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Obstructive Sleep Apnea and Abnormal Glucose Metabolism

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Obstructive sleep apnea (OSA) is a chronic disorder that is prevalent, especially in subjects with obesity or diabetes. OSA is related to several metabolic abnormalities, including diabetes, insulin resistance, hypertension, and cardiovascular diseases. Although Koreans are less obese than Caucasians, the prevalence of OSA is comparable in both groups. Thus, the impact of OSA on metabolism may be similar. Many epidemiologic and experimental studies have demonstrated that OSA is associated with glucose intolerance and insulin resistance via intermittent hypoxia, sleep fragmentation, and sleep deprivation. The effect of continuous positive airway pressure treatment on glucose metabolism is still controversial. Randomized controlled trials are needed to evaluate the ability of OSA treatment to reduce the risk of diabetes and insulin resistance in subjects without diabetes and to ameliorate glucose control in patients with diabetes.

Keywords: Diabetes mellitus; Glucose intolerance; Glucose metabolism; Insulin resistance; Sleep apnea, obstructive

INTRODUCTION

Obstructive sleep apnea (OSA) is a chronic sleep disorder. Its prevalence is 24% of adult men and 9% of adult women in the U.S. [1] and 27% and 16% of middle-aged Korean men and women, respectively [2]. OSA prevalence appears to increase steadily with advancing age, and men are at 2- to 3-fold greater risk for OSA compared to women [3]. OSA is recognized as an independent risk factor for cardiovascular disease [4], such as stroke [5] and coronary heart disease [6]. In addition, there has been growing evidence that OSA is independently associated with insulin resistance, glucose intolerance, and type 2 diabetes [7]. In this article, we will review the current evidence that links OSA to diabetes and the possible mechanisms underlying the association. Also, we will describe the effect of OSA treatment on glucose metabolism.

DEFINITION AND DIAGNOSIS OF OSA

OSA is characterized by recurrent episodes of apnea or hypopnea due to total or partial pharyngeal collapse and temporary upper airway obstruction during sleep, resulting in repeated episodes of hypoxemia and hypercapnea. Frequent arousal ensures pharynx opening and restores airflow but fragments sleep and changes its quality. OSA associated with excessive daytime sleepiness is referred to as the OSA syndrome.

The gold standard for the diagnosis of OSA is still polysomnography (PSG) performed in a sleep laboratory. PSG monitors many physiologic functions during sleep, such as electroencephalography, eye movements, muscle tone, airflow, and oxygen saturation during sleep. An apnea is defined as the complete cessation of airflow for a minimum of 10 seconds. Hypopnea is defined as a reduction in airflow that is associated with an arousal or oxygen desaturation of at least 3% or 4%

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[8]. OSA is diagnosed when the apnea-hypopnea index (AHI) is greater than five. The severity of OSA is graded as mild (AHI <15), moderate (15≤AHI<30), or severe (AHI ≥30). Recent guidelines recommend the use of an unattended portable home monitoring system as an alternative to laboratory-based PSG for the diagnosis of OSA in selected patients with a high pretest probability of moderate to severe OSA [9].

PREVALENCE OF OSA IN TYPE 2 DIABETES

The reported prevalence of OSA in patients with diabetes varies from 58% to 86% depending on different study populations and different criteria for OSA [10-13]. If the prevalence of OSA in diabetic subjects is comparable in Korea, among the 3.5 million diabetic patients [14], about 2 to 3 million diabetic patients might suffer from OSA in Korea.

PREVALENCE AND INCIDENCE OF TYPE 2 DIABETES IN OSA

Epidemiological studies have suggested a link between OSA severity and the risk of type 2 diabetes, independent of obesity [14,15]; however, the majority of these studies were cross-sectional. Furthermore, OSA severity in these studies was not always assessed by PSG; instead, some studies used snoring as a marker of OSA [16]. There were a few prospective studies that evaluated OSA as a risk factor for diabetes. In the Wisconsin Sleep Cohort Study, 1,387 participants were followed-up for 4 years. OSA was not an independent risk factor for diabetes after adjusting for age, sex, and body habitus [17]. Botros et al. [18], on the other hand, demonstrated that the presence of OSA increased the risk for incident diabetes by 43% during 2.7-year follow-up after adjusting for age, sex, body mass index, and fasting glucose. Although there is a lot of evidence showing the association between OSA and type 2 diabetes, more prospective studies are needed to determine if OSA is s risk factor for diabetes independent of the shared risk factors.

