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Sleep Duration and the Risk of Diabetes Mellitus: Epidemiologic Evidence and Pathophysiologic Insights

Ferdinand Zizi, **Girardin Jean-Louis**, **Clinton D. Brown**, **Gbenga Ogedegbe**, **Carla Boutin-Foster**, and **Samy I. McFarlane**
Department of Medicine, SUNY Downstate Medical Center, Box 1199, 450 Clarkson Avenue, Brooklyn, NY 11203-2098, USA

Girardin Jean-Louis: gjean-louis@downstate.edu

Abstract

Evidence from well-defined cohort studies has shown that short sleep, through sleep fragmentation caused by obstructive sleep apnea (OSA) or behavioral sleep curtailment because of lifestyle choices, is associated with increased incidence of diabetes. In this report, we review epidemiologic and clinical data suggesting that OSA is involved in the pathogenesis of altered glucose metabolism. Evidence suggesting increased risk of developing diabetes resulting from curtailed sleep duration is also considered. Proposed mechanisms explaining associations between short sleep and diabetes are examined and clinical management of OSA among patients with diabetes is discussed.

Introduction

Findings from well-defined cohort studies (eg, the American Cancer Prevention Survey, the Nurses' Health Study, the Sleep Heart Health Study, and the National Health and Nutrition Examination Survey [NHANES]) have shown that short or long sleep is associated with negative health outcomes [1–3]. Since the initial observation from the American Cancer Prevalence Survey that Americans were sleeping habitually 8 h to 9 h in 1979, self-reported sleep duration has declined gradually, with the current population modal sleep duration approximating 7 h [4,5]. Although the population as a whole has been sleeping less [5], the number of Americans receiving a diagnosis of diabetes has dramatically increased in the same time span [6]. The concomitant decrease in sleep duration and the increased incidence of diabetes has led to the belief that short sleep (<5 h to 6 h) might be a risk factor for diabetes [7,8]. This article examines evidence supporting associations of short sleep with diabetes and explores current approaches for managing patients with diabetes that target impaired sleep.

Prevalence of Diabetes

One of the characteristic features of diabetes mellitus is the inability to regulate serum glucose levels, resulting in impaired glucose tolerance, affecting 11% to 15.6% of the US population [6]. Research conducted to define the biochemistry of the insulin-response pathway has shown that type 1 and type 2 diabetes are associated with insulin deficiency, but type 2 diabetes is further complicated by cellular resistance to insulin action. According to data from the third NHANES, 5.1% of US adults have an existing diagnosis for diabetes; an additional 2.7% met criteria for the diagnosis, but have yet to receive one [6]. Analysis from the same research

Correspondence to: Girardin Jean-Louis, gjean-louis@downstate.edu.

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group 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]. According to the National Institutes of Health, diabetes mellitus is the sixth leading cause of disease-related deaths in the United States [9].

Sleep Loss and Diabetes

There is a growing body of evidence indicating that sleep loss, through sleep fragmentation caused by obstructive sleep apnea (OSA) or behavioral sleep curtailment because of lifestyle choices, is associated with diabetes (Fig. 1). OSA is a prevalent sleep-related breathing disorder, with estimates suggesting that 2% of middle-aged women and 4% of middle-aged men meet the criteria for a diagnosis [10,11]. Data from the Wisconsin Sleep Cohort Study, an epidemiologic study surveying the US adult population, showed that sleep apnea affects as much as 15% of men and 5% of women between the ages of 30 years and 60 years [12]. More recent studies suggest that the number of adults at risk for OSA is increasing. According to the 2005 National Sleep Foundation survey, 26% of US adults (men, 31%; women, 21%) are at high risk for OSA [13].

