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Obstructive Sleep Apnea and Type 2 Diabetes*

Interacting Epidemics

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Type 2 diabetes is a major public health concern with high morbidity, mortality, and health-care costs. Recent reports have indicated that the majority of patients with type 2 diabetes also have obstructive sleep apnea (OSA). There is compelling evidence that OSA is a significant risk factor for cardiovascular disease and mortality. Rapidly accumulating data from both epidemiologic and clinical studies suggest that OSA is also independently associated with alterations in glucose metabolism and places patients at an increased risk of the development of type 2 diabetes. Experimental studies in humans and animals have demonstrated that intermittent hypoxia and reduced sleep duration due to sleep fragmentation, as occur in OSA, exert adverse effects on glucose metabolism. Based on the current evidence, clinicians need to address the risk of OSA in patients with type 2 diabetes and, conversely, evaluate the presence of type 2 diabetes in patients with OSA. Clearly, there is a need for further research, using well-designed studies and long-term follow-up, to fully demonstrate a causal role for OSA in the development and severity of type 2 diabetes. In particular, future studies must carefully consider the confounding effects of central obesity in examining the link between OSA and alterations in glucose metabolism. The interactions among the rising epidemics of obesity, OSA, and type 2 diabetes are likely to be complex and involve multiple pathways. A better understanding of the relationship between OSA and type 2 diabetes may have important public health implications. ***(CHEST 2008; 133:496–506)***

Key words: diabetes; glucose intolerance; insulin resistance; sleep apnea

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; CPAP = continuous positive airway pressure; DI = disposition index; Hb = hemoglobin; HOMA = homeostatic model assessment; IVGTT = IV glucose tolerance test; OGTT = oral glucose tolerance test; OSA = obstructive sleep apnea

Type 2 diabetes is a major chronic disease with high morbidity, mortality, and economic burden.[1,2] There is an alarming rise in the prevalence of type 2 diabetes that may be largely attributed to the epidemic of obesity.[3] Excess weight is also an important factor for obstructive sleep apnea (OSA),[4] an increasingly common sleep disorder that is characterized by repetitive upper airway obstructions leading to intermittent hypoxia and sleep fragmentation. Data from the 2005 "Sleep in America" poll of the National Sleep Foundation[5] indicate that as many as one in four adults and 57% of obese individuals are at high risk for OSA, which is consistent with the fact that OSA remains frequently undiagnosed.[6] Young et al[7] have estimated that the prevalence of OSA (apnea-hypopnea index [AHI], ≥5) in adults 30 to 69 years of age is approximately 17%, and the proportion of mild-to-moderate OSA attributable to excess weight is 41 to 58%.

There is rapidly growing evidence from population, clinic-based, and laboratory studies to suggest that these two expanding epidemics, namely, type 2 diabetes and OSA, may be associated independently of the

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Table 1—*Population-Based Studies Linking OSA Defined by Polysomnography to Altered Glucose Metabolism and Type 2 Diabetes

Study/Year	Study Sample	Measures of Glucose Metabolism	Main Findings
Stoohs et al[48]/1996	50 (34 women) healthy subjects, United States	*In vivo* insulin action by insulin suppression test	**Elevated insulin resistance in OSA (AHI ≥ 10) is entirely dependent on BMI**
Elmasry et al[73]/2001	116 hypertensive men, Sweden	Fasting glucose, fasting insulin, and HbA1c	Higher prevalence of severe OSA (AHI ≥ 20) in diabetic patients than normoglycemic subjects (36% vs 14.5%, respectively). The severity of OSA is associated with indices of glucose metabolism in normoglycemic subjects independently of central adiposity and antihypertensive use
Punjabi et al[74]/2002	155 men, United States	OGTT and HOMA	Increasing severity of AHI and oxygen desaturations were associated with worsening glucose tolerance and insulin resistance after adjustment for BMI and percentage of body fat
Ip et al[75]/2002	270 (197 men) Chinese individuals	Fasting insulin and HOMA	AHI and minimum oxygen saturation are independent determinants of insulin resistance
Punjabi et al[76]/2004	Sleep Heart Health Study, United States, 2,656 (1,214 men) participants	Fasting and 2-h glucose during OGTT, and HOMA	AHI and average oxygen saturation are independently associated with both fasting and 2-h glucose levels; independent link between degree of insulin resistance and severity of OSA
Reichmuth et al[11]/2005†	Wisconsin Sleep Cohort, United States, 1,387 (779 men) participants, 4-yr follow-up in 987 subjects	Diabetes diagnosed by physician and/or fasting glucose concentration of ≥ 126 mg/dL	More prevalent diabetes with OSA (AHI ≥ 15): OR, 2.3 (95% CI, 1.28–4.11) after adjustment for age, gender, and body habitus; **no independent relationship between incident diabetes and OSA at 4-yr follow-up**
Lam et al[77]/2006	255 (150 men) Chinese individuals	Fasting glucose	Association between OSA and fasting glucose after adjustment for age, gender, BMI, smoking, and alcohol use; adjusted OR for fasting glucose concentration of ≥ 110 mg/dL, 2.74 (95% CI, 1.16–6.49) for AHI ≥ 5 vs < 5
Okada et al[78]/2006	207 Japanese men	HbA1c and fasting glucose	Higher levels of HbA1c and fasting glucose in sleep apnea patients (AHI ≥ 15) compared to nonapneic subjects with similar BMI
Sulit et al[79]/2006	Cleveland Family Study, United States, 394 (177 men) subjects	OGTT	Threshold dose response for measures of hypoxic stress (≥ 2% time spent < 90% oxygen saturation) and glucose intolerance; adjusted OR, 2.33 (95% CI, 1.38–3.94)

*OR = odds ratio; CI = confidence interval. Bold type indicates negative studies.
†Includes prospective data analysis.

degree of adiposity. In a report by West et al,[8] the overall prevalence of OSA in diabetic men was estimated at 23% compared with 6% in a community-based sample. A preliminary analysis of cross-sectional data from a multicenter study[9] revealed an exceptionally high prevalence of undiagnosed OSA in obese patients with type 2 diabetes with > 75% of patients having moderate-to-severe OSA diagnosed by polysomnography. These remarkable associations raise the possibility that OSA may be a novel risk factor for type 2 diabetes and/or, conversely, that chronic hyperglycemia may promote OSA. Whether the treatment of OSA may delay the development or reduce the severity of type 2 diabetes is another important question.

In this article, we will review the current evidence from population, clinic-based, and interventional studies that links OSA to alterations in glucose metabolism and type 2 diabetes, and will briefly discuss the potential mechanisms that may play a role in this link. It is noteworthy that OSA has also been linked to the metabolic syndrome, a clinical entity that is closely related to type 2 diabetes risk and is most commonly defined as a cluster of cardiometabolic abnormalities including hypertension, dyslipidemia, obesity, and insulin resistance. A comprehensive review of the putative relationship between OSA and the metabolic syndrome is beyond the scope of this article.

Evidence From Population-Based Studies

A growing number of epidemiologic studies, originating from various geographic regions and involving diverse study populations, have suggested the existence of an independent link between markers of severity of OSA and an increased risk of type 2 diabetes. The association between OSA and altered

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