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Sleep and Glucose Intolerance/Diabetes Mellitus

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Glucose metabolism and its clinical disorders

Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia caused by various pathogenetic processes in glucose homeostasis [1,2]. In health, glucose homeostasis is achieved by regulating glucose production by the liver (gluconeogenesis) and glucose use by insulin-dependent tissues, such as muscle and fat, and non-insulin-dependent tissues, such as the brain [3]. Insulin is secreted by pancreatic β cells, both constitutionally and acutely in response to glucose loading, and its vital function is to mediate glucose disposal by peripheral tissues. It also suppresses hepatic gluconeogenesis and adipose tissue lipolysis. The biologic response of target tissues to the actions of insulin (insulin sensitivity) has many physiologic determinants, the major one being adiposity (Box 1), and impairment of tissue response (insulin resistance) results in reduced glucose disposal [4]. Insulin resistance plays a major role in the development of type 2 diabetes [5] and some other disease states (Box 2).

Two major forms of diabetes mellitus exist. Type 1 diabetes is caused primarily by β -cell destruction that results in insulin deficiency, whereas type 2 diabetes, which is the most prevalent form, is characterized by insulin resistance with relative deficient insulin secretion (inadequate compensatory hyperinsulinemia), although some individuals may have predominant insulin deficiency. Both genetics and environmental factors are important in the pathogenesis of type 2 diabetes, and abdominal obesity is an important risk factor.

Clinically, diabetes mellitus has stages of disease progression [1,6]. Impaired glucose regulation is the intermediate stage between normal glucose tolerance and diabetes, and can be identified by impaired fasting glucose or impaired glucose tolerance, which is assessed with an oral glucose tolerance test. This metabolic state is predictive of type 2 diabetes.

Insulin resistance or glucose intolerance is also an intrinsic component of the metabolic syndrome (insulin resistance syndrome) [7,8], which is a cluster of cardiometabolic risk factors. Although different sets of defining criteria have been proposed for this syndrome, most experts agree that these consist of insulin resistance and glucose intolerance, abdominal obesity, hypertension, and dyslipidemia (hypertriglyceridemia and low high-density lipo-protein cholesterol) [9,10]. Other features that are related include hyperuricemia, inflammatory and thrombogenic profile, hyperleptinemia, and micro-albuminuria [8,11].

Diabetes mellitus carries major morbidity and is among the five leading causes of death from disease in many countries [12], attributed to its devastating complications, particularly cardiovascular disease. Moreover, as obesity becomes epidemic, the prevalence of diabetes

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will also rise [13]. Type 2 diabetes afflicted an estimated 5% of the world's population in 2003. In the United States, its prevalence is estimated to rise from 14.2% in 2003 to 26.2% in 2025, and the rise is forecasted to be particularly sharp in Asia [14].

Box 1: Determinants of insulin sensitivity

Well-established determinants

Adiposity
Diet
Exercise and physical activity
Stress
Hyperglycemia

Possible determinants

Sleep, sleep deprivation, and sleep-related disorders

Sleep and glucose metabolism

Influence of sleep on glucose metabolism

Contrary to most mammals, human sleep is generally consolidated into a single 7- to 9-hour period, leading to an extended period of fasting overnight. Both pancreatic β -cell responsiveness and insulin sensitivity are influenced by sleep. Despite the extended fast during overnight sleep, blood glucose levels remain stable or fall only minimally. By comparison, when individuals are awake and fasting in a recumbent position without any physical activity, glucose levels decrease an average of 10 to 20 mg/dL over a 12-hour period [15].

