general population, which reaches 40–70% in obese subjects and 58–86% in individuals with type 2 diabetes mellitus (T2DM), therefore significantly higher than the total population [12–14]. In fact, an OSA prevalence of 86% was observed in 306 individuals with T2DM with severe obesity, body mass index > 36.5 ± 5.8 kg/m^2, and waist circumference > 115.0 ± 13.0 cm [15]. The prevalence of moderate to severe OSA (AHI ≥ 15) was 46.3% in long-standing type 1 diabetes mellitus (T1DM) with 29 ± 14 years duration [16•]. The high prevalence of OSA in both T2DM and T1DM would therefore suggest the possibility that this disorder is associated not only with an excess of adiposity but also with hyperglycemia [17].

In several studies, a clear association between obesity and AHI has been demonstrated; in particular, it seems that visceral obesity and neck circumference (NC) are more specifically related to the development of OSA [18, 19]. Furthermore, it has been shown in a cross-sectional analysis of a population sample of 1912 Turkish adults subjected to biochemical investigations and measurement of neck circumference that the NC correlates with homeostasis model assessment of insulin resistance (HOMA-IR), as index of insulin resistance, and NC was associated significantly with metabolic syndrome [20]. This latter result was confirmed in another cross-sectional study carried out in 120 subjects with obesity, subjected to anthropometric and biochemical assessments and polysomnography, which showed that NC is independently associated with the metabolic syndrome and OSAS, and in particular, a NC of ≥ 38 cm had a sensitivity of 54% and 58% and a specificity of 70% and 79% in predicting the presence of metabolic syndrome and OSAS, respectively [21]. Prolonged obesity causes some adverse health outcomes such as hypertension, insulin resistance, dyslipidemia, increased risk of cardiovascular morbidity and mortality, T2DM, some types of tumors and neurological disorders, and increased mortality for all causes. Overall, this set of risk factors results in metabolic syndrome [22]. The same risk factors for metabolic syndrome along with middle age, sedentary life, poor diet, and genetic factors increase the risk of developing OSA. Therefore, it is clear that there is a connection between these pathologies and that this link originates from common physiopathological mechanisms triggered by excess weight. The aim of this manuscript is to review the epidemiologic evidence, biologic insights, and therapeutic strategies linking OSA, obesity, and disturbed glucose homeostasis.

Physiophathologic Interconnections Between OSA, Obesity, and Disturbed Glucose Homeostasis

It has been reported that obesity, OSA, and disturbed glucose homeostasis share common links [3, 15]. The accumulation of fat in the neck, tongue, and pharyngeal tissue involves a greater effort for the muscles assigned to the patency of the upper airways, which in a phase like that of rapid eye movement (REM) sleep, characterized by reduction in muscle tone, they may not be able to prevent obstruction, leading to apnea or hypopnea [5, 23]. Moreover, excess weight can also directly worsen the pulmonary dynamics, in particular by reducing the residual functional capacity and tidal volume [24].

These mechanisms that we could define as "direct weight-dependent" are not sufficient to justify the pathogenesis of OSA, since it also affects lean subjects, and not all the obese ones [7, 25], suggesting that there may be other mechanisms definable as "indirect weight-dependent."

The most studied "indirect weight-dependent" mechanisms are hyperglycemia, insulin resistance, and leptin resistance, typical of the obese and diabetic subject, which on the one hand can contribute to the pathogenesis and worsening of OSA, while on the other hand, they themselves can be influenced by the presence and intensity of sleep disorders.

