Sleep Apnea in Type 2 Diabetes
Jimmy Doumit and Bharati Prasad

Obstructive sleep apnea (OSA) is a common chronic respiratory disorder characterized by sleep-induced recurrent upper airway collapse. The prevalence of symptomatic OSA is estimated to be 2–4% in the general population, in both children and adults (1,2). Pathophysiological consequences of upper airway collapse include intermittent hypoxia and sleep fragmentation, resulting in sympathetic activation, systemic inflammation, and oxidative stress. These perturbations underlie the increased cardiometabolic morbidity and mortality observed in populations with OSA (3,4). OSA has been shown to increase the risk and severity of type 2 diabetes independent of age and obesity. This is notable because age and obesity are risk factors for both OSA and type 2 diabetes. There are limited data on the relationship of OSA to type 1 diabetes and the cardiometabolic impact of OSA in children (5,6). Recent studies suggest that treatment of OSA with continuous positive airway pressure (CPAP) therapy reduces insulin resistance and improves glycemic control in patients with prediabetes or type 2 diabetes.

This article focuses on the effects of OSA and its treatment on glucose metabolism in adults with prediabetes or type 2 diabetes. Data supporting screening, diagnosis, and treatment of OSA in patients with prediabetes or type 2 diabetes are outlined. Finally, the impact of CPAP therapy on diabetes care is discussed.

Insulin Resistance and β-Cell Dysfunction in OSA

Mechanisms

Figure 1 elucidates the biological pathways through which OSA leads to abnormal glucose homeostasis and the clinical conditions of prediabetes and type 2 diabetes. Intermittent hypoxia (IH) in animal models has been shown to decrease insulin sensitivity (measured via glucose tolerance test [GTT]) and increase the homeostatic model assessment (HOMA) index (7–9). IH affects hepatocytes directly, resulting in increased cellular glycogen content and gluconeogenic enzymatic activity (9). Prolonged periods of IH exposure in mice cause an increase in proinflammatory cytokines (interleukin-1β, interleukin-6, and macrophage inflammatory protein 2) and transcription factor nuclear
factor-κB (10). Reduction in proliferation and apoptosis of pancreatic β-cells and reduced conversion of pro-insulin to insulin has been observed in response to IH in mice (11–13). Adipose tissue is also affected by IH, with downregulation of adiponectin, an insulin-sensitizing hormone, and an increase in resistin (14,15). Finally, IH has been observed to be associated with sympathetic activation in both animal models and humans (16,17). Louis and Punjabi (18) studied healthy adults under conditions of normoxia and after 5 hours of IH exposure during wakefulness. IH was induced at a rate of 24 per hour, simulating moderate OSA. Intravenous GTT results showed a decrease in insulin sensitivity and glucose effectiveness (i.e., blood glucose-induced suppression of hepatic glycogenesis and increased tissue glucose uptake). Sympathetic activation (i.e., increased heart variability) by hypoxia was also noted, but pancreatic insulin secretion and serum cortisol levels remained unchanged.

Sleep fragmentation (SF; electroencephalographic activation in response to intrathoracic pressure changes against an occluded airway and to hypoxia) affects glucose homeostasis. SF induced in rodent models leads to adiposity, insulin resistance, and hyperglycemia via increased cortisol and biomarkers of inflammation and oxidative stress. SF and IH are associated with insulin resistance in young adults independent of age and obesity (19). Experimentally induced SF and reduction in slow-wave (i.e., deep) sleep in healthy adults causes decline in insulin sensitivity (20,21). Similarly, SF in the setting of OSA and in patients with type 2 diabetes interferes with glucose homeostasis (22,23).

**Epidemiology**

The mechanisms of insulin resistance and pancreatic β-cell dysfunction, as discussed above, explain the epidemiological observations that the prevalence of prediabetes and type 2 diabetes are increased in OSA. Most studies have used quantitative and validated measures for diabetes and OSA, such as fasting glucose or GTT and polysomnography, respectively. Interestingly, there is evidence to suggest that type 2 diabetes independently increases the likelihood of sleep-disordered breathing (24), possibly through the effects of diabetes on the autonomic and central nervous system. The prevalence of OSA in people with type 2 diabetes is variable, and estimates range from 18% in primary care (25), to 58% in an older cohort (24), and as high as 86% in obese populations with type 2 diabetes (26).

**OSA, Prediabetes, and Type 2 Diabetes**

Several cross-sectional studies have shown that OSA is associated with impaired glucose tolerance independent of obesity (27–29), and the risk is strongly associated with the severity of nocturnal hypoxia (30). A longitudinal study of a community-dwelling cohort of men without diabetes showed that OSA was an independent predictor of the development of insulin resistance (31). Longitudinal cohort studies from North America, Europe, and Australia found an overall increased risk of incident diabetes, particularly in moderate to severe OSA (32–35). These findings are further supported by a recent meta-analysis estimating that the risk for incident diabetes in the setting of moderate to severe OSA was increased by 63% (36). However, there is heterogeneity in the findings of these longitudinal studies when adjusted for confounders, including age, sex, and BMI. This suggests that shared risk factors are important moderators of the association between OSA and type 2 diabetes and should be considered in the clinical evaluation and management decisions pertaining to individual patients. In this regard, emerging data suggest that OSA expression in rapid eye movement (REM) sleep (in which more frequent respiratory events and more severe oxygen desaturation may be observed) has significant effects on insulin resistance and glycemic control (37,38).

