REVIEW ARTICLE

Association of OSA and Type 2 Diabetes Mellitus

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Abstract

The recent epidemiological studies have shown that the obstructive sleep apnea (OSA) and type 2 diabetes mellitus are independently associated. There exist real and potential links between the risk factors for and comorbidities associated with diabetes and sleep apnea. There is a common occurrence of obesity, hypertension and disorders of metabolism in the two disorders. While the occurrence of sleep apnea with glucose intolerance or insulin resistance could present sampling bias, an alternative hypothesis is that the events in OSA trigger different, perhaps unique, adaptations in metabolic processes involving insulin action and glucose regulation. Impaired glucose tolerance and worsening insulin resistance can lead to further weight gain, exacerbating the severity of disordered breathing during sleep. This review aimed to define the extent and potential mechanisms for alterations in insulin and glucose levels in OSA.

Introduction

The associations between obstructive sleep apnea (OSA) and diabetes are widely accepted, establishing them both to be closely related diseases. Obesity is usually a common factor for both the conditions, but there is also evidence for a potential independent association between OSA and diabetes. It is also recognized that many subjects with OSA have features of metabolic syndrome characterized by hyperinsulinemia, glucose intolerance, dyslipidemia, central obesity and hypertension. Both the sleep disruption and intermittent hypoxia, which occur with OSA, can influence glucose metabolism. However, the relationship between insulin resistance and OSA has continued to be a controversy. Mostly, only data from observational interventions with small sample size exist on OSA and insulin resistance. The data on independent influence of OSA on insulin resistance are increasing; yet, the goal is far from reaching. Our aim is to review data on whether these two disorders are causally associated.

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Association of OSA and Diabetes

Some clinical studies[1–6] comprising few number of patients have produced conflicting results, whereas, recently, an independent association between OSA and insulin resistance in adults has been established by many studies. Lam et al.[7] reported that subjects, in a community-based cohort with OSA, defined as an apnea–hypopnea index (AHI) of ≥5 had a fivefold risk of having the metabolic syndrome. They also found an increasing association with the metabolic syndrome as the severity of OSA increased. Gruber et al.[8] found that patients with OSA were about six times more likely to have metabolic syndrome than patients without OSA, adjusted for body mass index (BMI), smoking and age.

In a group of 50 healthy subjects of whom one-third showed an AHI > 10, no correlation was identified between insulin resistance and sleep-disordered breathing after adjusting for BMI[9]. On the other hand, in a study[10] involving 261 men, those with BMI > 29 showed indications for an independent relationship between sleep apnea and fasting insulin levels. In a study by Vgontzas et al.[11], women with polycystic ovary syndrome were compared with premenopausal controls. The insulin resistance was shown to have a stronger association with sleep-disordered breathing than with BMI or testosterone, supporting a close independent link between insulin resistance and OSA in these subjects. In an observational Indian study[12], a total of 325 patients with type 2 diabetes mellitus (T2DM) were screened with Berlin Questionnaire, amongst whom 16.3% patients belonged to high-risk group and 9.9% to the low-risk group of OSA. The prevalence of OSA was found to be 24.3%. There were significant differences in arousal index, oxygen desaturation index, minimum oxygen saturation, respiratory disturbance index (RDI) and BMI between the patients with T2DM in high-risk and low-risk groups and OSA. An increased level of HbA1C alone was found to be associated with increased severity of OSA with a positive and significant correlation between HbA1C and various sleep parameters such as RDI, ODI and minimum oxygen saturation. About 21.9% variation in RDI was contributed by HbA1C alone. A very recent large cross-sectional analysis of 6,616 participants in the European Sleep Apnea Cohort (ESADA) study[13] revealed that T2DM prevalence increased with OSA severity, from 6.6% in subjects without OSA to 28.9% in those with severe OSA. Patients with mild, moderate or severe disease revealed an odds ratio (OR) [95% confidence interval (CI)] of 1.33 (1.04–1.72), 1.73 (1.33–2.25) and 1.87 (1.45–2.42) ($P < 0.001$), respectively, for prevalent T2DM. Patients with diabetes and more severe OSA showed bad glucose control, with 0.72% higher levels of adjusted mean HbA1c in patients with severe OSA than in those without sleep-disordered breathing (analysis of covariance, $P < 0.001$). This recent study with a very large cohort concluded that increasing OSA severity is related to elevated probability of concomitant T2DM and worse diabetic control in patients with T2DM.

