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Sleep Apnea and Diabetes: Insights into Emerging Evidence

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Abstract

The rampant diabetes pandemic over the last few decades has been associated with an increased rise in cardiovascular events and deaths. Risk factors such as obesity, family history of diabetes, decreased physical activity, and aging are among the most common in the development of diabetes. Emerging evidence in the last 10 years has suggested that sleep apnea is a novel risk factor in the development of diabetes. Associations between diabetes and sleep apnea are supported by both epidemiologic and clinical sleep apnea studies. In this report, we discuss epidemiologic and clinical evidence suggesting that sleep apnea is involved in the pathogenesis of altered glucose metabolism. In light of current evidence, sleep apnea treatment should be incorporated into existing pharmacotherapeutic regimens for optimal management of diabetes among diabetic patients with sleep apnea in order to reduce associated cardiovascular risk. Suggestions to improve practice guidelines in the management of diabetic patients with sleep apnea are provided.

Keywords

diabetes; sleep apnea; obesity; management; race/ethnicity

Prevalence of diabetes and sleep apnea

The rampant diabetes pandemic [1] over the last few decades has been associated with an increased rise in cardiovascular events and deaths [2]. Epidemiologic studies have suggested that an ascent in A_{1C} by 1% is associated with 15–20% greater cardiovascular risk [3–4]. One of the characteristic features of diabetes mellitus is the inability to regulate serum glucose levels, resulting in impaired glucose tolerance affecting 221 million people worldwide [5]. Analysis from the Third National Health and Nutrition Examination Survey indicated that 15.6% of American adults exhibit glucose intolerance (140 mg/dl) and 6.9% showed impaired fasting glucose levels (≥ 110 mg/dl) [6].

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On a parallel tract, there is a growing body of evidence suggesting that sleep apnea is involved in the pathogenesis of altered glucose metabolism. Sleep apnea is a major public health problem in the United States, affecting an estimated 18 million Americans [7–9]. Sleep apnea is a potentially life-threatening condition that is characterized by repeated sleep interruptions due to breathing abnormalities. According to NIH reports, sleep apnea is thought to be as prevalent as adult diabetes [10]. Others view it as big a public health hazard as smoking [11–12]. Using a respiratory disturbance index[1] ≥10, the Wisconsin Sleep Cohort Study estimated that sleep apnea affects as much as 15% of men and 5% of women (ages 30 to 60 years)[13]. Prevalence rates are even higher in this age group when polysomnographic criteria are used, indicating that 24% of men and 9% of women may have sleep apnea [14].

Associations between diabetes and sleep apnea

A number of epidemiologic and experimental studies have shown that patients with sleep apnea have increased glucose levels and increased insulin resistance [15–18]. This might predispose afflicted individuals to developing Type 2 diabetes mellitus. The prevalence of sleep apnea among obese diabetics as defined by the Sleep AHEAD (Action for Health in Diabetes) has been estimated to be 86% (n = 306) [19].

Data from the Sleep Heart Health Study, which enrolled 2000 patients, indicated that the odds ratio for having an abnormal glucose tolerance was 1.44 among patients with an AHI ≥ 15. Moreover, data from the Nurse's Health Study suggest that curtailed sleep duration resulting from sleep fragmentation induced by sleep apnea may also lead to the development or exacerbation of type 2 diabetes mellitus [20–21]. This is corroborated by analysis of data from the Sleep Heart Health Study [22]. Compared with Individuals sleeping 7 to 8 hours per night, individuals sleeping ≤ 5 hours or < 6 hours per night had adjusted odds ratios for diabetes of 2.51 (95% confidence interval, 1.57 – 4.02) and 1.66 (95% confidence interval, 1.15 – 2.39), respectively.

It is importance to note, on balance, that there are data suggesting that associations between sleep apnea and diabetes might be mediated through obesity, a common risk factor [23], although the prevalence of periodic breathing itself remained significantly higher among individuals with diabetes, even after control for covariates. While definitive conclusions regarding associations between these two conditions cannot yet be reached, emerging cross-sectional data suggest that associations of sleep apnea with greater glucose levels and increased insulin resistance might be independent of the presence of obesity [24–29]. Two large cross-sectional studies from Korea involving participants (n = 9,700) with BMI < 25 demonstrated that frequent snoring was associated with impaired glucose metabolism as demonstrated by elevated HbA_{1c} level and postload glucose and insulin levels [30–31]. The pathway linking sleep apnea and diabetes is yet to be fully elucidated. However, available data suggests that sleep apnea causes an increase in sympathetic activity [32–33], and

[1]The apnea-hypopnea index (AHI) or respiratory disturbance index (RDI) refers to the total number of apneas (complete cessation of breathing lasting ≥ 10 s) and hypopneas (50% reduction in airflow or < 50% but ≥ 30% decrease in flow associated with either a cortical arousal or Sa02 desaturation) divided by the patient's total sleep time. The AHI or RDI provides a measure of the severity of sleep apnea.

increased sympathetic activity impairs glucose homeostasis by enhancing glycogen breakdown and gluconeogenesis [34]. Hence, recurrent hypoxemia along with abnormal sympathetic activity, commonly observed among patients with sleep apnea, might mediate the relationships between impaired glucose metabolism and sleep apnea.

