Sleep, Sleep Apnea, Diabetes, and the Metabolic Syndrome: The Role of Treatment

Commentary on Weinstock et al. A controlled trial of CPAP therapy on metabolic control in individuals with impaired glucose tolerance and sleep apnea. SLEEP 2012;35:617-625.

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Studies from the last decade have demonstrated the great importance of sleep in metabolic control in general, and glycemic control in particular. It appears that there is a clear U-shaped association between sleep duration and the risk for diabetes, with substantial increased risk of diabetes in people sleeping less than 6 hours per night or more than 8 hours per night. However, these epidemiological studies do not prove causality. Just as sleep periods either too short or too long may contribute to the development of diabetes, diabetes may result in fragmented sleep that is too short or sleep that is deeper and longer (especially if hypoglycemia occurs). Thus, there seems to be complex relations between sleep and diabetes. Interventional experiments may shed light on the directionality of these effects. Experimental sleep deprivation in healthy volunteers resulted in insulin resistance, which normalized following recovery sleep. The most common cause for insulin resistance in patients with hypersomnolence is the obstructive sleep apnea (OSA) syndrome.

Several studies have demonstrated an association between OSA and diabetes. Diabetes is significantly more prevalent in patients with OSA, and OSA is more prevalent in patients with diabetes. However, again, these studies do not demonstrate the direction of causality, if it exists. These associations may result from bidirectional relationships, or be the outcome of a third factor affecting both glucose/insulin metabolism and breathing during sleep, such as obesity or stress. Similarly, it has been shown that bidirectional relationships occur between OSA and obesity, likely resulting in a vicious cycle with positive feedback between the two. While obesity contributes to OSA due to impaired airway anatomy and reduced dilator muscle physiology, OSA may result in increased weight due to reduced physical activity (perhaps from daytime sleepiness), insulin resistance, and increased appetite (perhaps mediated by high ghrelin levels). Thus, showing that glycemic control in patients with diabetes or glucose intolerance is improved solely by treating the OSA is of great importance, both in terms of understanding the interrelationships/causality between the two and in terms of clinical ramifications.

Submitted for publication February, 2012
Accepted for publication February, 2012
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SLEEP, Vol. 35, No. 5, 2012
http://dx.doi.org/10.5665/sleep.1804

Several studies have examined the effect of treatment of OSA on diabetes, providing some conflicting results. Thus, although most studies have shown clear improvement in insulin resistance and glycemic control following CPAP treatment, some have not. Several methodological issues may explain these conflicting results, including small sample sizes, type of patients recruited, severity of OSA, concomitant diseases, medications used (especially glucose lowering medications), duration of study, lack of a control arm, lack of randomization, and/or blinded analyses of the results. Of special interest is the recent study by Chung et al., which reported data from 25 patients with moderate-severe OSA who had 5 months of CPAP treatment, but did not show improvement in glucose levels or insulin resistance. In the light of the study by Weinstock and colleagues in the current issue of SLEEP, these results are surprising and may have occurred due to the relatively small sample size in Chung’s study and relatively small baseline glucose metabolism impairment.

Weinstock et al. studied 50 patients with preexisting impaired glucose tolerance tests and moderate-severe OSA. Their study adds some very important contributions to the body of knowledge. First, this is a very carefully and scientifically designed study, utilizing sham CPAP in a randomized, crossover, double-blinded regimen, objectively assessing CPAP (and sham CPAP) adherence, and objectively quantifying sleep duration by actigraphy (ruling out potential confounding effects such as sleep duration). Second, it shows a dose-response effect for both the severity of disease and adherence to treatment. For patients with severe OSA (AHI ≥ 30/h) there was a clear improvement in insulin sensitivity index (and insulin levels in the 2-h oral glucose tolerance test) following 2 months of CPAP treatment compared to sham CPAP, while in less severe patients the improvement was not significant. In addition, each additional hour of active CPAP usage was associated with a significant improvement in insulin sensitivity index. Their results also suggest that improvement was greater in sleepier participants. Therefore, this study is of great importance, both for understanding cause and effect in the association between OSA and diabetes, and for clinical purposes. Findings showing that insulin resistance and glucose tolerance impairment are the result of the sleep disordered breathing are convincing. Potential mediating mechanisms that were not assessed in this study but are plausible, consist of sympathetic activation, stress induced by hypoxemia, reoxygenation, and sleep fragmentation; inflammatory processes involving adhesion molecules; and endothelial dysfunction. From the clinical point of view, CPAP treatment...
is essential for patients with OSA to achieve improved glucose metabolism, and that treatment should be especially encouraged in patients with severe OSA and subjective sleepiness. Thus, the study by Weinstock et al. adds further evidence to the great importance and clinical imperative to ensure patients with OSA are effectively treated even if treatment is inconvenient.

The reason Weinstock et al. found a lack of effect of CPAP on the less severe patients is unknown and requires additional studies to be clarified. Weinstock et al. show that on a background of obesity and only mild-to-moderate sleep disordered breathing, intervening with CPAP for 8 weeks is inadequate for improving indices of glucose metabolism. The Sleep Heart Health Study reported a positive correlation between OSA severity and glycemic indices (fasting glucose levels and oral glucose tolerance tests at 2 h), after adjusting for body weight. Thus, it is unclear whether the lack of improvement in the mild-to-moderate patients in the Weinstock study resulted from obesity or from other yet to be studied factors. In a recent similar study, 3 months of CPAP treatment in patients with moderate-to-severe OSA showed a significant reduction in glycated hemoglobin compared to sham CPAP.

In conclusion, there is growing body of evidence associating sleep disturbances with metabolic disorders in general, and glucose metabolism impairment in particular. It appears that one obvious consequence of OSA is glucose intolerance and diabetes, which may be relieved by treatment of only the sleep disordered breathing, especially when it is severe. This knowledge should continue to encourage clinicians to ensure patients with OSA are effectively treated, particularly during epidemics of obesity and diabetes.

CITATION

DISCLOSURE STATEMENT
The authors have indicated no financial conflicts of interest.

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