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Interactions between sleep, circadian function, and glucose metabolism: implications for risk and severity of diabetes

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Sleep disturbances, including sleep insufficiency and sleep fragmentation, have been linked to abnormal glucose metabolism and increased diabetes risk. Well-controlled laboratory studies have provided insights regarding the underlying mechanisms. Several large prospective studies suggest that these sleep disturbances are associated with an increased risk of incident diabetes. Obstructive sleep apnea, which combines sleep fragmentation and hypoxemia, is a major risk factor for insulin resistance and possibly diabetes. Whether glycemic control in type 2 diabetes patients can be improved by treating sleep apnea remains controversial. Recently, sleep disturbances during pregnancy and their relationship to gestational diabetes and hyperglycemia have received considerable attention owing to potential adverse effects on maternal and fetal health. Additionally, evidence from animal models has identified disruption of the circadian system as a putative risk factor for adverse metabolic outcomes. The purpose of this review is to provide an update on the current state of knowledge linking sleep disturbances, circadian dysfunction, and glucose metabolism. Experimental, prospective, and interventional studies are discussed.

Keywords: sleep; circadian rhythms; glucose metabolism; diabetes; sleep apnea

Introduction

Humans spend approximately a third of their lives sleeping. Sleep is viewed as a state of energy conservation and replenishment of energy stores. Normal human sleep is composed of rapid eye-movement (REM) sleep and stages N1, N2, and N3 of non-REM (NREM) sleep. N3, the deepest stage of NREM sleep is also known as slow-wave sleep (SWS). Oscillations between REM and NREM stages occur roughly every 90 min and repeat four to six times during the night.

This important physiologic process is controlled in part by an internal circadian clock and in part by a homeostatic mechanism where the pressure for sleep increases in proportion to the duration of prior wakefulness. Human behavior may override these physiological control mechanisms, resulting in alterations of sleep duration and quality. Experimental and epidemiologic data have linked insufficient sleep duration, abnormal sleep timing, and poor sleep quality to insulin resistance, increased risk of obesity, and diabetes. In patients with type 2 diabetes, sleep disturbances may adversely affect glycemic control.

The epidemic of obesity has been associated with a marked increase in the prevalence of obstructive sleep apnea (OSA). OSA is well recognized as a risk factor for insulin resistance, independently of the degree of obesity, and is highly prevalent in patients with type 2 diabetes. OSA is a complex disorder involving intermittent hypoxia (IH), sleep fragmentation, low amounts of SWS, and reduced total sleep time. Well-documented studies in animal models have indicated that IH is one of the mechanisms linking OSA to abnormal glucose metabolism. Whether treatment of OSA with continuous positive airway pressure

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(CPAP) may improve glucose metabolism remains controversial.

Pregnant women are a special population that may be particularly vulnerable to the adverse effects of abnormal sleep. Recently, sleep disturbances in pregnancy were found to be associated with adverse maternal and fetal outcomes, including gestational diabetes, preeclampsia, and premature delivery. Because of these potential complications, the body of literature on this topic has grown rapidly in the past few years.

Besides sleep duration, sleep quality, and OSA, emerging evidence from well-controlled clinical research studies has revealed that conditions where the behavioral sleep/wake cycle is not in synchrony with the biological circadian timing system, so-called "circadian misalignment," may result in impaired glucose tolerance. In cross-sectional analyses, circadian misalignment has been found to be associated with increased diabetes risk in nondiabetic individuals and with poor glycemic control in patients with established type 2 diabetes.

The present review summarizes the evidence linking different type of sleep disturbances to abnormal glucose metabolism, including insufficient sleep, sleep fragmentation, OSA, and circadian misalignment. We discuss potential underlying mechanisms as well as findings from prospective and cross-sectional epidemiologic studies and from interventional studies.