Box 2: Common clinical states associated with insulin resistance

Type 2 diabetes mellitus
Metabolic syndrome
Hypertension
Polycystic ovary syndrome
Nonalcoholic fatty liver disease
Obstructive sleep apnea
Insulin resistance as a secondary
phenomenon in:
 Acute illness
 Cushing's syndrome
 Pregnancy

Therefore, several mechanisms operative during nocturnal sleep must intervene to maintain stable glucose levels during the overnight fast. Sleep and the circadian rhythm play roles in modulating insulin production, insulin sensitivity, glucose use, and thus glucose tolerance throughout the night. In normal healthy individuals, glucose tolerance varies throughout the day; plasma glucose responses to exogenous glucose are markedly higher in the evening than

in the morning, and glucose tolerance is at its minimum in the middle of the night [15]. The reduced glucose tolerance during the evening and sleep is partly caused by a reduction in insulin sensitivity concomitant with a reduction in the insulin secretory response, a marked reduction in cerebral glucose uptake because of slow-wave sleep, and a reduction in peripheral glucose use [16,17]. During the latter part of the night, glucose tolerance begins to improve, and glucose levels progressively decrease toward morning values, reflecting increased glucose uptake partly because of decreased slow-wave sleep and increased rapid eye movement sleep. These major modulatory effects of sleep on glucose regulation can also be observed when the sleep period occurs during the daytime [18].

Sleep duration or sleep disturbance and glucose homeostasis

Duration of sleep is essentially determined by individual and societal behavioral modes. Voluntary sleep curtailment to the minimum tolerable duration is highly prevalent and has become a hallmark of the modern society. Surveys conducted by the National Sleep Foundation [19] in the United States have documented that self-reported sleep duration of Americans has decreased by 1.5 to 2 hours over the past 40 years. The proportion of young adults reporting that they sleep less than 7 hours per night increased from 16% in 1960 to 37% in 2002 [20]. More than 30% of middle-aged men and women report sleeping less than 6 hours per night [21]. The dramatic increase in the incidence of obesity and diabetes over the past 3 to 4 decades [22] overlaps the progressive decrease in self-reported sleep duration.

Because sleep itself modulates glucose tolerance and homeostasis, changes in the quantity or quality of sleep may affect glucose tolerance. Voluntary sleep curtailment can cause decreased sleep quantity, whereas chronic intrinsic sleep disorders such as insomnia or sleep-disordered breathing (SDB) can affect both sleep quality and quantity. Both conditions are highly prevalent in the community. Chronic insomnia occurs in 6% to 15% of the general adult population [23]. In middle-aged adults, SDB (apnea–hypopnea index [AHI] ≥ 5) has been reported to affect 24% of men and 9% of women [24]. This article reviews the growing body of experimental and epidemiologic evidence linking sleep loss and sleep disturbance with alterations in glucose homeostasis.

Laboratory studies on sleep and glucose metabolism—Although initial animal studies that subjected rats to prolonged total sleep deprivation were unable to show elevated fasting glucose levels despite a marked increase in food intake by the rodents [25,26], total sleep deprivation in humans resulted in decreased glucose tolerance or increased food intake [27]. However, in daily life, partial sleep deprivation, either acute or chronic, is more common than total sleep deprivation. A landmark study evaluating the effect of short-term partial sleep deprivation on glucose homeostasis subjected 11 young, healthy, lean men to sleep restriction of 4 hours per night over 6 days followed by 7 days of sleep extension of 12 hours per night. After 6 days of sleep restriction, evidence of impaired glucose tolerance was seen. Furthermore, with sleep restriction, the mean leptin level—an anorexigenic hormone produced by adipocytes—was 19% lower and sympathetic nervous system activity was increased [28]. The degree of decrease in the acute insulin response with short-term sleep curtailment was similar to that observed in aging and gestational diabetes [29,30].

The same investigators repeated the experiment in 12 healthy men, but used a randomized crossover design. In this study, the sleep curtailment was limited to 2 days. Despite a shorter manipulation of sleep duration, evidence of impaired glucose tolerance was still seen. When compared with extended sleep, 2 days of sleep curtailment led to higher glucose levels, lower insulin levels, and a 30% increase in appetite for high caloric density carbohydrates. The anorexigenic hormone leptin decreased by 18% and levels of the orexigenic factor ghrelin—

a stomach-derived peptide that stimulates appetite—increased by 28%, matching the significant increase in hunger and appetite on a visual analog scale [31].

