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Obstructive Sleep Apnea and Glucose Metabolism Disorders

Lu-lu Li, Qiang Zhang*, Jin Tan* and Yun-yun Fang[1]

[1]Tianjin Medical University, *Institute of Geriatrics,
Tianjin Medical University General Hospital, Tianjin, China.

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Obstructive sleep apnea (OSA) is characterized by repetitive upper airway closures or partial collapses that occur during sleep. Evidence from well-defined studies has shown that OSA is associated with increased incidence of diabetes. In this article, we will review the current evidence that links OSA to glucose metabolism disorders, discuss the potential mechanisms by which OSA may contribute to the development of glucose metabolism disorders, and summarize briefly the studies on the impact of treatment of OSA on glucose metabolism.

Key words: Obstructive Sleep Apnea, glucose metabolism disorders, type 2 diabetics, CPAP, sympathetic nervous system activity, sleep fragmentation, oxidative stress, Inflammatory mediators.

OSA is a common and treatable form of sleep disordered breathing. Current epidemiological studies supports an association between OSA and glucose metabolism disorders, such as glucose intolerance, insulin resistance, and the risk of type 2 diabetes, independent of other risk factors. Evidence from models that mimic OSA supports a potential role for OSA in glucose metabolism disorders. The possible mechanisms between OSA and glucose metabolism disorders seem to be multiple. More randomized and prospective clinical trials are still needed to examine the hypothesis that efficient treatment of OSA may influence the development of type 2 diabetes, even reduce its severity. In this report, we review epidemiologic and experiment data suggesting that OSA is involved in the pathogenesis of glucose metabolism disorders.

* To whom all correspondence should be addressed.
E-mail: zhangqiangyulv@yahoo.com.cn

Prevalence

To date, studies including a large number of 2 diabetic patients have reported an alarming prevalence of OSA. The highest estimate was 86%[1], reported in 306 participants enrolled in the Sleep AHEAD study, a multi-center ancillary study of the Look AHEAD trial. One of the study investigators in two years from the Primary Care and Endocrinology Clinics at the University of Chicago reported that a total of 77% of patients with diabetes had OSA[2].

There are also several evidence demonstrating a significant prevalence of diabetes in patients with OSA. One study[3] investigating 2149 patients with OSA at either the Foothills Medical Centre or private respiratory care companies within the Calgary Health Region reported that 738 (34.3%) patients had mild OSA, 443 (20.6%) had moderate OSA and 536 (24.9%) had severe OSA. The overall prevalence of DM was 8.1%, which increased as OSA severity increased. Moreover, another observational cohort study[4] have also found a significant dose-response relationship between the severity of OSA and the prevalence of diabetes[4].

These studies suggests that type 2 diabetes is very pervasive among patients with OSA. and this association appears to be independent of other risk factors. However, more evidences are needed to clarify that OSA represents an independent risk for the development of diabetes.

Correlation between OSA and glucose metabolism

A large number of experimental studies have shown that there is significant correlation between OSA and glucose metabolism. Some treatments that reducing the severity of OSA may be an important method of treatment to optimize glucose control.

In a recent study, Aronsohn[2] performed full-night PSG and measured hemoglobin A1c (HbA1c) levels in 60 patients with physician-diagnosed diabetes. The author found that increasing severity of OSA was associated with poorer glucose control, after controlling for age, sex, race, BMI, number of diabetes medications, years of diabetes and total sleep time. Compared to patients without OSA, the adjusted mean HbA1c was increased by 1.49% in patients with mild OSA, 1.93% in patients with moderate OSA, and 3.69% in patients with severe OSA.

Botros[4] examined 544 OSA participants without preexisting diabetes in an observational cohort study. The incident diabetes was defined as fasting glucose level > 126 mg/dL and a physician diagnosis, CPAP was also examined. The result found that sleep apnea increases the risk of developing diabetes, independent of other risk factors. Among patients with more severe sleep apnea, regular positive airway pressure use may attenuate this risk.