OSA is characterized by recurrent apnea and hypopnea episodes resulting from partial or complete closure of the upper airway during sleep [14]. Resulting breathing pauses lead to intermittent nighttime hypoxemia, which in turn causes recurrent cortical arousals associated with sleep fragmentation, loud snoring [15], and hemodynamic changes [16,17]. Consequences of untreated OSA include altered sleep architecture [18], cognitive deficits and poor performance [19], excessive daytime sleepiness and fatigue [20], increased cardiovascular morbidity [21–24], automobile accidents [23,25], and excess mortality [22,26].

OSA and Diabetes

Evidence suggests that OSA is involved in the pathogenesis of altered glucose metabolism [27,28]. Several epidemiologic and experimental studies have shown that patients with OSA have increased glucose levels and increased insulin resistance that predispose genetically predetermined individuals to developing type 2 diabetes [8]. Cross-sectional data suggest that associations of OSA with glucose intolerance and increased insulin resistance might be independent of the presence of obesity [29], an important risk factor for OSA and diabetes [30,31]. Obese and nonobese patients with sleep apnea are insulin resistant, whereas not all apnea patients are obese [29–31].

Investigators have proposed the following scenario to explain the underlying pathway linking OSA to insulin resistance and type 2 diabetes. Intermittent hypoxemia and sleep fragmentation caused by OSA engender a cascade of pathophysiologic events, which include autonomic activation, alterations in neuroendocrine function, and release of proinflammatory mediators (eg, tumor necrosis factor-α and interleukin-6) [8,29]. Investigators have also shown elevated circulating levels of C-reactive protein, reactive oxygen species, and advanced glycation end products among patients with OSA [32]. In summary, OSA produces an increase in sympathetic activity [17], and increased sympathetic activity impairs glucose homeostasis by enhancing glycogen breakdown and gluconeogenesis [33]. Thus, recurrent hypoxemia along with abnormal sympathetic activity and the proinflammatory state, commonly observed among patients with OSA, might mediate the relationships between insulin resistance and OSA (Fig. 1).

OSA's severity is determined by the apnea-hypopnea index (AHI). AHI refers to the total number of apneas (complete cessation of breathing lasting ≥10 s) and hypopneas (50% reduction in airflow lasting ≥10 s, followed by $Sa0_2$ desaturations) divided by the patient's total sleep time; an AHI less than 5 is considered normal. Data from the Sleep Heart Health

Study indicated that the prevalence of 2-h glucose tolerance increased from 9.3% among patients with an AHI less than 5–15% among those with an AHI greater than 15 [34].

Multivariate-adjusted analysis of data obtained from participants in the Wisconsin Sleep Cohort showed that the odds ratio (OR) for having a physician-diagnosed type 2 diabetes with an AHI ≥ 15 referenced to an AHI less than 5 was 2.30 [35]. The OR for developing type 2 diabetes within 4 years with an AHI ≥ 15 compared with an AHI less than 5 was 1.62 [35]. This is consistent with analysis of the Sleep Heart Health Study data showing that the OR for having an abnormal glucose tolerance was 1.44 among patients with an AHI ≥ 15 [34]. Analysis of those data also indicated that insulin resistance was also greatest among the latter group. That study provided evidence that apnea-induced hypoxemia is associated with glucose intolerance and insulin resistance [34]. Moreover, data from the Nurses' Health Study suggest that short sleep resulting from sleep fragmentation induced by OSA may also lead to the development or exacerbation of type 2 diabetes [36].

Short Sleep Duration and Diabetes

According to data from the Sleep Heart Health Study, short sleep duration induced by behavioral restriction of bedtime may also place individuals at risk for diabetes [7]. Several large-scale studies have investigated the link of sleep duration to insulin resistance and diabetes [7,37•,38–40,41••]. Analysis of data from the NHANES I indicated that individuals reporting sleep durations ≤5 h had significantly greater odds (OR, 1.47) of having incident diabetes over the 10-year follow-up period than those sleeping 7 h habitually [41••]. This is consistent with results of a 12-year follow-up investigation, which found that the relative risk of developing diabetes was higher among individuals with short sleep duration (<5 h; OR, 2.8) [39]. Data from the Sleep Heart Health Study suggest that compared with individuals sleeping 7 h to 8 h habitually, individuals sleeping ≤ 5 h or less than 6 h had adjusted ORs for diabetes of 2.51 and 1.66, respectively [42].