Insufficient sleep

Insufficient sleep has been linked to reduced insulin sensitivity and increased risk of type 2 diabetes, both in laboratory studies in healthy humans and in epidemiologic studies. A causative role of partial sleep restriction in promoting alterations in glucose metabolism was first established in 1999.[1] Intravenous glucose tolerance testing (IVGTT) following sleep restriction to 4 h per night for five nights resulted in a 24% decrease in insulin sensitivity as well as a 30% decrease in the acute insulin response to intravenous glucose.[1,2] Moreover, an increase in the HOMA (homeostatic model assessment, an index of insulin resistance) response to breakfast was observed on the following day and occurred despite similar insulin secretory responses. These findings indicated that a state of sleep debt caused a decrease in insulin sensitivity that was not compensated by increased insulin release, leading to a more than 40% decrease in glucose tolerance compared to the fully rested condition.

Several subsequent well-controlled experimental studies in healthy human subjects involving sleep restriction to 4–5.5 h/night for 5–14 nights and assessments of glucose metabolism by IVGTT or euglycemic–hyperinsulinemic clamp have confirmed a reduction of insulin sensitivity ranging from 18 to 24% in response to sleep restriction without simultaneous increases in insulin levels, resulting in reduced glucose tolerance and an increased risk of diabetes[3–5] (Fig. 1). A few studies that included assessments after sleep recovery found that the metabolic disturbances induced by sleep restriction were at least partially reversible (improved glucose tolerance as assessed by IVGTT[1] and a reduction in the insulin-to-glucose ratio[6]). In addition, three nights of in-laboratory catch-up sleep in men with chronic intermittent sleep restriction led to improved insulin sensitivity as assessed by a 2-h glucose tolerance test.[7]

Multiple cross-sectional epidemiologic studies have indicated that short sleep duration (usually $<$6 h/night) is associated with increased diabetes risk (for review, see Ref. 8). To date, 8 of 10 large prospective studies with a follow-up duration of 5–17 years have observed that short sleep duration is associated with an increased risk of incident diabetes.[9–18] A recent meta-analysis, including 7 of these 10 studies (total 107,756 participants), concluded that short sleep ($\leq$5–6 h/night) predicts the development of type 2 diabetes with a pooled relative risk (RR) of 1.28.[19] In addition, there is evidence that long sleep duration ($>$8–9 h/night) also predicts incident diabetes, with a pooled RR of 1.48,[9,12,13,19] suggesting a U-shaped relationship between sleep duration and risk of diabetes. The main limitation of these studies is that sleep duration was self-reported.

There are only a few studies examining the impact of insufficient sleep on glycemic control in patients with established type 2 diabetes. Normally, glycemic control is assessed by the measurement of glycated hemoglobin (i.e., HbA1c) with a normal level of $<$5.7%, a prediabetes level of 5.7–6.4%, a diabetes level of $\geq$ 6.5%, and a target level for good glycemic control of $<$7% in patients with diabetes.[20] A questionnaire survey study of 161 African Americans with type 2 diabetes found that 3 h of perceived sleep debt per day (i.e., a self-report of