Mechanistic links mediating the effects of sleep loss on glucose homeostasis

—The mechanisms behind alterations in glucose homeostasis after recurrent partial sleep restriction are multifactorial (Box 3). In addition to a decrease in cerebral glucose metabolism, a reduction in insulin release occurs, probably because of increased sympathetic nervous activity at the level of the pancreatic β cell. Furthermore, alterations in the secretory profiles of the counter-regulatory hormones may also contribute to the disturbances of glucose homeostasis, causing elevated nighttime growth hormone and evening cortisol levels [15,32, 33]. Proinflammatory cytokines can increase with even 1 night of partial sleep loss [34]. A low-grade inflammation caused by chronic sleep loss may predispose to insulin resistance and diabetes [35,36].

Taken together, these laboratory studies suggest that sleep loss and sleep disturbances contribute to the development of insulin resistance and type 2 diabetes through multiple pathways, including a deleterious effect on glucose homeostasis, increased inflammation, and adversely affecting appetite regulation, leading to increased food intake, weight gain, and ultimately obesity (Fig. 1) [37].

Observational and epidemiologic studies on sleep duration and disturbance, and glucose intolerance and diabetes mellitus—Several population-based or large cohort studies have examined the relationship between the amount or quality of sleep and glucose tolerance [38–50].

The Sleep Heart Health Study (SHHS) data showed that sleep duration of either 6 hours or less or 9 hours or more was associated with increased prevalence of diabetes or glucose intolerance, compared with 7 to 8 hours of sleep per night, adjusted for AHI and other confounders [38]. The Nurses Health study included approximately 70,000 middle-aged women who did not have diabetes mellitus at baseline, and showed that both short and long sleepers had significantly increased risks for developing diabetes after 10 years, although the risk became nonsignificant in the short sleepers after adjustment for body mass index (BMI) and other confounders [39]. For the 1187 subjects who had symptomatic diabetes, the adjusted risk ratios were modestly elevated in both short and long sleepers. In more than 1100 men in the Massachusetts Male Aging Study, those reporting shorter and longer sleep duration were two and three times as likely to develop incident diabetes, respectively [40]. In two Swedish studies, men, but not women, who experienced shorter duration of sleep were found to have increased incident diabetes in a 12-year follow-up. Similarly, no association between sleep duration at baseline and diabetic risk was shown in women in a 32-year follow-up [41,42].

Box 3: Mechanisms linking sleep and sleep loss to altered glucose homeostasis

Sleep

- Reduced insulin sensitivity
- Reduced insulin secretory response to elevated glucose level
- Decrease cerebral glucose use related to slow-wave sleep
- Reduction in peripheral glucose use

Sleep loss

- Impaired glucose tolerance
- Increased appetite and hunger (elevation of ghrelin and reduction of leptin)

Increased sympathetic nervous system activity Alterations in counter-regulatory hormones (growth hormone and cortisol)

Increased proinflammatory markers

The influence of sleep quality on glucose tolerance has also been investigated in several longitudinal cohorts [41–45]. All except one study [42] reported an increased risk for incident diabetes in relation to sleep disturbances, such as difficulty initiating sleep, difficulty maintaining sleep, need for regular use of hypnotics, or frequently disrupted sleep.

In addition to studies of the general population, several studies evaluated sleep duration or sleep quality in individuals who have diabetes mellitus [46–50]. Most found that poor sleep quality was more prevalent in individuals who had diabetes compared with those who did not [46,48–50], and that this adversely influenced diabetic control [49,50].