With regard to hyperglycemia, there are several studies that support an association between apnea and poor glycemic control: in fact, nocturnal hypoxemia has been independently associated with abnormal glycemic metabolism both in diabetic and non-diabetic subjects, defined in these last by the finding of glycosylated hemoglobin (HbA1c) values between 6 and 6.5%, and with a higher incidence of T2DM in men previously euglycemic [26•, 27•, 28•]. Furthermore, the association between OSA and alteration of glucose metabolism could precede the onset of T2DM, as demonstrated by the fact that in non-diabetic individuals, the severity of OSA is associated with greater variability of the circadian glucose rhythm [8]. In T2DM and T1DM, hyperglycemia alters the responsiveness of the carotid body to the hypoxic stimulus [29]. Interestingly, oxygen and glucose signals on glomus cells in the carotid body can enhance each other, leading to episodes in which hyperglycemia may lead to a dysregulation of oxygen and carbon dioxide, consequently altering breathing [30]. It was observed that the injection of glucose into the isolated carotid sinus of cats reduced by 20% the activity of carotid body chemoreceptors and increased their threshold to hypoxia, while in the mouse, the reduced sensitivity of the carotid body due to hyperglycemia worsened the ventilatory response [31, 32]. Moreover, in the diabetic subjects, the carotid atherosclerosis could also lead to a dampening of the reactivity to hypoxemia, predisposing to the OSA [33]. The effect of hyperglycemia could also depend on the long-term development of autonomic neuropathy, which has been shown to have an effect on the chemical control of respiration by altering the signal of central and peripheral chemoreceptors and of glossopharyngeal, vagal, and proprioceptive nerves [34–36]; this may partly justify the prevalence of 26% of mild OSA found in diabetic subjects with autonomic neuropathy compared with non-autonomic neuropathy diabetic control group [37].

In turn OSA may blunt glycemic homeostasis. Several experimental studies using animal and in vitro models have suggested that IH, typically found in OSA, leads to pancreatic β-cell dysfunction and insulin resistance in insulin target organs, skeletal muscle, and adipose tissue [38••]. In particular, an increased sympathetic activity would appear to be involved, with increased secretion of epinephrine and norepinephrine and consequently an increase in hepatic gluconeogenesis and a reduction in glucose uptake from target tissues, as demonstrated in IH exposed mice [39, 40]. IH can also lead to hyperactivation of the corticotropic axis, as a response to a stressful stimulus, resulting in higher cortisol-circulated levels, whose effects are well-known: hyperglycemia, reduced insulin secretion, and insulin sensitivity that results in increased risk of developing T2DM [41, 42]. Subjects with OSA present high concentrations of proinflammatory cytokines, just as mice subjected to IH experience an alteration of inflammatory mediators in the upper and lower airways [43••]. Therefore, this condition of chronic systemic inflammation can also lead to the worsening of glucose metabolism [44].

Insulin resistance and secondary hyperinsulinemia also seem to play an important role in the intricate cross-talk between sleep disorders and metabolism. Several clinical studies have found that insulin resistance is independently associated with OSA; however, the mechanisms responsible for this association are only partially known [7, 45•, 46•](Table 1). It has been demonstrated that hyperglycemia induced in rats by streptozotocin (STZ) treatment resulted in altered control of ventilation, including reduction in the hypercapnic ventilatory response and hypoxic ventilatory response and an increase of apnea episodes, and that treatment with insulin or oral antidiabetic drugs improved respiratory disorders in mice with secondary diabetes, suggesting a potential causal role of hyperglycemia in the pathophysiology of OSA [51, 52]. Regarding the role of OSA in worsening insulin sensitivity, various mechanisms have been suggested including in particular a hyperactivation of the sympathetic system. In fact, it has been reported that patients with OSA show an increase in sympathetic tone: this could be explained by the evidence that the blocking of the sympathetic response by alpha adrenergic blockade or adrenal medullectomy in rodents seems to prevent the insulin resistance induced by prolonged exposure to IH [53–55]. Probably, this is due to the fact that the sympathetic hypertone stimulates lipolysis, favoring the release of free fatty acids that worsen insulin sensitivity, as supported by evidence that acipimox lipolysis inhibitor prevented impairments in fasting glycemia, glucose tolerance, and insulin sensitivity in mice exposed to IH [56, 57•]. In addition, in a polygenic rodent model of T2DM, it was shown that IH leads to an increase in pancreatic oxidative stress, insulin-secreting cell apoptosis, and worsening of β-AR agonist-mediated insulin release, demonstrating that oxidative stress may represent a linking mechanism between OSA and insulin resistance [58].