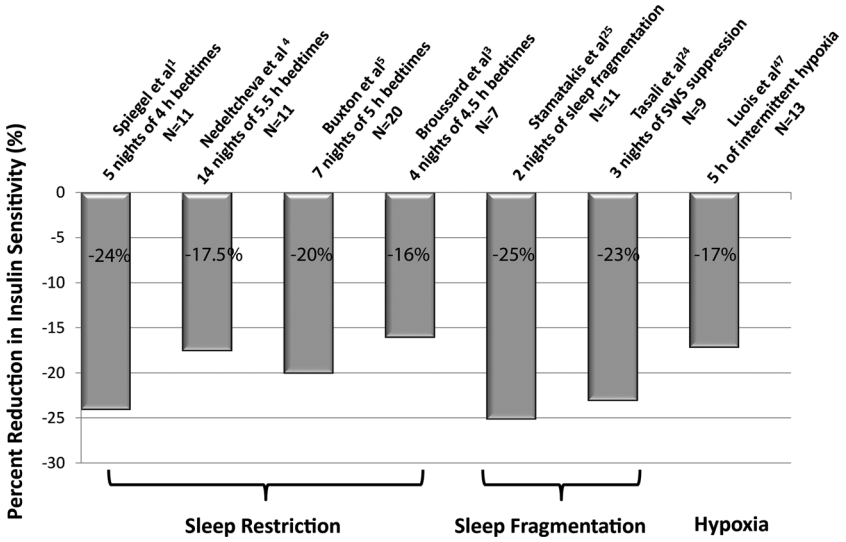

Figure 1. Reduction in insulin sensitivity as assessed by IVGTT from laboratory studies involving sleep restriction, sleep fragmentation, and intermittent hypoxia.

insufficient sleep duration) predicted an HbA1c level of 1.1% above the median.[21] The magnitude of this difference is comparable to the effect size of several FDA-approved diabetes medications. Recently, a large cross-sectional study of 4870 Japanese participants revealed a U-shaped relationship between sleep duration and glycemic control, with higher HbA1c levels in patients with self-reported sleep duration less than 5.5 h/night and greater than or equal to 8.5 h/night compared to those with 6.5–7.4 h/night.[22] These data support a role of sleep duration on glycemic control in patients with type 2 diabetes.

Sleep fragmentation and insomnia

Sleep fragmentation is a hallmark of poor sleep quality. Laboratory studies of healthy volunteers demonstrated that sleep fragmentation without changes in total sleep duration results in abnormal glucose metabolism. Suppression of SWS using acoustic stimuli for three nights resulted in a 25% decrease in insulin sensitivity as assessed by minimal-model analysis of a frequently sampled IVGTT[23] without a compensatory increase in insulin secretion as assessed by the acute insulin response to intravenous glucose.[24] Similarly, sleep fragmentation throughout the night by acoustic stimuli and mechanical vibrations for two nights was associated with a 25% decrease in insulin sensitivity[25] (Fig. 1).

Prospective population-based studies have linked poor sleep quality to incident diabetes.[11,14,26–28] Meta-analyses of these studies revealed that self-reported difficulty in maintaining sleep predicted the development of diabetes with an RR of 1.84 (total participants 24,192), while self-reported difficulty in initiating sleep was associated with an increased RR of 1.57 (total participants 18,213).[19] By comparison, estimates of the RR of developing diabetes in adults with a family history of type 2 diabetes in four studies have ranged from 1.7 to 2.3,[29–33] with only one study in South African blacks estimating the RR at a substantially higher value of 4.1.[34] Thus, the RR of incident diabetes in individuals with short sleep duration or reporting difficulty initiating or maintaining sleep is of the same order of magnitude as the RR imparted by having a family history of type 2 diabetes, usually considered as one of the strongest predictors of diabetes risk. Three subsequent cross-sectional studies reported that a high level of sleep disturbances, or increased psychological distress (which includes symptoms of anxiety, depression, fatigue, and insomnia) as well as living in an area with a lot of traffic noise (presumably causing sleep disturbances) all predict an increase in the risk of being diagnosed with type 2 diabetes.[35–37]

Only a few cross-sectional studies have examined the relationship between sleep quality and glycemic control in patients with type 2 diabetes.

The largest study included 161 African American patients, and found that in those with at least one diabetes complication (i.e., retinopathy, neuropathy, nephropathy, cardiovascular or cerebrovascular diseases) there was a graded relationship between glycemic control as assessed by HbA1c and the score on the Pittsburgh Sleep Quality Index (PSQI).[21] Specifically, a five-point increase in PSQI score predicted an elevation of HbA1c level of 1.9% above the median. Another cross-sectional study of 46 Taiwanese patients found an association between poor glycemic control (defined as HbA1c $\geq$7%) and poor sleep quality (PSQI Score $\geq$ 8) as well as poor sleep efficiency.[38] Recently, Knutson *et al.* reported a cross-sectional association between an objective estimation of sleep quality and markers of glucose metabolism in participants of the CARDIA study.[39] The sleep parameters were derived from actigraphy recordings, which have been shown to be well correlated with those obtained by polysomnography (PSG).[40] While there were no correlations between sleep and metabolic variables in nondiabetic participants, sleep fragmentation and insomnia were associated with significantly higher fasting glucose, insulin, and HOMA levels in diabetic participants.[39] Another study conducted in Italy, involving 47 patients with type 2 diabetes, reported that HbA1c correlated inversely with sleep efficiency as measured by actigraphy.[41]