An increase in obesity will also pose increased risk for glucose intolerance, and studies have addressed the issue of sleep and obesity. Studies in Japanese adults and children and the United States adult primary care population have shown that sleeping less increased the likelihood of obesity [51–54]. Data from 1024 subjects in the Wisconsin Sleep Cohort Study showed that 5 hours of habitual sleep compared with 8 hours led to hormonal changes promoting appetite, independent of SDB and other confounding factors. Furthermore, the increase in BMI was proportional to the decrease in sleep duration [54]. The degree of hormonal changes promoting appetite in this study was strikingly comparable to a previously reported laboratory study of partial sleep restriction [31].

Taken together, the findings of observational and epidemiologic studies validate those of the laboratory studies: that sleep disturbance can lead to alterations in glucose homeostasis, adversely affect appetite and hunger, and ultimately increase the risk for obesity and type 2 diabetes.

Sleep-disordered breathing and glucose metabolism

Obstructive sleep apnea (OSA) is the most common form of SDB worldwide [55,56]. A high association between OSA and glucose intolerance/diabetes mellitus would not be unexpected because they share the common risk factor of obesity. Research momentum has focused on the hunt for evidence of independent pathogenetic links between SDB and glucose metabolism disorders. The identification of a causal role would have implications not only on the understanding of disease pathogenesis but also on clinical management. The spreading obesity epidemic and the high prevalence of OSA and diabetes mellitus pose a colossal threat to health care [57].

Relationship between sleep-disordered breathing and derangements in glucose metabolism

Population-based studies—Several epidemiologic studies consistently showed that heavy snoring with or without observed breathing pauses was associated with increased frequency of disturbances of glucose metabolism, independent of obesity [58–63].

In a population-based sample of 116 men who had hypertension, 25 had diabetes mellitus. Although obesity was the main risk factor for diabetes, coexistent severe OSA added to the risk, and SDB influenced plasma insulin and glycemia independently of central obesity [63]. In 150 healthy, overweight, middle-aged men recruited from the community, OSA (defined as AHI ≥ 5) was associated with a twofold risk for glucose intolerance, independent of BMI and percent body fat measured with hydrodensitometry [64]. The impairment in glucose tolerance correlated with the severity of oxygen desaturation, whereas an increasing AHI was independently associated with worsening insulin resistance.

Among 2656 participants of the SHHS, those who had mild or moderate-to-severe OSA based on AHI criteria had increased risks (risk ratios of 1.27 and 1.46, respectively) for fasting glucose intolerance [65]. Sleep-related hypoxemia was associated with glucose intolerance independent of age, gender, BMI, and waist circumference.

Subjects in the SHHS who had diabetes mellitus were reported to experience more periodic breathing and central apneas than obstructive events [66]. Only periodic breathing was significantly and independently associated with diabetes when adjusted for confounders, and the breathing disorder was attributed to autonomic dysfunction. This finding contrasts with that reported by many other studies, population-based or clinic-based, in which a high association was seen between obstructive, rather than central, sleep apnea and diabetes mellitus.

Observational clinical studies—The relationship between SDB and metabolic dysfunction has been investigated repeatedly in subjects recruited from clinical settings [67, 68]. Findings involving smaller sample sizes conflict, with some showing a positive independent relationship [69,70], whereas others do not [71,72]. Studies with larger sample sizes have more consistently reported a positive independent association between SDB and insulin resistance/glucose intolerance [73–75] or the metabolic syndrome [76,77]. In a clinic sample of 261 subjects, the severity of SDB was associated with higher fasting insulin, but not glucose, with adjustment for BMI [73]. In 270 Chinese subjects who had polysomnograms in the sleep laboratory, insulin resistance, indicated by the homeostasis model assessment of fasting insulin and glucose measurements, was independently predicted by obesity and, to a lesser extent, AHI, and insulin resistance was a determinant of hypertension [74]. In a case-controlled study, whole-body and hepatic insulin sensitivity indices were significantly lower in individuals who had OSA compared with obese controls who did not have OSA and normal-weight controls, with adjustment for obesity and age, whereas insulin secretion was similar in the three groups [75].