Lecube[5] performed examinations in obese patients through a cross-sectional case-control study, including a pulmonary function testing and oxygen saturation (the percentage of time spent at saturation below 90% (CT90)). The author found that in diabetic patients, a significantly increase in the CT90 was detected, residual volume (RV) was significantly higher in T2DM. The result showed that T2DM adversely affects breathing during sleep, becoming an independent risk factor for the hypoxemia in obese patients.

Treatment with CPAP on diabetes has been evaluated in many studies, but results were conflicting. Wei[6] studied 23 patients with OSA and type 2 diabetes (OWD) to assess the effects of short-term CPAP on un-treatment hour glucose control via a continuous glucose monitoring system (CGMS). CGMS was applied for 2 days before and 4 days during CPAP treatment. Insulin resistance was assessed with fasting plasma blood glucose (FPG), plasma insulin (FINS) and homeostatic model assessment of insulin resistance index (HOMA-IR). The result showed that treatment and un-treatment hour glucose level were decreased, insulin sensitivity was increased after CPAP treatment. In addition, HOMA-IR was also decreased significantly.

However, a pilot crossover study evaluated 13 diabetic patients, with mean Hba1c 5.8%, known to have OSA, who were initially randomized to either CPAP or no therapy for 4 weeks. The result demonstrated that there was no significant improvement in HbA1c in the CPAP group compared to no therapy[7].

These inconsistent findings can be related to differences in sample size, treatment duration, population recruited, adherence to CPAP and the primary endpoints assessed. Thus more studies still need to be carried out.

Mechanisms of glucose metabolism disorders by OSA

OSA is intrinsically associated with chronic intermittent hypoxia and sleep disorders, both of which could potentially be detrimental to glucose metabolism via intermediate mechanisms including sympathetic nervous system, sleep fragmentation, oxidative stress and inflammatory mediators.

Increase of sympathetic nervous system activity

Intermittent hypoxia, such as occurs in OSA, induces increase of sympathetic nervous system activity , which is associated with altered glucose metabolism.

Tamisier[8] assessed muscle sympathetic nerve activity (MSNA) in 12 healthy subjects before and after 2 weeks of intermittent hypoxia exposure. The author found that MSNA increased across the exposure, which could conclude that intermittent hypoxia causes an increase in sympathetic activity.

González-Martín[9] used male rats model of intermittent hypoxia to evaluate plasma catecholamines. The result found that plasma epinephrine (E) and norepinephrine (NE) levels

showed a tendency to increase. The results showed that sympathoactivation and a concomitant increase in NE levels were very likely be induced by intermittent hypoxia, Licht[10] examined through a prospective cohort study the relationship between the autonomic nervous system and the metabolic syndrome by measuring preejection period (PEP; high PEP reflecting low sympathetic activity). The study showed that PEP were independently negatively associated with the presence of the metabolic syndrome. This research suggested that increased sympathetic activity is associated with metabolic syndrome.

Thus, we can clarify that sympathetic nervous system is probably a putative mediator in the mechanisms of glucose metabolism disorders by OSA.

Sleep fragmentation

The current studies showed that sleep fragmentation leads to changes in glucose metabolism, which when experienced repeatedly may increase the risk for type 2 diabetes.

Reynolds[11] studied the impact of short term sleep restriction on glucose metabolism, by examining glucose, insulin, adrenocorticotropic hormone (ACTH), cortisol. The author found that glucose, insulin and cortisol were increased, and there were no significant changes in ACTH. The result showed that sleep fragmentation impaired glucose metabolism, and this was associated with an increase in afternoon cortisol, without significant changes in ACTH, suggesting enhanced adrenal reactivity.

Stamatakis[12] studied the impact of experimental sleep fragmentation across all sleep stages on alter glucose metabolism in 11 healthy, normal volunteers. By examining sensitivity decreased(SI) and glucose effectiveness(SG) after two nights, the results showed that SI decreased, SG which is the ability of glucose to mobilize itself independent of an insulin response, also decreased. This study illustrated that sleep fragmentation led to changes in glucose metabolism.