Recently, analyses of the Penn State Cohort, a large prospective study of 1741 participants who had one night of laboratory PSG and were followed for 14 years, found that men with a complaint of insomnia for $\geq$1 year who also had a sleep duration of less than 6 h on PSG had significantly higher mortality compared to men with "normal sleep duration and no insomnia" (odds ratio (OR) 4.00) after adjusting for confounders.[42] This analysis suggested that "insomnia with short sleep" may be a more biologically severe phenotype than insomnia with normal sleep duration, at least in men. Insomnia with short sleep in women was not associated with increased mortality. In the same cohort, the risk of type 2 diabetes was nearly threefold higher in insomniacs with PSG-defined sleep duration under 5 h, irrespective of sex, while insomniacs with longer sleep duration did not have an increased risk.[43] The fact that sleep duration was assessed via a single night of PSG is an obvious limitation of the Penn State Cohort studies.

Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a complex sleep disorder characterized by repetitive episodes of upper airway closures or partial collapse during sleep, resulting in IH, fragmented sleep, shallow sleep with low amounts of SWS, and generally reduced total sleep time. The gold standard diagnostic test is overnight laboratory PSG, which allows for the quantification of episodes of apnea and hypopnea per hour of sleep, yielding an apnea–hypopnea index (AHI). A diagnosis of OSA is made when the AHI $\geq$ 5. In 1993, the prevalence of OSA in the Wisconsin Sleep Cohort was 24% in men and 9% in women.[44] In 2013, the prevalence in the same cohort had increased by as much as 55%.[45] Current estimates of OSA prevalence from multiple studies have ranged from 33 to 77% in men and 11 to 46% in women,[46] partly due to the obesity epidemic.

OSA, glucose metabolism, and insulin resistance

In addition to reductions in sleep duration and quality, IH is the hallmark of OSA. There is only one experimental study in humans that examined the impact of intermittent hypoxemia on glucose metabolism. In this study, 13 healthy volunteers were subjected to 5 h of IH while awake, resulting in an average of 24.3 desaturation events per hour,[47] equivalent to hypoxia in OSA of moderate severity ($15 < \text{AHI} \leq 30$). Insulin sensitivity and glucose effectiveness, as assessed by IVGTT, were reduced by 17 and 31%, respectively, without simultaneous increase in insulin secretion (Fig. 1). These results suggest that hypoxic stress may have an intrinsic adverse impact on glucose metabolism and diabetes risk.

Since adiposity is a major risk factor for both OSA and insulin resistance, it is important to know if OSA affects glucose metabolism in lean individuals who are otherwise healthy and free of cardiometabolic disease. This question was addressed in a recent study in which 12 lean, healthy young men with OSA were matched with 20 control subjects.[48] All subjects underwent an oral glucose tolerance test (OGTT). The presence of OSA in the lean participants was associated with 27% lower insulin sensitivity and 37% higher total insulin secretion, despite glucose levels comparable to those without OSA, indicating that OSA is a risk factor for insulin resistance independently of adiposity. This study directly

confirmed the findings of multiple large population-based studies that had found strong associations between the presence of OSA and insulin resistance, as well as glucose intolerance in participants who did not have diabetes after statistical adjustment for BMI and other confounders.[49–51]

