Obstructive Sleep Apnea and Abnormal Glucose Metabolism

Nan Hee Kim
Division of Endocrinology, Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Korea

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%
Obstructive sleep apnea and glucose metabolism

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 a 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.

REFERENCES

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230-5.
2. Kim J, In K, You S, Kang K, Shim J, Lee S, Lee J, Park C, Shin C. Prevalence of sleep-disordered breathing in middle-aged Korean men and women. Am J Respir Crit Care Med 2004;170:1108-13.
3. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002;165:1217-39.
4. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. Lancet 2009;373:82-93.
5. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O’Connor GT, Resnick HE, Diener-West M, Sanders MH, Wolf PA, Geraghty EM, Ali T, Lebowitz M, Punjabi NM. Obstructive sleep apnea-hypopnea and incident stroke: the Sleep Heart Health Study. Am J Respir Crit Care Med 2010;182:269-77.
6. Gottlieb DJ, Yenokyan G, Newman AB, O’Connor GT, Punjabi NM, Quan SF, Redline S, Resnick HE, Tong EK, Diener-West M, Shahar E. Prospective study of obstructive sleep apnea and
incident coronary heart disease and heart failure: the Sleep Heart Health Study. Circulation 2010;122:352-60.
7. Pamidi S, Aronsohn RS, Tasali E. Obstructive sleep apnea: role in the risk and severity of diabetes. Best Pract Res Clin Endocrinol Metab 2010;24:703-15.
8. Iber C, Ancoli-Israel S, Cheson AL, Quan SF. The AASM manual for scoring of sleep and associated events: rules, terminology, and technical specifications. 1st ed. Westchester: American Academy of Sleep Medicine; 2007.
9. Collop NA, Anderson WM, Boehlecke B, Claman D, Goldberg R, Gottlieb DJ, Hudgel D, Sateia M, Schwab R; Portable Monitoring Task Force of the American Academy of Sleep Medicine. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 2007;3:737-47.
10. Resnick HE, Redline S, Shahar E, Gilpin A, Newman A, Walter R, Ewy GA, Howard BV, Punjabi NM; Sleep Heart Health Study. Diabetes and sleep disturbances: findings from the Sleep Heart Health Study. Diabetes Care 2003;26:702-9.
11. Einhorn D, Stewart DA, Erman MK, Gordon N, Philis-Tsimikas A, Casal E. Prevalence of sleep apnea in a population of adults with type 2 diabetes mellitus. Endocr Pract 2007;13:355-62.
12. Aronsohn RS, Whitmore H, Van Cauter E, Tasali E. Impact of untreated obstructive sleep apnea on glucose control in type 2 diabetes. Am J Respir Crit Care Med 2010;181:507-13.
13. Foster GD, Sanders MH, Millman R, Zammit G, Borradaile KE, Newman AB, Wadden TA, Kelley D, Wing RR, Sunyer FX, Darcey V, Kuna ST; Sleep AHEAD Research Group. Obstructive sleep apnea among obese patients with type 2 diabetes. Diabetes Care 2009;32:1017-9.
14. Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE; Sleep Heart Health Study Investigators. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. Am J Epidemiol 2004;160:521-30.
15. Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med 2002;165:677-82.
16. Tasali E, Mokhlesi B, Van Cauter E. Obstructive sleep apnea and type 2 diabetes: interacting epidemics. Chest 2008;133: 496-506.
17. Reichmuth KJ, Austin D, Skatrud JB, Young T. Association of sleep apnea and type II diabetes: a population-based study. Am J Respir Crit Care Med 2005;172:1590-5.
18. Botros N, Concato J, Mohsenin V, Selim B, Doctor K, Yaggi HK. Obstructive sleep apnea as a risk factor for type 2 diabetes. Am J Med 2009;122:1122-7.
19. Punjabi NM, Beamer BA. Alterations in glucose disposal in sleep-disordered breathing. Am J Respir Crit Care Med 2009;179:235-40.
20. Priou P, Le Vaillant M, Meslier N, Chollet S, Masson P, Humeau MP, Pigeanne T, Bizieux-Thaminy A, Goupil F, Gagnadoux F; The IRSR Sleep Cohort Group. Independent association between obstructive sleep apnea severity and glycated hemoglobin in adults without diabetes. Diabetes Care. Epub 2012 Jun 11. DOI: http://dx.doi.org/10.2337/dc11-2538.
21. Lindberg E, Theorell-Haglow J, Svensson M, Gislason T, Berne C, Janson C. Sleep apnea and glucose metabolism: a long-term follow-up in a community-based sample. Chest. Epub 2012 Apr 12. DOI: http://dx.doi.org/10.1378/chest.11-1844.
22. Seiecan S, Kirchner HL, Gottlieb DJ, Punjabi NM, Resnick H, Sanders M, Budhiraja R, Singer M, Redline S. Sleep-disordered breathing and impaired glucose metabolism in normal-weight and overweight/obese individuals: the Sleep Heart Health Study. Diabetes Care 2008;31:1001-6.
23. Iiyori N, Alonso LC, Li J, Sanders MH, Garcia-Ocana A, O’Doherty RM, Polotsky VY, O’Donnell CP. Intermittent hypoxia causes insulin resistance in lean mice independent of autonomic activity. Am J Respir Crit Care Med 2007;175:851-7.
24. Louis M, Punjabi NM. Effects of acute intermittent hypoxia on glucose metabolism in awake healthy volunteers. J Appl Physiol 2009;106:1338-44.
25. Muraki I, Tanigawa T, Yamagishi K, Sakurai S, Ohira T, Imano H, Kitamura A, Kiyama M, Sato S, Shimamoto T, Konishi M, Iso H; CIRCS Investigators. Nocturnal intermittent hypoxia and the development of type 2 diabetes: the Circulatory Risk in Communities Study (CIRCS). Diabetologia 2010;53:481-8.
26. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, Nakayama O, Makishima M, Matsuda M, Shimomura I. Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest 2004;114:1752-61.
27. Tasali E, Leproult R, Ehrmann DA, Van Cauter E. Slow-wave sleep and the risk of type 2 diabetes in humans. Proc Natl Acad Sci U S A 2008;105:1044-9.
28. Spiegel K, Knutson K, Leproult R, Tasali E, Van Cauter E. Sleep loss: a novel risk factor for insulin resistance and type 2 diabetes. J Appl Physiol 2005;99:2008-19.
29. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on
metabolic and endocrine function. Lancet 1999;354:1435-9.

30. West SD, Nicoll DJ, Wallace TM, Matthews DR, Stradling JR. Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes. Thorax 2007;62:969-74.

31. Babu AR, Herdegen J, Fogelfeld L, Shott S, Mazzone T. Type 2 diabetes, glycemic control, and continuous positive airway pressure in obstructive sleep apnea. Arch Intern Med 2005;165:447-52.

32. Sharma SK, Agrawal S, Damodaran D, Sreenivas V, Kadhira-van T, Lakshmy R, Jagia P, Kumar A. CPAP for the metabolic syndrome in patients with obstructive sleep apnea. N Engl J Med 2011;365:2277-86.