Although the preponderance of studies demonstrated associations of short sleep duration with diabetes, a few reports have indicated that individuals sleeping ≥ 9 h might also be at risk for diabetes (OR, 1.52) [37•,39]. Our own analysis of data from the 2005 National Health Interview Survey, sampling over 30,000 adults of representative gender and race/ethnicity, has shown the adjusted risk of long sleep associated with diabetes was 1.48 [43]. Thus, more definitive explanation of associations of habitual sleep with insulin resistance and diabetes awaits further empirical studies.

Whether short sleep is caused by OSA or behaviorally determined, short sleepers appear to be at greater risk for insulin resistance and diabetes. Although several possible mechanisms have been advanced to explain the short-sleep diabetes link—increased sympathetic activity, increased cortisol levels resulting from elevated hypothalamic-pituitary-adrenal axis activity, and dysregulated leptin and ghrelin, which may lead to obesity and hypertension (two important markers for diabetes [37•])—an explanation for the long-sleep diabetes link is much less convincing. Results from two independent studies have led investigators to posit that long sleep observed among patients with diabetes might result from the sleep-inducing effects of diabetes itself and/or proinflammatory cytokines [37•,41••].

Other investigators explaining the long-sleep diabetes association point to the high prevalence of depression among patients with diabetes [44,45]. On balance, we should note that evidence also indicates that adults with depression have a 37% increased risk of developing type 2 diabetes [46]. It may be that individuals with diabetes and who are also depressed are more prone to experiencing long sleep. Whereas short sleep is believed a risk factor for diabetes, long sleep may be one of the many symptoms experienced by individuals with diabetes.

Treating OSA Among Individuals with Diabetes

Continuous positive airway pressure (CPAP) is a therapeutic method that 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; the patient is able to breathe easier, thus diminishing sleep fragmentation. Use of CPAP as a therapeutic modality for sleep apnea is often coupled with some form of behavior modification, targeting individual's weight [47,48]. Thus, treatment objectives include eradicating not only physiologic abnormalities including sleep fragmentation, apneic episodes, and oxygen desaturations, but also symptoms such as snoring and daytime sleepiness and reducing risk for comorbid conditions. This constitutes the standard of care according to the American Academy of Sleep Medicine [49]. CPAP is used routinely to treat OSA, leading to improvement in daytime sleepiness, improved quality of life, and improved daytime performance [49].

Intervention studies aiming to treat OSA with nasal CPAP have further demonstrated the link of short sleep (caused by OSA) to diabetes. New clinical evidence suggests that diabetes control can be achieved through treatment of OSA. In one clinical study investigating the effects of an 8-week CPAP trial, it was found that patients adhering to the prescribed regimen exhibited improved insulin sensitivity, in addition to improved blood pressure, total cholesterol, and tumor necrosis factor-α [50•]. CPAP therapy also has been shown to eliminate apneic episodes and associated hemodynamic changes occurring during sleep that might increase risk for insulin resistance and diabetes [17]. Using a 72-h continuous glucose monitoring system, another CPAP study showed a significant reduction in hemoglobin A_{1c} level (9.2%±2.0% to 8.6%±1.8%) [51].

Conclusions

Review of the extant literature does not yield any evidence supporting a cause-and-effect relationship between habitual sleep and diabetes. However, data suggest that OSA is independently associated with altered glucose metabolism and may predispose genetically predisposed individuals to developing type 2 diabetes. If causal associations between OSA and impaired glucose metabolism can be shown, this might offer another mechanism to explain increased cardiovascular morbidity. It seems clear at this point that CPAP therapy holds great promise in enhancing diabetes control. CPAP studies have shown significant improvement in insulin sensitivity, blood pressure, lipid profile, and left ventricular function [8,17,51]. CPAP therapy can also normalize leptin and ghrelin levels [52], thereby reducing central obesity, an important risk factor of type 2 diabetes.