The role of leptin in sleep disorders is still a subject of discussion. Leptin is a satiety hormone produced by adipose tissue in proportion to its extension, but according to clinical evidence, there would seem to be a positive association between OSA and leptin, independent from body fat, suggesting that leptin plays a role independently from weight in the pathogenesis of OSA [59, 60]. However, the data available so far are discordant: if on the one hand, the positive association between OSA and leptin is well-known and documented, on the other one, knockout mice for the leptin ob gene seem to present respiratory disorders and a reduced hypercapnic ventilatory response, just as subjects with lipodystrophy present a greater risk of developing OSA [61–63]. This discordance could be explained considering that in obese, leptin resistance may not affect all the actions of leptin, preserving its sympathetic system stimulating function, thus justifying its effect on the regulation of respiration [64].Moreover, it has been shown in a human study that leptin resistance also has a role in the obesity hypoventilation syndrome, causing a worsening of hypercapnic ventilatory response, probably due to an effect on the chemoreceptors [65•].

Regarding hormonal mechanism, melatonin seems to be another hormone involved in the link between OSA, obesity, and disturbed glucose homeostasis. Melatonin is a hormone produced by the pineal gland, with a peak of nocturnal secretion modulated by suprachiasmatic afferents, which regulates the sleep-wake circadian rhythm [66]. It has been shown that patients with OSA have lower melatonin levels, measured by the ratio of their urinary metabolite to creatinine [67••]. Even in subjects with T2DM, lower melatonin concentration compared with controls was found, which could partly contribute to the etiology of glycemic decompensation since there are melatonin receptors on pancreatic alpha and beta cells, modulating insulin secretion [68, 69].Therefore, as already suggested by some studies, the severity of OSA may correlate with nighttime melatonin levels, which are in turn associated with worse glycemic control and an increased risk of T2DM [69, 70]. (Fig. 1).

Potential Connections Based on Response to Treatment

Another way to explore the relationship between OSA obesity and diabetes mellitus is to evaluate the effect that the treatment of each of these conditions has on others. Some studies have shown that dietary weight loss programs are effective in reducing the severity of OSA, measured by AHI [71]. In particular, in obese subjects with T2DM, an intensive lifestyle intervention lasting 1 year has shown to lead to a reduction in AHI and in the prevalence of severe OSA, as well as a remission rate of 3 times higher than in the control group [72]. The main limitation of intensive diet programs is poor long-term

Table 1 Clinical studies showing association between insulin resistance and OSA

Study	Patients	Main findings
Pamidi et al. [7]	52 healthy subjects	Subjects with OSA had 27% lower insulin sensitivity and 37% higher total insulin secretion than the control subjects, despite comparable glucose levels.
Brúsik et al. [45•]	40 healthy subjects	Subjects with moderate-to-severe OSA had increased REE paralleled by impaired insulin resistance.
Araujo et al. [46•]	53 subjects with obesity	Minimum O_2 saturation was inversely related with insulin resistance in subjects with obesity.
Lam et al. [47]	61 subjects with moderate/severe OSA	CPAP treatment of OSA for 1 week improved insulin resistance, and the improvement was maintained after 12 weeks of treatment in those with moderate obesity.
West et al. [48]	42 diabetic subjects with OSA	A 3-month CPAP treatment did not significantly improve glycemic control or insulin resistance.
Kohler et al. [49]	41 subjects with OSA receiving CPAP	Insulin resistance did not change significantly after 2 weeks of CPAP withdrawal compared with the CPAP group.
Hoyos et al. [50]	65 subjects with OSA, CPAP naıve	There were no significant changes in insulin resistance and fasting plasma glucose over the first 12 weeks of CPAP treatment; at week 24 improved ISx.

OSA Obstructive sleep apnea, *REE* resting energy expenditure, *CPAP* continuous positive airway pressure

compliance and recovery of lost weight. However, Kuna et al. have shown that in obese adults with T2DM and OSA, beneficial effects of intensive lifestyle intervention on AHI at 1 year persisted at 4 years, despite an almost 50% weight regain, suggesting that the effect of intensive lifestyle intervention on AHI was largely, but not entirely, due to weight loss [73].