Recently, a study in the United Kingdom assessed the risk for OSA in 1682 men who had type 2 diabetes using a survey followed by overnight oximetry in 240 men selected from groups considered to be at high or low risk for OSA. The study found that approximately 23% of the men who had type 2 diabetes had OSA [78], and that OSA was significantly associated with diabetes mellitus ($P = .03$), independent of BMI and neck circumference.

Data on children are scanty. One study of obese children showed significant correlations between AHI and fasting insulin independent of BMI [79]. However, two subsequent studies reported that insulin resistance was related to BMI rather than severity of SDB [80,81].

Longitudinal cohort studies—Several prospective population-cohorts have evaluated for new incident diabetes on longitudinal assessment. In Sweden and the United States, middle-aged men and women, respectively, have been followed-up for 10 years or more, and snoring at baseline was found to be associated with increased incident diabetes [82,83]. However, in an analysis of the Wisconsin Sleep Study Cohort [84], despite an independent association between SDB and insulin resistance at baseline, new incidence of diabetes over 4 years' follow-up was not more in subjects who had a baseline AHI of 5 or more compared with those who had an AHI less than 5.

Treatment intervention studies—In contrast to epidemiologic or observational studies, treatment intervention studies have been much less positive regarding the pathogenic role of OSA [67], and most failed to show any improvement in glucose metabolism [71,85–92].

More recently, several studies reported a positive treatment effect of OSA on insulin resistance or diabetic control. Using the hyperinsulinemic euglycemic clamp in 40 men who had severe OSA, 2 nights of treatment with continuous positive airway pressure (CPAP) led to significant improvement in insulin sensitivity, and the effect was sustained after 3 months of therapy. The improvement in insulin sensitivity was more marked in patients who were not obese compared with those who were [93]. Another study evaluated glycemic control with HbA1c and interstitial glucose levels using a continuous glucose monitoring system in 25 patients who had diabetes and OSA [94]. Treatment of OSA with CPAP reduced morning postprandial glucose values, and those who had worse initial glycemic control showed a significant decrease in HbA1c. A retrospective cohort analysis of 38 subjects who had diabetes and severe OSA similarly showed that HbA1c decreased after CPAP treatment for several months [95]. In one study, a population-based sample of 38 men who had severe OSA treated with CPAP for 3 weeks showed a decrease in insulin resistance and increase in insulin-like growth factor-1 (IGF-1) compared with controls who had an AHI less than 10 and did not undergo treatment [96].

Although the data from these recent intervention studies are encouraging, preliminary data from a randomized controlled study of therapeutic CPAP versus sham-CPAP reported that neither insulin resistance, evaluated with euglycemic clamp studies, nor diabetic control, indicated by HbA1c, showed any significant change with treatment of OSA [97].

Mechanistic links of sleep-disordered breathing and derangements of glucose metabolism

In line with the mediation of the effect of sleep on glucose metabolism, the mechanistic links of SDB and regulation of glucose metabolism are likely multifaceted (Fig. 2) [98]. The common factor of adiposity cannot be ignored, but both theoretical basis and evidence suggest that SDB itself may generate pathogenetic effects on glucose homeostasis.

OSA is believed to pose chronic stress caused by recurrent intermittent hypoxia and cerebral arousals. The recurrent sleep fragmentation and disrupted sleep architecture also cause sleep loss. These adverse physiologic effects may trigger downstream mechanisms that promote insulin resistance or glucose intolerance.

The role of counter-regulatory hormones of glucose metabolism have been investigated in OSA. Enhanced sympathetic activity has been shown consistently in OSA, reflected by microneurography of skeletal muscles [99] or increased catecholamines in plasma or urine [100,101] that improved with effective control of OSA. Several studies showed that the magnitude of sympathetic activation correlated with the severity of hypoxemia in OSA [102, 103].