**Effects of OSA on Type 2 Diabetes**

**Metabolic Control**

Several cross-sectional studies have found a detrimental impact of untreated OSA on glycemic control in type 2 diabetes (38–41). Aronsohn et al. (40) prospectively examined the relationship between polysomnography-derived apnea hypopnea index...
(AHI), the gold-standard measure of OSA severity, and A1C in 60 people with type 2 diabetes. There was a significant positive correlation between AHI and A1C after controlling for multiple confounders. Notably, this study reported that the effect size of AHI on A1C was greater than that of some antidiabetic drugs. In contrast, the largest prospective analysis of a substudy (Sleep AHEAD [42], involving 305 of 5,145 participants from 4 of 16 centers) failed to show a relationship between AHI derived from polysomnography and A1C. Only a weak correlation was found between fasting glucose and sleep efficiency (a measure that is partly indicative of sleep fragmentation). This study included more obese, older individuals with a longer duration of diabetes, which may account for the discrepant findings. Tamura et al. (43) showed that, although in glucose-intolerant patients AHI predicts long-term glucose control measured by A1C, lowest oxygen saturation appears to correlate better with A1C in people with type 2 diabetes. Overall, these data support the notion that OSA, particularly moderate to severe OSA, is associated with poorer metabolic control in patients with type 2 diabetes.

Organ System Dysfunction
OSA leads to increased cardiovascular disease (CVD). The mechanisms underlying vascular dysfunction in OSA include sympathetic activation and oxidative stress (from intermittent hypoxia, hypercapnia, and arousals). These perturbations result in reduced production of endothelium-dependent vasodilators such as nitric oxide (44). Moreover, OSA is associated with a proinflammatory and hypercoagulable state—another pathway that causes vascular injury (45). These mechanisms explain the observation that OSA severity, as indicated by AHI, is significantly associated with risk of stroke (odds ratio 2.5) in patients with type 2 diabetes (46). It should be noted that this study included older and obese populations with a high prevalence of OSA (86%). The independent effects of OSA on CVD should be further examined in lean and younger populations with type 2 diabetes.

There are limited empirical data regarding acceleration of other organ system dysfunction in patients with type 2 diabetes as a result of OSA. OSA leads to progression of chronic kidney disease independently, and this effect is compounded in patients with diabetes (47). A Japanese study evaluated a cohort of ~500 patients with type 2 diabetes using nocturnal oximetry for IH used as a screening test for OSA (48). The researchers found that significant nocturnal hypoxia (in the range seen in OSA) was associated with increased prevalence of hypertension, hyperlipidemia, microalbuminuria, and macroalbuminuria. Notably, this association was robust and significant after adjustment for confounding factors only in women. Similar findings have been reported in super-obese British populations with type 2 diabetes, suggesting that this effect is independent of obesity (49). A recent systematic review and meta-analysis reported a significant association between OSA severity and increased risk of diabetic kidney disease, with an overall odds ratio of 1.73 (50).

A cross-sectional study of >200 patients examined the prevalence and possible mechanisms of peripheral neuropathy in a clinic population of people with diabetes, with and without OSA. The prevalence of peripheral neuropathy, particularly severe neuropathy, was higher in patients with OSA. Moreover, nitrotyrosine and lipid peroxide levels (biomarkers of nitrosative and oxidative stress) were elevated in the OSA group and correlated with nocturnal hypoxemia (51). Several cross-sectional studies from diverse populations have demonstrated that OSA is associated with increased prevalence and severity of ocular complications such as retinopathy and maculopathy from type 2 diabetes (52–55). Furthermore, Tahrani et al. (56) showed that the incidence of ocular complications in patients with type 2 diabetes and OSA is higher than in those without OSA.

Effects of OSA Treatment on Diabetes
Treatment to control the signs and symptoms of OSA includes behavioral approaches to improving sleep habits and weight control. Both medical and surgical weight loss significantly reduce the severity of OSA. More recently, weight loss related to lifestyle interventions in people with type 2 diabetes has been shown to significantly improve OSA severity (57,58). However, it is unclear whether the improvement in OSA (as a result of weight loss) in these studies had an independent effect on control of type 2 diabetes. Other treatments for OSA include ear, nose, and throat or maxillofacial surgeries with the objective of improving the patency of the upper airway. In recent years, maxillary advancement devices, fitted by orthodontists to cause maxillary protrusion, have become increasingly used and studied. Data regarding the effects of these treatment interventions for OSA in type 2 diabetes are limited and beyond the scope of this review.