In addition, there seems to be a graded relationship between the severity of OSA and the degree of insulin resistance and glucose intolerance levels in individuals without a diagnosis of diabetes.[52–54] The Sleep Heart Healthy Study, involving 2656 participants who were not receiving diabetes medications, revealed that fasting and 2-h glucose levels after an OGTT were independently associated with OSA severity after adjusting for age, gender, BMI, and waist circumference.[53] In another large cross-sectional study of 1599 participants without diabetes, increasing severity of OSA was associated with increasing risk of having a HbA1c level greater than 6%.[52] In a well-documented laboratory study, detailed assessments of glucose metabolism, insulin release. and insulin action were performed using the IVGTT in 118 nondiabetic subjects.[55] Those with mild, moderate, and severe OSA displayed, respectively, 26.7, 36.5, and 43.7% reduction in insulin sensitivity independent of age, sex, race, and percent body fat. In addition, pancreatic β cell function, as measured by the disposition index (a product of insulin sensitivity and the acute insulin response to intravenous glucose), was reduced in patients with moderate and severe OSA. These data indicated that OSA is associated with insulin resistance without a compensatory increase in insulin secretion, independently of multiple confounding factors, resulting in an increased risk for glucose intolerance and type 2 diabetes.

OSA and diabetes

Numerous cross-sectional studies have documented bidirectional associations between OSA and diabetes, independent of BMI (recently reviewed in Refs. 51 and 56). The prevalence of diabetes in patients with OSA ranges from 15 to 30%, depending on study population, the AHI cut-off used to define OSA, and the methods used to diagnose diabetes.[50,57–60] The relationship between the presence of OSA and the incidence of diabetes was established in longitudinal studies. To date, six prospective cohort studies, totaling 6094 participants, have been conducted to explore whether the presence of OSA at baseline predicted incident diabetes during a follow-up, after adjusting for BMI or other measures of adiposity and other confounders.[57,61–65] The studies varied in the methods and diagnosis criteria used to diagnose OSA (pulse oximetry versus full or limited PSG, and cut-off for AHI/oxygen desaturation index), verification of diabetes diagnosis, and duration of follow-up period (2.7–16 years). The Wisconsin Sleep Cohort found that OSA was a risk factor for incident diabetes after 4 years, but the association became nonsignificant after adjusting for age, gender, and body habitus.[57] A study of 261 participants followed for 16 years found that OSA predicted incident diabetes in women but not in men.[65] The other four studies revealed significant associations between OSA and development of diabetes.[61–64] A recent meta-analysis, including five of these studies (total 5953 participants), revealed that moderate-to-severe OSA was associated with a significantly greater risk of developing diabetes, with RR of 1.63 compared to those without OSA.[66] In those with mild OSA (AHI < 15), RR was 1.22, but this was not statistically significant. These data strongly support that the presence of moderate-to-severe OSA is a risk factor for diabetes development independent of other confounding factors.

In patients with an established diagnosis of type 2 diabetes who were generally obese, OSA was shown to be highly prevalent, from a lowest estimate of 58% to a highest estimate of 86%, on the basis of seven independent studies involving a total of 1272 participants[67–73] (Fig. 2). The weighted average was 67%. This proportion is alarming given that in 2011, 20.9 million Americans were estimated to have diabetes, which could possibly translate to as many as 14 million individuals suffering from both diabetes and OSA. Unfortunately, this highly prevalent comorbidity of type 2 diabetes often remains unrecognized. A retrospective analysis of 27 primary care practices involving 16,066 diabetes patients found that only 18% were diagnosed with OSA, suggesting that a majority of diabetic patients may not be diagnosed and are therefore untreated.[74]

Similar to nondiabetic populations, the severity of untreated OSA has been found to be associated with lower glucose tolerance in diabetic populations. Aronsohn *et al.* utilized PSG to assess OSA severity in 60 diabetic patients.[67] There was a graded relationship between the severity of untreated OSA as measured by AHI and higher HbA1c levels after