Besides dietary intervention, it has been reported that pharmacological treatment of obesity could result in an improvement of OSA. Liraglutide is a glucagon-like peptide-1 (GLP-1) analog that was born as a drug for the treatment of T2DM and is currently indicated at a dose of 3 mg for the treatment of obesity, exploiting its pleiotropic metabolic effects such as

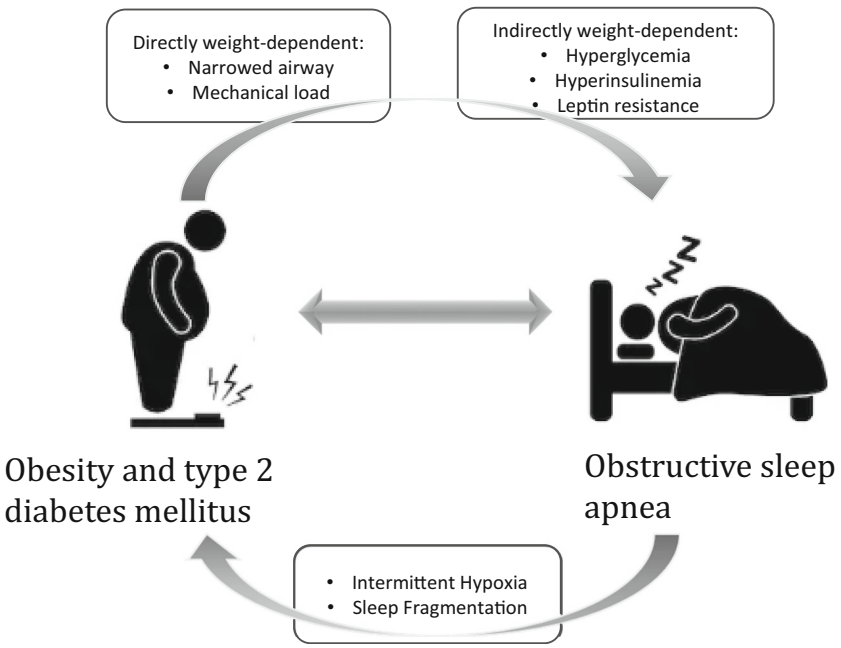

Fig. 1 The bidirectional link between obesity, type 2 diabetes mellitus, and obstructive sleep apnea (OSA). OSA causes intermittent hypoxia and sleep fragmentation which results in an impairment of obesity and type 2 diabetes mellitus (T2DM) that in turn can induce or worsen OSA through direct weight-dependent and indirect weight-dependent mechanisms. Increased mechanical load and narrowed airway are the principal direct weight-dependent mechanisms, and they are directly associated with the accumulation of adipose tissue. The indirect weight-dependent mechanisms, such as hyperglycemia, hyperinsulinemia, and leptin resistance, are metabolic and hormonal alterations very common in obesity and T2DM that can contribute to the pathogenesis of OSA.

stimulation of insulin secretion and inhibition of glucagon secretion by the pancreas, slowing of gastric emptying, increase in the sense of satiety, and reduction of appetite, acting directly on the centers of regulation of hunger in the central nervous system [74]. In the SCALE sleep apnea, a double-blind randomized clinical trial, obese subjects with moderate or severe OSA were randomized for 32 weeks to liraglutide 3.0 mg or placebo, both following a diet (500 kcal day−deficit) and lifestyle recommendations [75•]. This study showed a reduction of AHI greater with liraglutide than with the placebo, in addition to a greater percentage reduction in weight. The ameliorative effect of the drug on OSA could depend both on the greater weight loss of the treated group and on the direct metabolic effects of liraglutide, as the reduction of hyperglycemia. In the field of bariatric surgery, it has been reported that patients undergoing a Roux-en-Y Gastric Bypass (RYGB) showed a significant improvement in excessive daytime sleepiness (EDS) as scored by the Epworth Sleepiness Scale, already in the first month after the surgery, therefore before a satisfactory weight loss was achieved [76].