CPAP treatment is the first-line and most effective treatment for OSA. Randomized, placebo-controlled trials show that CPAP has a beneficial effect on glucose homeostasis in obese and nonobese populations with prediabetes (59,60). In addition, metabolic effects of CPAP versus oral placebo were recently examined in a randomized, controlled study in patients with prediabetes (59). CPAP significantly improved insulin sensitivity by oral GTT and reduced 24-hour blood pressure compared to placebo. These results are consistent with a previous meta-analysis that included only randomized, controlled trials, with a total of ~240 patients without type 2 diabetes showing significant improvement.
TABLE 1. CPAP Treatment and Type 2 Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size (n)</th>
<th>Design</th>
<th>Primary Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasad et al. (62)</td>
<td>221</td>
<td>Retrospective cohort; CPAP effects over 2 years</td>
<td>No change in A1C before and after CPAP treatment</td>
</tr>
<tr>
<td>Guest et al. (63)</td>
<td>300</td>
<td>Retrospective case control; CPAP vs. no treatment over 5 years</td>
<td>A1C significantly lower in CPAP group</td>
</tr>
<tr>
<td>Myhill et al. (64)</td>
<td>44</td>
<td>Prospective, randomized; CPAP early (&lt;1 week) or late (&gt;1 month) for 3 months</td>
<td>Decreased insulin resistance in CPAP group by oral GTT</td>
</tr>
<tr>
<td>Guo et al. (65)</td>
<td>40</td>
<td>Prospective; pre-treatment vs. post-CPAP treatment for 1 month</td>
<td>Decreased 24-hour mean blood glucose and nighttime mean blood glucose after CPAP, as determined by continuous glucose monitoring</td>
</tr>
<tr>
<td>Salford et al. (66)</td>
<td>80</td>
<td>Prospective, randomized, controlled trial; CPAP vs. conservative treatment for 3 months</td>
<td>Decreased insulin resistance by oral GTT in CPAP group</td>
</tr>
</tbody>
</table>

in HOMA index with CPAP treatment compared to placebo (61).

Table 1 summarizes studies published in the past 5 years that have examined the effects of CPAP treatment on metabolic markers of glucose homeostasis in type 2 diabetes (62–66). For a more detailed discussion, including a comprehensive listing of all relevant publications, readers are referred to focused literature reviews and meta-analyses on this topic (67–69).

Although the data regarding effects of CPAP treatment on control of type 2 diabetes remain limited by small sample size or lack of control group, it appears that, overall, CPAP treatment benefits glucose homeostasis in patients with type 2 diabetes. The effect size of CPAP treatment is possibly less than that of weight loss and oral hypoglycemic agents, but it remains clinically significant (70). This effect is enhanced with increased CPAP adherence and is more marked in cases with moderate to severe OSA, obesity, and poorly controlled diabetes (60,63,71). The duration of CPAP treatment exerts significant influence on glucose homeostasis; improvements can be expected to occur after 3 months of treatment. It is important to note that the data supporting the salutary effects of CPAP on glucose homeostasis are more robust in populations with prediabetes than in those with type 2 diabetes. This is partly because a smaller number of studies have addressed this question in populations with type 2 diabetes. However, biologically plausible explanations for this observation include that type 2 diabetes is a more advanced form of dysregulated glucose metabolism (irreversible β-cell dysfunction) and that patients with established type 2 diabetes are more likely to be older and to have other medical illnesses. These observations suggest that interventions to diagnose and treat OSA in populations with or at risk for type 2 diabetes should be instituted early, and compliance with treatment should be optimized (38).

Conclusion
In summary, OSA, via sympathetic activation, oxidative stress, inflammation, and neuroendocrine dysregulation, alters glucose homeostasis, including in patients with type 2 diabetes. Early recognition and interventions for OSA can be expected to improve insulin sensitivity and control of hyperglycemia in many patients. Clinicians must remain vigilant for signs and symptoms of OSA and monitor compliance with CPAP along with weight management, diet control, and medication adherence in patients with type 2 diabetes. Important goals of care that require further definition with empirical data include duration of treatment, necessary level of CPAP compliance, effect of alternate OSA treatments such as behavioral and weight loss interventions, and subpopulations with type 2 diabetes most likely to benefit from CPAP treatment.

Acknowledgments
Dr. Prasad is a recipient of a Career Development Award (CDA2, IK2CX001026-01; U.S. Department of Veterans Affairs Clinical Science, Research, and Development [VA CSR&D]). The views expressed in this article are those of the authors and not those of VA CSR&D.

Duality of Interest
No potential conflicts of interest relevant to this article were reported.

References
5. Perfect, M.M., Patel, P.G., Scott, R.E., et al. Sleep, glucose, and daytime function-
ing in youth with type 1 diabetes. Sleep 2012;35:81–88
23. Pogach MS, Punjabi NM, Thomas N, Thomas RJ. Electrocardiogram-based sleep spectrogram measures of sleep stability and glucose disposal in sleep disordered breathing. Sleep 2012;35:139–148
45. Drager LF, Polotsky YV, Lorenzi-Filho G. Obstructive sleep apnea: an emerg-
69. Feng Y, Zhang Z, Dong ZZ. Effects of continuous positive airway pressure therapy on glycaemic control, insulin sensitivity and body mass index in patients with obstructive sleep apnea and type 2 diabetes: a systematic review and meta-analysis. Diabetologia 2015;58:1103–1116