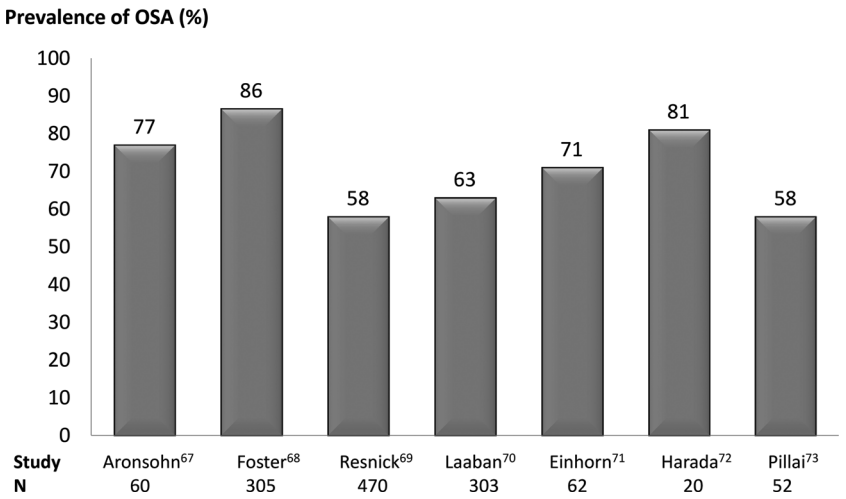

Figure 2. Prevalence of OSA as assessed by PSG among type 2 diabetes patients from seven studies.

adjusting for age, sex, race, BMI, years of diabetes, numbers of diabetes medications, exercise, and total sleep time, with an effect size as large as that associated with the impact of antidiabetes drugs. Another cross-sectional study in 52 diabetic patients also found that increased severity of OSA was associated with increased HbA1c levels, after adjusting for age, sex, BMI, diabetes duration, and insulin dose.[73] Adjusted mean HbA1c was 8.62% in those without OSA, 9.36% in mild OSA, 10.61% in moderate OSA, and 9.91% in severe OSA. However, not all of the studies supported a link between OSA severity and glycemic control. The Sleep AHEAD study involving obese type 2 diabetes analyzed the relationship between sleep and metabolic parameters in 305 subjects.[75] The only significant association was an inverse correlation between fasting glucose levels and sleep efficiency, but not AHI or other sleep variables. A limitation of this study is that PSG was performed in the home of the participants, and was thus often of lower quality and shorter duration than in the laboratory.

Altogether, current evidence is in support of an adverse impact of OSA on glycemic control in patients with type 2 diabetes. As differences in HbA1c levels among patients with different degrees of severity of OSA are comparable to the effect size of the most powerful combinations of available diabetes medications, multiple studies have attempted to determine if OSA treatment with CPAP in patients with diabetes will improve glycemic control, as discussed later.

OSA and diabetes complications

The development of microvascular complications of diabetes is associated with poor long-term glycemic control and increased healthcare costs. Because OSA is associated with activation of the sympathetic nervous system and of inflammatory processes as well as oxidative stress, it is likely that OSA contributes to the development and/or progression of these complications irrespective of strategies to optimize diabetes control. Although the details are beyond the scope of this current review, there is evidence that type 2 diabetes patients with OSA may suffer more complications, including peripheral neuropathy, retinopathy, and nephropathy,[76–78] than those without OSA, with the degree of oxygen desaturation being an independent predictor in some studies.[76,77] This field is a subject of ongoing research to establish whether OSA is an independent predictor of diabetes complications and whether OSA treatment will delay the development or decrease the severity of microvascular complications.

REM-related OSA

The reduction in pharyngeal muscle activity that normally occurs during REM sleep is associated with more prolonged obstructive events and more severe oxygen desaturation in OSA patients.[79] In some patients, the respiratory events occur predominantly during REM sleep. This phenomenon has been termed *REM-related OSA* and is prevalent in 10–36% in OSA patients.[80] Compared to NREM sleep, apneas and hyponeas during REM sleep are

associated with higher sympathetic nervous system activation and greater degrees of hypoxemia.[81] It has been suggested that REM-related OSA may lead to greater cardiometabolic derangements and more adverse health consequences.[80] This hypothesis was addressed for the first time in a recent cross-sectional study involving laboratory PSG in 115 participants with type 2 diabetes. Higher REM AHI and REM microarousal index were significantly correlated with higher HbA1c levels, supporting the significance of REM-related OSA for glucose metabolism.[82] In contrast, associations between NREM AHI or NREM microarousal index and HbA1c were nonsignificant.