Some studies have not shown significant improvement in metabolic disorders subsequent to CPAP treatment, but those clinical studies had several limitations [53]. These include limited treatment compliance, inadequate duration of treatment, and some may have been underpowered to detect statistical effects. In light of such evidence, therapeutic approaches might integrate methods to increase sleep time via reduction of OSA severity and through lifestyle modifications. Synergistically, these therapeutic strategies may confer significant benefits in managing cardiovascular complications, resulting from uncontrolled diabetes and/or untreated sleep apnea.

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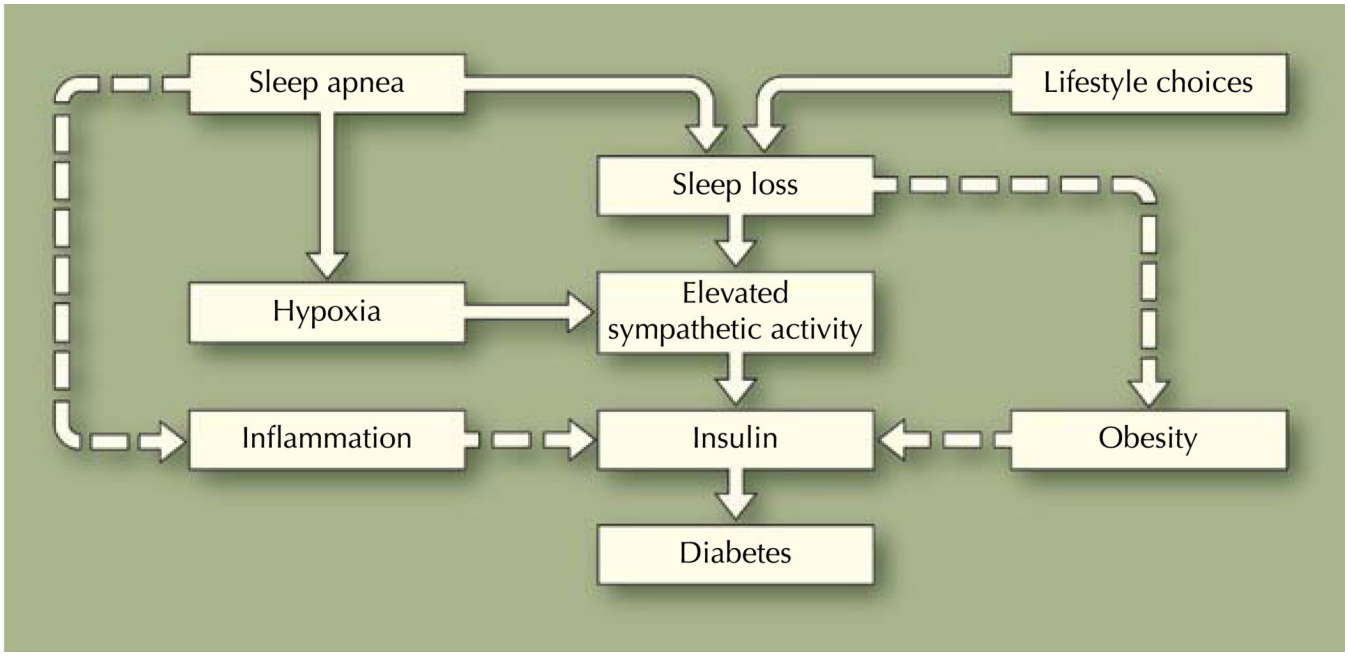

Fig. 1.
Pathway linking sleep loss to insulin resistance and diabetes