Furthermore, bariatric surgery interventions have a different impact on glucose metabolism to such an extent that the RYGB and vertical sleeve gastrectomy (VLS) are defined as metabolic surgery procedures unlike the laparoscopic adjustable gastric band (LAGB) [77•]. It is possible to summarize these metabolic effects as the acronym BRAVE: bile flow alteration, restriction of gastric size, anatomical gut rearrangement and altered flow of nutrients, vagal manipulation, and enteric gut hormone modulation [78]. In the LAGB, there is an improvement in glycemic metabolism parallel to weight loss, while in the other procedures, there are mechanisms independent of weight that make this improvement occurring earlier [77•, 79]. Two studies evaluated the percentage of OSA remission 1 year after bariatric surgery: in the first case, it is of 62% after the VSG, of 38% after the LAGB, and of 66% after the RYGB, and also in the second, study overlapping percentages of 66% after RYGB, 57% after VSG, and 29% after LAGB have been found [80, 81], concluding that the remission rate after VSG and RYGB is comparable and approximately the double of LAGB. Furthermore, it has been shown that the LAGB, although achieving a greater weight loss than the diet, did not have a better effect on OSA [82]. So, it would probably seem that OSA improves more after metabolic surgery or diet than with LAGB, supporting the hypothesis of the importance of "indirect weight-dependent" effects on respiratory disorders. A recent study also showed a correlation between OSA, obesity, and systemic inflammation, showing that soluble TNF-alpha receptor 2 is the biomarker best correlated with OSA [83]. Because malabsorptive bariatric techniques reduce the main biomarkers of inflammation, this could help to create an anti-inflammatory state that is also protective for sleep disorders [83]. Looking at the link between OSA, glycemic derangements, and T2DM, we could hypothesize that the first-line treatment of OSA syndrome, i.e., continuous positive airway pressure (CPAP), could result in an improvement of glycemic control. However, the evidence currently available is not all in favor of this hypothesis.

Some studies have shown an improvement in insulin sensitivity and glycemic derangements after CPAP in obese patients with severe OSA [47•, 84•]. On the contrary, other studies after treatment with CPAP of at least 3 months failed to demonstrate an improvement in glycemic control and insulin sensitivity evaluated using HbA1c, HOMA index, and hyperinsulinemic–euglycemic clamp, respectively [48, 49, 85, 86].These conflicting results could be due to poor adherence to the use of CPAP, a treatment with well-known poor compliance by patients, or the duration of treatment. In fact, one study showed an improvement in insulin sensitivity after 24 weeks, but not after 12 weeks [50]. Maybe the CPAP could have an effect in prediabetes but not in the overt diabetes, as suggested by a study in which CPAP treatment improved glycemic variability in non-diabetic, but not in diabetic subjects and by a meta-analysis according to which this therapy could prevent the incidence of T2DM in non-diabetic subjects [9••, 87••].

Regarding the effect of hypoglycemic therapy on OSA, unfortunately, the data are still insufficient; however, preclinical studies in non-obese rats have shown that sleep apnea is induced by high-fat diet and prevented and reversed by metformin, independently from weight, probably thanks to its insulin sensitizing effect due to the increased number and affinity of insulin receptors, thus decrease circulating insulin concentrations [88]. In another study, the administration of metformin to adolescent girls with polycystic ovarian syndrome (PCOS) resulted in significant decrease in sleep disturbances scale, and Epworth Sleepiness Scale compared with the untreated PCOS group [89]. In two Japanese studies, the administration of sodium glucose cotransporter 2 inhibitors (SGLT2i) to obese diabetic subjects demonstrated an improvement in the oxygen desaturation index of 3% in case of moderate or severe disease [90••], and a reduction in AHI, respectively [91••]. Although the clinical improvement reported in these studies may depend on a significant reduction in BMI, it cannot be excluded that it depends on the effect of these antidiabetic drugs on glycemic control and insulin resistance, according to those mechanisms previously discussed. About melatonin treatment, there is not sufficient consensus regarding its use in patients with OSA and T2DM. In fact, if on the one hand, the serum levels of melatonin in subjects with OSA are lower than normal and supplementation with melatonin has been associated with an improvement in insulin resistance, inflammation, and oxidative stress in an animal model [92, 93], on the other hand, it has been shown that melatonin can worsen insulin secretion [94•]. Therefore, the use of this hormone in diabetic patients certainly needs further investigation.

Conclusions

In light of these evidences, we could conclude that OSA, obesity, and disturbed glucose homeostasis are connected with each other. OSA causes episodes of IH that can lead to an increase in insulin resistance, sympathetic tone, and systemic inflammation, all of which underlie the development and maintenance of diabetes. At the same time, both hyperglycemia and diabetic neuropathy can make the carotid body less sensitive to hypoxic stimulation, promoting OSA. Although there is still no sufficient evidence to recommend the use of anti-obesity or antidiabetic drugs as a first-line treatment for OSA, an adequate control of body weight, healthy eating habits, and regular physical activity are recommended along with standard treatment of OSA, as well as the treatment of OSA is suggested in subjects with obesity, mostly in diabetic ones, in order to improve glucose metabolism.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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