Effects of CPAP treatment on glucose metabolism and diabetes control

A detailed review of the effects of CPAP treatment on various indexes of glucose metabolism has been recently published.[56] Multiple studies with different designs (observational versus randomized controlled trial (RCTs)), utilizing sham-CPAP or placebo, different duration of treatment and/or nightly CPAP use, different participant characteristics (diabetes versus metabolic syndrome versus nondiabetes versus combination, adiposity, sex distribution), and markers and methods of assessing glucose metabolism (glucose level, insulin level, insulin sensitivity, disposition index and HbA1c, single blood sample versus OGTT versus euglycemic clamp) have been used. These methodological differences may partially account for the inconsistent results. Sham-CPAP generally delivers the pressure of less than 1 cm H_2O and its use as a placebo has been endorsed in CPAP intervention studies.[83] Among the eight RCTs utilizing sham-CPAP with duration between 1 week and 3 months and between 2.8 and 6.2 h/night of treatment, five found that active CPAP did not improve fasting glucose levels or insulin sensitivity,[84–88] one observed an improvement of insulin sensitivity at 24 weeks (nonrandomized part of the study) but not at 12 weeks during randomization,[89] and two reported an improvement in insulin sensitivity mainly in obese patients or those with severe OSA.[90,91]

Three meta-analyses have tried to summarize the impact of CPAP treatment on markers of glucose metabolism.[92–94] The inclusion criteria of these meta-analyses also differed, with one including only studies with inactive control or sham-CPAP, two including both observation and RCTs, and one including only the studies that utilized HbA1C as a part of the outcome measures. Therefore, these three meta-analyses included different studies with some overlap. Hetch *et al.* reported no effect of CPAP treatment on insulin, HOMA, or HbA1c levels from six studies utilizing inactive control or sham-CPAP (total 296 participants).[94] Iftikhar *et al.* reported no effects on HbA1c from nine studies (both observational and RCTs) involving 151 participants.[92] The only analysis that demonstrated a positive result found an improvement in HOMA with a mean difference of −0.55 (95% CI −0.91 to −0.20) in nondiabetic subjects with moderate-to-severe OSA (from nine studies, both observation and RCTs, totaling 248 subjects) but no differences in fasting glucose levels in 39 diabetic participants from two studies.[93]

Therefore, despite the strong association between OSA and abnormal glucose metabolism, the results of interventional CPAP studies remain inconsistent and inconclusive. Several potential confounding factors, including nightly duration of CPAP usage, number of days or months on CPAP treatment, and baseline characteristics of the patients, need to be rigorously controlled in future studies.

Sleep disturbances during pregnancy: relationship with glucose metabolism and gestational diabetes

Sleep alterations are common during pregnancy due to hormonal and physical changes. Progesterone has strong sedative effects and can stimulate respiratory drive, while estrogen increases hyperemia, mucosal edema, and upper airway resistance, resulting in nasal stuffiness and snoring.[95] Upward displacement of the diaphragm may cause a reduction in functional residual volume of the lungs and, therefore, oxygen reserve. Nausea, vomiting, frequent urination, and backache can decrease sleep efficiency and increase nocturnal awakenings.

During the first trimester, sleepiness is common, and women report an increase in sleep duration of approximately 0.7 h.[96] However, sleep efficiency and percentage of SWS decrease significantly.[97] Sleep duration decreases in the late second trimester[97] although there is an observed increase in percentage of SWS.[98] During the third trimester, a majority of women report sleep disturbances. There is a decrease in percentage of SWS and REM sleep,[95] with an increase in time spent in light NREM sleep