Effect of Obesity

Obesity is the main confounding factor in the analysis of insulin resistance in OSA. Consistently, insulin resistance has been linked to AHI and minimum oxygen saturation as independent factors; however, obesity has more effects than these two factors. In the HOMA regression models, only BMI, waist circumference and minimum oxygen saturation were significant determinants of insulin resistance[14]. In a study[1], it has been reported that the effect of OSA on insulin resistance was seen only in obese subjects but not in non-obese subjects. OSA is associated with an increased nocturnal sympathetic output[15], which also increases circulating free fatty acid via stimulation of lipolysis promoting insulin resistance[16]. A major problem with epidemiological studies of the relationship between OSA, diabetes and metabolic syndrome is taking into account the impact of visceral adiposity, which is poorly measured by BMI. Premenopausal women were found to be more insulin sensitive then men because women have less visceral fat despite a higher total body fat mass, whereas postmenopausal women have insulin sensitivity similar to men[17]. A study[6] indicated that mean plasma insulin levels in 14 subjects with OSA and visceral obesity were significantly higher than BMI-matched controls with no OSA. These data indicate that the obesity, particularly with a visceral distribution, plays a significant role when OSA and diabetes are associated.

Effect of AHI

The Wisconsin Sleep Cohort in a cross-sectional study[18] found that self-reported diabetes was three to four times more prevalent in subjects with an AHI of 15 or greater than in those with an AHI of less than 5. Even controlling of shared risk factors such as body habitus did not have any effect on the independent relationship. However, a statistically significant independent causative outcome in the development of T2DM was not established in the prospective analysis. In a recently published Canadian study[19], during a median follow-up of 67 months, of the 8,678 patients, 1,017 (11.7%) of them developed diabetes, which resulted in a cumulative incidence at 5 years of 9.1% (95% CI, 8.4–9.8%). In fully adjusted models, patients with AHI more than 30 showed a 30% greater danger of developing diabetes than those with AHI less than 5. AHI in rapid eye movement sleep and time consumed with oxygen saturation lower than 90% were related to incident diabetes among all the other OSA-related variables. This large study concluded that, amongst people with OSA, with multiple confounders being controlled, early OSA severity and the consequent

physiological issues proposed subsequent risk for incident diabetes.

Effect of Hypoxia

Presently existing data propose that hypoxia plays an important role in the development of metabolic dysfunction. Cyclical hypoxia might result in intolerance to glucose and resistance to insulin by stimulating the release of proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor-a. Two clinic-based studies[20,21] have shown that plasma levels of interleukin-6 and tumor necrosis factor-a are higher in patients with sleep-disordered breathing than in control subjects. Interleukin-6 is correlated with indices of insulin resistance, and higher levels are associated with an increased risk of T2DM[22–24]. Recent data also indicate that tumor necrosis factor-a has a potential role in the development of insulin resistance[25–28]. Nonetheless, more insights are still needed on the mechanisms by which these cytokines stimulate metabolic dysfunction; however, in part, an inflammatory response to mediate glucose intolerance and insulin resistance has been increasingly accepted. The importance of hypoxia in the pathogenesis of metabolic dysfunction is further evident in animal studies[29–31] that illustrated an increase in insulin levels with exposure to hypoxic conditions.

Effect of Arousals

No data exist on the outcomes of repeated arousals on metabolic function. Glucose intolerance is shown to be induced by partial sleep deprivation that was established experimentally, in normal, healthy men[32]. The Nurses' Health Study[33] supported the hypothesis that sleep loss may lead to T2DM. However, it is yet to be known whether the secondary sleep loss found to occur in sleep-disordered breathing owing to repeated arousals produce a similar effect on metabolic function. Some authors[34–38] speculate that, in patients with OSA, the elevated resistance to insulin is partly mediated by a higher sympathetic activity, which occurs owing to numerous nocturnal micro-arousals and nocturnal hypoxemia.