If it can be demonstrated that there is an independent association of sleep apnea with impaired glucose metabolism [35–36], this might offer another mechanism to explain increased cardiovascular morbidity. Evidently, this will require better delineation of the contribution of cytokines and leptin. Investigators have demonstrated that sleep disturbance is associated with mononuclear cell NF-κB activation in women that leads to an inflammation cascade; this then increases the chances of cardiovascular events and deaths [37].

Evidence from CPAP studies

CPAP is the most effective, noninvasive treatment for sleep apnea [38]. This treatment requires the patient to wear a sealed mask over the nose, or in certain cases both the nose and mouth while sleeping. The patient receives forced room air via the mask (that has been fitted by a technician), titrating the pressure in the oropharyngeal airway, which helps to maintain airway patency. Use of CPAP as a therapeutic modality for sleep apnea is often coupled with some form of behavior modification, targeting individual's weight [39–40]. Hence, the objectives of treatment are to eradicate not only physiologic abnormalities including sleep fragmentation, apneic episodes, and oxygen desaturations but also symptoms such as snoring and daytime sleepiness and to reduce risk for comorbid conditions. This constitutes the standard of care according to the American Academy of Sleep Medicine [41].

While CPAP is very effective in the management of sleep apnea, low adherence to treatment guidelines remains a concern. Emerging literature on CPAP adherence indicates that about 50% of patients initially accepted CPAP devices [42]. However, 40% of patients discontinued home CPAP therapy during the first week [43, 44]. CPAP adherence is defined as the mean number of hours per day and days per week patients report using CPAP (adherence: >4hrs for 70% of the nights or no report of symptomatic complaints). Patients turn on CPAP devices for a period of 3.7 to 6.0 hours and actually used them at the prescribed pressure level for 3.4 to 4.5 hours [45]. Factors that may increase CPAP adherence include satisfaction with disease management;[46] adherence during the first week augurs greater adherence a year later [45] and personality characteristics [47, 48]. Adherence can be enhanced when CPAP management-related issues are addressed, including monitoring disease severity, depressive symptoms, oxygen deficits, and CVD sequelae. Better outcome is observed when family members are involved in the process of overcoming barriers interfering with nightly CPAP use [49], particularly when incorporated in educational programs [50]. CPAP intervention programs suggest that education should endeavor to improve patients' lifestyle through weight reduction, increased physical activity, and tobacco avoidance [51, 52]. More importantly, such programs should be instituted in the first two weeks of treatment because patients exhibiting satisfaction with CPAP during those two weeks are likely to remain adherent a year later [53–58].

In support of hypotheses advanced to explain associations between diabetes and sleep apnea, investigators have pointed out that continuous positive airway pressure (CPAP) studies produced significant improvement in glucose control and left ventricular function [59]. These effects have accompanied a corresponding decrease in blood pressure [17, 60]. Evidence from several clinical trials shows that CPAP therapy can also normalize leptin [61] and ghrelin [62] levels, thereby reducing central [63] and visceral obesity [64].

Studies have shown beneficial effects among participants who adhered to recommendations to use CPAP treatment (≥ 4 hours per night) [49–50]. In one such study, investigators demonstrated that sleeping glucose level was more stable after treatment, with the median SD (spell out) decreasing from 20.0 to 13.0 mg/dL ($p = 0.005$) and the mean difference between maximum and minimum values decreasing from 88 to 57 mg/dL [65, 66]. Consistent with this finding, another adherence study showed that patients adhering to CPAP therapy had significantly reduced post prandial glucose values and hemoglobin A_{1C} level [67]. Another important finding from that study is that among patients who used CPAP for more than 4hours/day, the reduction in HBA_{1C} level was correlated with days of CPAP use [68]. Adequate usage of CPAP therapy is effective in reducing global Cardiovascular Disease Risk ($18.8 \pm 9.8\%$ vs $13.9 \pm 9.7\%$, $p = 0.001$) [69].

Management of diabetic patients with sleep apnea

Associations between diabetes and sleep apnea are supported by both epidemiologic and clinical sleep apnea studies. Thus, in light of current evidence, intense pharmacotherapy for diabetes should be coordinated with treatment for sleep apnea to reduce associated cardiovascular risk. An important recommendation in the treatment of diabetes is to avoid drugs that promote weight gain, as they might hasten the development of sleep apnea and/or aggravate the severity of existing sleep apnea.