Other aspects of hypothalamic–pituitary–adrenal axis activation have been more controversial. The timing of measurements may be an important factor, because hormones have intrinsic diurnal rhythms and spot measurements may not be sufficiently sensitive. Studies on cortisol have reported conflicting results, with a few showing an elevation of cortisol levels and others not, and intervention studies have been negative. A recent study showed that cortisol was increased in the evenings in some subjects who had OSA [104], consistent with findings in healthy subjects subjected to sleep restriction [32]. SDB may also influence the somatotrophic axis, with some studies showing decreased levels of growth hormone [90] or IGF-1 [88,105] in OSA, which then increased after treatment with CPAP. The observations were dissimilar to the pattern of growth hormone secretion seen in experimental sleep restriction [32,33]. In relation to glucose tolerance, a decrease in growth hormone would be favorable, whereas a decrease in IGF-1 was reported to predict type 2 diabetes [106]. Given the complexity of growth hormone dynamics, the biologic significance of these observations in OSA in relation to glucose homeostasis remains speculative.

Hypoxia–reoxygenation in OSA may be a stimulus for insulin resistance and glucose intolerance. Using intermittent hypoxia exposure (30 seconds of hypoxia alternating with 30 seconds of normoxia for 16 hours in the 24-hour cycle) for 5 days and 12 weeks to simulate hypoxic stress of OSA, obese leptin-deficient mice developed a time-dependent worsening of insulin resistance and glucose intolerance that could be abolished by prior leptin infusion, whereas lean mice showed no change in insulin levels and an increase in leptin [107]. However, studies of circulating leptin levels in humans have conflicted, with some reporting increased leptin level in individuals who had OSA compared with those who did not [108,109], whereas others showed that the increase was only attributed to obesity rather than sleep apnea [110]. Another experimental model exposing HeLa cells to 5 minutes of hypoxia alternating with 10 minutes of normoxia showed up-regulation of the nuclear factor- κ B pathway, which is involved in mediating inflammation and glucose transport and use [111]. Consistent with the up-regulation of this pathway, the study also reported an increase in plasma tumor necrosis factor (TNF) in individuals who had OSA. Although oxidative stress is considered a pathogenetic mechanism in diabetes mellitus [112], and increased oxidative stress has been repeatedly shown in subjects who have OSA [113–115], these findings are inconsistent [116]. Furthermore, the relationship of increased oxidative stress and glucose metabolism in OSA has not been explored.

Adipose tissue, and in particular visceral abdominal fat, is a rich source of adipokines and cytokines that influence insulin sensitivity. SDB may modulate the expression and secretion of these inflammatory mediators from fat and other tissue. Several studies have reported that individuals who had OSA had elevated levels of TNF- α or interleukin-6 [117,118], which are cytokines that are antagonistic to the actions of insulin [119,120]. Eventually more adipokines and adipocytokines will likely be explored for their role in glucose metabolism in OSA.

Summary

The sleep state itself has modulatory effects on glucose homeostasis. Epidemiologic and experimental studies suggest that sleep loss and sleep disturbances are detrimental to metabolic function and may predispose to obesity or glucose intolerance. Apart from the common risk factor of obesity, increasing data also support that OSA exerts independent adverse effects on glucose intolerance/diabetes mellitus, although definitive evidence is still needed.

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Fig. 1. Mechanisms through which sleep loss may lead to weight gain and increased risk for type 2 diabetes. (Adapted from Knutson K, Spiegel K, Penev P, et al. Metabolic consequences of sleep deprivation. *Sleep Med Rev*, in press; with permission.)

Fig. 2. Putative mechanisms leading to insulin resistance and increased diabetes risk in obstructive sleep apnea. (Adapted from Spiegel K, Knutson K, Leproult R, et al. Sleep loss: a novel risk factor for insulin resistance and type 2 diabetes. *J Appl Physiol* 2005;99:2008–19.)