OSA ASSOCIATED WITH GLUCOSE INTOLERANCE AND INSULIN RESISTANCE

Many population and clinic-based cross-sectional studies have found that OSA is associated with glucose intolerance and insulin resistance. In 2,656 subjects participating the Sleep Heart Health Study, sleep-disordered breathing and sleep-related hypoxemia were independently associated with glucose intolerance and homeostasis model assessment of insulin resistance (HOMA-IR) [14]. Among patients without diabetes, OSA was related to impairments in insulin sensitivity, glucose effectiveness, and pancreatic β-cell function, which were measured by frequently sampled intravenous glucose tolerance tests [19]. Recently, Priou et al. [20] showed that increasing OSA severity was independently associated with higher HbA1c. Furthermore, deterioration in HOMA-IR was significantly related to all variables of baseline OSA in a more than 10-year follow-up study, which clarified the causal relationship between OSA and insulin resistance [21]. Because most of these studies were conducted in Caucasians, the clinical importance of OSA in Koreans has not yet been explored. Given that OSA's association with impaired fasting glucose and impaired glucose tolerance was similar in non-overweight and overweight individuals [22], the impact of OSA on glucose metabolism might be similar in Koreans, who are less obese than Caucasians.

MECHANISMS LINKING OSA WITH GLUCOSE INTOLERANCE AND INSULIN RESISTANCE

Intermittent hypoxia and sleep deprivation are the well-known mechanisms linking OSA and altered glucose metabolism, and abundant experimental and epidemiologic data supports this understanding. In animal studies, intermittent hypoxia caused acute insulin resistance in lean, healthy mice [23]. This was also demonstrated in human studies. Intermittent hypoxia or normoxia for 5 hours during wakefulness decreased insulin sensitivity measured by intravenous glucose tolerance test in healthy human volunteers [24]. Furthermore, in 4,400 middle-aged Japanese participants, nocturnal intermittent hypoxia was proven to be a risk factor for the development of type 2 diabetes after a 3-year median follow-up period [25]. Increased oxidative stress, increased lipid peroxidation, and upregulation of nuclear factor-κB and hypoxia-inducible factor-1 are probably the main mechanisms of insulin resistance induced by hypoxia [26].

The other important aspects of OSA are sleep fragmentation and sleep loss. Even in the absence of breathing disorders, these sleep disturbances have affected glucose tolerance in several epidemiologic studies [16,27]. In laboratory studies of healthy young adults submitted to recurrent partial sleep restriction, marked alterations in glucose metabolism including decreased

glucose tolerance and insulin sensitivity have been demonstrated [28]. Sleep restriction also increased sympathetic nervous system activity [29] and changed the neuroendocrine regulation of leptin and ghrelin concentration [28], which control appetite. Furthermore, an experimental study in humans demonstrated that all-night selective suppression of slow-wave sleep, without any changes in total sleep time, resulted in marked decreases in insulin sensitivity [27]. This study suggests that reduced sleep quality with low levels of slow wave sleep may contribute to increased risk of type 2 diabetes.

EFFECT OF CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) TREATMENT ON GLUCOSE METABOLISM

There are conflicting reports on the effects of CPAP treatment on OSA. Most of the studies addressing this question are not randomized controlled trials. There are, however, a few randomized in both diabetic and non-diabetic subjects. West et al. [30] showed that 3 months of CPAP treatment did not significantly improve measures of glycemic control or insulin resistance in men with type 2 diabetes. CPAP use in that study was only 3.3 hours per night. In contrast, improvement in HbA1c and postprandial glucose level was observed in another study, where the subjects used CPAP for 4.2 hours per night [31]. This discrepancy suggests that sufficient CPAP treatment time is necessary to obtain a favorable metabolic effect. In a recent double-blind, placebo-controlled, cross-over trial in 86 participants, most of whom had metabolic syndrome, 3 months of CPAP treatment improved blood pressure, lipid profile, and HbA1c but had no effect on glucose, insulin concentrations, and insulin resistance [32]. Although their results are confusing, change in HbA1c may better reflect the effect of CPAP on glucose metabolism due to the day-to-day variation of glucose and insulin concentration.

In summary, the findings from studies of CPAP treatment are inconsistent. Differences in study population, study duration, sample size, treatment adherence, and possibility of changes in body composition may explain these discrepancies. More randomized studies on CPAP treatment with larger sample sizes are needed to evaluate the cause-effect relationship of OSA and abnormal glucose metabolism.

CONCLUSION

OSA is a chronic disorder that is especially prevalent in subjects with obesity or diabetes. OSA is related to several metabolic abnormalities, including diabetes, insulin resistance, hypertension, and cardiovascular diseases. Although Koreans are less obese than Caucasians, the prevalence of OSA is comparable in both groups. Thus, the impact of OSA on metabolism may be similar. Many epidemiologic and experimental studies have demonstrated that OSA is associated with glucose intolerance and insulin resistance via intermittent hypoxia, sleep fragmentation, and sleep deprivation. The effect of CPAP treatment on glucose metabolism is still controversial. Randomized controlled trials are needed to evaluate the ability of OSA treatment to reduce the risk of diabetes and insulin resistance in subjects without diabetes and to ameliorate glucose control in patients with diabetes.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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