These new findings are important, as they call into question approaches that rely only on pharmacotherapeutic management of diabetes, withouth consideration of the presence of sleep apnea. This is a particular concern in cases requiring frequent changes in pharmacotherapeutic doses. Among diabetic patients, there is an inverse graded relationship between the severity of sleep apnea and glycemic control, after controlling for multiple potential confounders, including adiposity [70]. Moreover, compared to patients without sleep apnea, the presence of mild, moderate, or severe sleep apnea increased mean adjusted HbA_{1c} values by 1.49, 1.93, and 3.69%, respectively [70]. Hence, a comprehensive evaluation of sleep apnea among patients with diabetes and other cardiometabolic risk profile patients seems warranted; it provides an opportunity to consider non-pharmacological interventions (e.g., CPAP therapy), which might enhance effectiveness of traditional pharmacologic intervention. This also has the potential to reduce unwanted pharmacological side effects from drugs.

Future Directions and Clinical Implications

Available data led to many important issues that require empirical testing. It appears that initial questions regarding relationships between sleep apnea and the abnormal glucose metabolism have been addressed to some extent. Whether the impaired glucose metabolism

represents a mediating factor in the link of sleep apnea to cardiovascular diseases remains to be determined. Alternatively, diabetes itself might potentiate the effects of sleep apnea on cardiovascular diseases.

Available data have not yielded evidence to support which factor is the root cause of the co-occurrence of obesity, diabetes, and sleep apnea [28]. This gives rise to the need for empirical studies testing causal models to explain links among these metabolic conditions. One could imagine the difficulties inherent in performing experimental tests of cause-and-effect relationships of those factors.

While we wait for answers to those important questions, many interventions can be developed to improve the management of existing metabolic disorders. First, as sleep apnea is highly prevalent among patients with diabetes, it seems prudent that a sleep apnea screening questionnaire [29] be administered to those at-risk patients (see Tables 1 and 2). Furthermore, questionnaires should be administered to patients with increased adiposity in the neck area and/or who present with abdominal (visceral) obesity. Second, patients meeting criteria for sleep apnea should be referred to a sleep clinic for a detailed laboratory study. Third, weight management programs should be designed to assist patients in their effort to reduce their body weight, as weight reduction helps diminish the severity of sleep apnea, thereby improving overall health and quality of well-being. Fourth, patients on intensive pharmacotherapy for diabetes and worsening sleep apnea should avoid weight gain drugs whenever possible to prevent the exacerbation of sleep apnea and cardiovascular events.

It is evident that the recent rise in metabolic disorders such as obesity, diabetes, and sleep apnea affects persons of differing age groups, of both gender, and across geographic regions. However, public health advocates have been particularly concerned about individuals living in at-risk, underserved communities that are traditionally underrepresented in the health care industry. In the African-American community, for instance, prevalence of these conditions is disproportionately higher [71–73]. Thus, ultimately adequate management of sleep apnea among African Amercians with sleep apnea will contribute to meaningful reductions of cardiovascular disease risk in this vulnerable population.

In the public health literature, many have argued in favor of greater access to health care, reasoning that with greater access there will be a commensurate decline in morbidity and mortality. There are data indicating that even when African Americans have adequate insurance coverage they are not as likely as their Caucasian counterparts to utilize available services [74]. Evidence has indicated that patients with chronic conditions often rely on their spiritual and/or religious leaders to make important health decisions [75]. This suggests that community physicians may have to develop novel strategies to encourage participation in healthcare practices in order to reduce metabolic risk and prevent premature deaths.

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Practice Points

- Sleep apnea is associated with diabetes independently of obesity and hypertension
- Treatment of sleep apnea improves diabetes
- Sleep apnea is associated with impaired glucose metabolism independently of obesity
- Sleep apnea contributes to stroke, as over 80% of stroke victims reportedly have sleep apnea
- Sleep apnea is more prevalent among African Americans; young African Americans are at increased risks
- Sleep apnea should be a key factor in the fight to reduce health disparities in cardiovascular diseases, obesity, diabetes, hypertension, and dyslipidemia
- Sleep apnea contributes to visceral obesity by increasing nocturnal cortisol and insulin, that promote visceral adiposity, metabolic abnormalities, and cardiovascular dysfunction
- Individuals with sleep apnea develop leptin resistance, which in turn contributes to further weight gain
- Assessment of sleep apnea is recommended for patients with hypertension, diabetes, obesity, and dyslipidemia
- Assessment of sleep apnea is recommended for patients with congestive heart failure, acute coronary syndrome, cardiac arrhythmias, and stroke

Table 1

Evidence-based signs and symptoms suggestive of the presence of sleep apnea

Signs and Symptoms of Sleep Apnea
• Loud snoring
• Frequent cessation of breathing during sleep
• Choking and gasping during sleep
• Waking up sweating during the night
• Feeling unrefreshed in the morning after a night's sleep
• Morning headaches
• Daytime sleepiness
• Lethargy
• Rapid weight gain
• Cognitive deficits
• Depression

Table 2

Questions commonly used by sleep clinicians to screen individuals who are at risk for sleep apnea.

Sleep Apnea Screening Questionnaire

- Do you snore on a regular basis?
- Do you ever wake up suddenly, gasping or choking for air?
- Do you experience excessive sleepiness during the day?
- Do you experience headaches, sore throat, or dry mouth in the morning after waking up?
- Do you have difficulty remembering things or concentrating on routine tasks?