Some studies also showed that increase of sympathetic nervous system activity could be a postulated intermediate mechanism for the effect of sleep fragmentation on development of glucose metabolism[13,14]. In addition, because the prevalence of OSA is extremely high in patients with diabetes, effective treatment for OSA and sufficient sleep duration, which improve sleep fragmentation might ameliorate glucose metabolism[15].

Mechanisms of oxidative stress

Studies have investigated that increased oxidative stress induced by intermittent hypoxia is also associated with altered glucose metabolism, and secundum oxidative stress in OSA was likely independently correlated with insulin resistance[16]. Louis[17] characterized the acute effects of intermittent hypoxia on glucose metabolism. Compared with the normoxia condition, intermittent hypoxia was associated with a decrease in sensitivity decreased (SI) and glucose effectiveness (SG). The result showed that short-term episodic hypoxia inducing increased oxidative stress altered glucose disposal by decreasing insulin sensitivity and glucose effectiveness.

Vatansever[18] measured oxidative stress markers (MDA and protein carbonyl concentrations) and serum adiponectin (an adipokine with insulin-sensitizing) in OSA patients and controls. The author found that serum adiponectin were decreased and oxidative stress markers were significantly elevated in OSA patients. Adiponectin levels were negatively correlated with MDA levels. The result indicated that the recurrent hypoxia-reoxygenation attacks in OSA patients may activate oxidative stress and leading to low levels of adiponectin, and induces insulin resistance.

Thus, we conjecture that intermittent hypoxemia by inducing increased oxidative stress lead to changes in glucose metabolism, which maybe a central mechanism responsible for metabolic dysfunction in OSA.

Mechanisms of inflammatory

Another possible mechanism that may participate in the association between OSA and glucose metabolism disorders is upregulation of inflammatory mediators.

Deboer[19] evaluated the level of inflammatory mediators in 23 children with OSA in a sleep study and tested C-reactive protein (hsCRP), fasting insulin and glucose levels calculated by the homeostasis model of insulin resistance (HOMA-IR). The result showed that hsCRP values were correlated with HOMA-IR, this meaned that degree of glucose metabolism disorders may be an necessary determinant of increased systemic inflammation.

Pallayova[20] studied 45 severely obese adults by testing fasting serum glucose, insulin, selected cytokines, and calculating homeostasis model assessment estimates of insulin sensitivity (HOMA-IS) and pancreatic beta-cell function (HOMA-B). The result showed that OSA severity was associated with significantly increased HOMA-B (a trend towards decreased HOMA-IS), OSA -related oxyhemoglobin desaturations correlated with TNF-α and IL-6. This study suggested that OSA are associated with specific cytokine stressors, which reflected links between sleep apnea and glucose metabolism.

In addition, some researches also showed that sleep deprivation affects adipokines - increasing tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) and decreasing leptin and adiponectin. This could lead to a chronic sub-inflammatory state that could play an important role in the development of glucose metabolism disorders[21].

At present, the exact mechanisms of glucose metabolism disorders by OSA was still unintelligible. Sleep fragmentation and increased oxidative stress induced by intermittent hypoxemia maybe the central parts between metabolic dysfunction and OSA, increase of sympathetic nervous system activity and upregulation of inflammatory mediators could be an intermediate mechanism. However, further studies are still very necessary to investigate the causal role of OSA in glucose metabolism disorders.

CONCLUSION

Review of the current research data suggest that OSA is independently associated with altered glucose metabolism. The available evidence also suggests that CPAP has inconsistent effect on the metabolic status of OSA subjects, large prospective studies are still needed. Intermittent hypoxia and sleep disorders in OSA could potentially be adverse to glucose metabolism via intermediate mechanisms, such as activations of sympathetic nervous system, sleep fragmentation, oxidative stress and inflammatory mediators. However, clinical and translational research is urgently needed in this field.

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