Neural and Hormonal Effects

Numerous studies[39–42] have shown that patients with sleep-disordered breathing exhibit elevated levels of sympathetic neural traffic. Sympathetic hyperactivity elevates glycogen breakdown and gluconeogenesis, thereby affecting glucose homeostasis. In addition, inclination to metabolic dysfunction can also result because of the influences of sleep-disordered breathing imposed on the hypothalamic-pituitary-adrenal axis. Experimentally induced incomplete or complete sleep deprivation has been established to elevate plasma cortisol levels on the following evening at a time when the circadian rhythm of the hypothalamic–pituitary–adrenal axis is at its nadir[43]. Repetitive apneas are followed by release of catecholamines, which cause hyperinsulinemia by stimulating glycogenolysis, gluconeogenesis and glucagon secretion. The elevated cortisol levels may lead to glucose intolerance, insulin resistance and hyperinsulinemia[44,45]. High circulating insulin concentrations in insulin-resistant patients may initiate tissue-specific growth effects through interactions with insulin-like growth factor receptor-effector systems[46]. These findings suggest a hormonal mechanism caused by repeated arousal and hypoxemia for an association between OSA and insulin sensitivity.

Effect of Continuous Positive Airway Pressure Treatment on Diabetes

There is conflicting evidence on the effects of continuous positive airway pressure (CPAP) treatment on insulin sensitivity. An uncontrolled study[47] with 40 patients found that insulin resistance improved with CPAP; however, this study was confined to lean patients with a BMI of <30 kg/m^2. Babu et al.[48] used a continuous glucose monitoring system and showed a decrease in postprandial blood glucose after 30–90 days of CPAP treatment. They also noted a decrease in HbA1c in those with a baseline level >7% (53 mmol/L) and that the decrease in HbA1c correlated with days on CPAP if compliance was more than 4 hours. In a randomized-controlled trial (RCT) of CPAP treatment on insulin sensitivity in Chinese male patients with OSA, Lam et al.[7] noted a decrease in HbA1c with CPAP, but only for those with a BMI $\geq$ 25 kg/m^2. On the other hand, a double-blind RCT of therapeutic and placebo CPAP for 3 months in men with T2DM and OSA found no significant improvement in HbA1c or insulin resistance measured by euglycemic clamp and HOMA. This study[48] was, however, carried out in patients with relatively good blood glucose control, which may have masked any effects of CPAP. Another trial of CPAP versus sham-CPAP on metabolic syndrome found that CPAP was associated with a non-significant 7.3%

improvement in impaired glucose tolerance[49]. Two studies[50,51] reported decrease in leptin, an adipocyte-derived hormone, with noteworthy functions in the behavior of appetite and energy homeostasis during CPAP treatment even without connected weight loss. But, in another report[52] on leptin and visceral fat in OSA, no significant change was seen in insulin levels in 12 subjects treated with CPAP. Another study[53] demonstrated that effective CPAP treatment quickly progresses insulin sensitivity in patients with OSA. Nevertheless, this study also showed that the less obese the patients are, the greater is the improvement in insulin sensitivity brought about by CPAP treatment. Similar results were shown in a study by Ip et al.[54]. It is clear that there is considerable disagreement among studies on the effects of CPAP treatment on glycemic control because of different patient population groups, sample size and control groups. Most studies have been uncontrolled or have had inadequate control of confounding factors. Differing techniques have been used to assess glucose metabolism. In addition, all the studies did not comment on CPAP adherence. Therefore, there is a need for longer-term, well-designed, large-scale RCTs to determine whether sustained treatment of sleep-disordered breathing with CPAP reverses the associated metabolic disturbance.

Conclusion

There is a major challenge to address the rise in both diabetes and OSA; recent data do suggest there is an independent association between the two. OSA establishes mechanisms of pathophysiology, which may possibly contribute to the insulin resistance development, including autonomic activation, modifications in neuroendocrine function, direct effects of hypoxemia on glucose regulation and release of proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-a. Because of these interactions, the International Diabetes Federation recommends that health professionals must look for the possibility of OSA when a patient presents with T2DM[55]. The Federation also recommends to conduct more epidemiological studies to determine prevalence of OSA with T2DM in different ethnic groups. There is also a need to find out association between OSA and gestational diabetes and preeclampsia. Another area of research could be in children with metabolic syndrome. More studies are still needed on the effects of OSA on insulin secretion, insulin resistance, mitochondrial function and inflammatory markers and complications of T2DM. The way forward is through collaboration between health-care service providers and researchers across all levels of care.

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