(stage N1).[99] Wake time after sleep onset increases, but total sleep time approximates the prepregnancy state.[97] At this stage of pregnancy, a majority of women report taking daytime naps.[100] Snoring is quite common, as two large studies, including in total more than 2700 pregnant women, revealed that about a third of participants reported snoring, with 25% reporting pregnancy-onset snoring.[101,102] Symptoms of OSA were shown to increase during pregnancy in a prospective study, especially in women whose BMI exceeded 25 kg/m^2.[103]

Gestational diabetes mellitus (GDM) affects 2–10% of pregnant women and is associated with adverse maternal–fetal outcomes. Recently, an increased risk for GDM and hyperglycemia has been found to be associated with sleep disturbances, including OSA and snoring, short sleep duration, and increased daytime sleepiness. Our review of the literature found 14 studies that investigated sleep and glucose tolerance in pregnancy, eight of which utilized questionnaires, five used objective sleep measurements, and one used both (Table 1).[101,102,104–115] Six studies assessed sleep duration (four by self-reporting, one combined self-reporting and PSG, and one utilized actigraphy).[106–108,111,113,114] Of these six studies, four found a significant association between short sleep duration and increased risk for GDM/hyperglycemia.[106,108,111,114] Eleven studies assessed symptoms of OSA or a diagnosis of OSA.[101,102,104–106,108,110–113,115] Of the eight studies using questionnaires, five found significant associations between OSA symptoms and GDM or maternal hyperglycemia.[102,106,108,111,113] Among the five studies using objective measurements (four utilized PSG and one utilized portable home monitoring),[104,105,112,113,115] four found a significant association between OSA and increased GDM/hyperglycemia risks.[104,105,112,115] Note that the numbers of GDM women in two of the studies were small (6 and 20).[104,105] The largest study had 167 women with GDM, but control subjects did not have a PSG study, and adjustment for adiposity was not done on the basis of BMI values but rather on the diagnosis of obesity.[112] A recent PSG-based case-control study compared women with GDM and pregnant women with normal glucose tolerance, matched for age, ethnicity, and stage of pregnancy.[115] The analysis revealed that the diagnosis of GDM was associated with a significant increase in risk of being diagnosed with OSA (OR 6.6) after adjusting for prepregnancy BMI. One study found an association between severe daytime sleepiness and GDM, although the number of women with severe daytime sleepiness was small.[109] In addition, increased daytime napping was found to be associated with maternal hyperglycemia in one study.[113] The mechanisms by which sleep disturbances increase the risk for GDM are likely to overlap those linking sleep disturbances and metabolic alterations in nonpregnant populations, but have not been studied specifically in pregnancy.

Short sleep, snoring, and OSA in pregnancy have been linked to other adverse maternal and fetal outcomes, including an increased risk of preeclampsia, pregnancy-induced hypertension, preterm birth, and unplanned caesarean delivery.[101,102,112,116,117] Oxidative stress, release of proinflammatory cytokines, increased sympathetic activation, peripheral vasoconstriction, and endothelial dysfunction resulting from sleep disturbances are all likely to contribute to these complications,[118] as will be discussed later.

Treatment with CPAP has been shown to be safe during pregnancy and improves blood-pressure control and pregnancy outcomes in women with hypertension and chronic snoring.[119] The question of whether treating OSA during pregnancy will improve glucose metabolism is crucial, as maternal glycemia affects fetal health, but has not been addressed so far.

Pathways linking sleep disturbances to abnormal glucose metabolism

Pathways involved in the adverse metabolic impact of insufficient sleep and sleep fragmentation

Laboratory studies in healthy humans have provided evidence for the implication of multiple pathways in the link between reduced sleep duration and/or quality, insulin resistance, and hyperglycemia (Fig. 3).

Decreased brain glucose use during waking hours. The brain uses glucose in an insulin-independent manner and is responsible for at least 50% of total glucose use in the fasting state. The rate of cerebral glucose metabolism as measured by positron emission tomography and $^{[18]}$fluorine-2-deoxyglucose following a 24-h period of total sleep deprivation has been found to be significantly

Table 1. Studies investigating the association between sleep in pregnancy and gestational diabetes or hyperglycemia[a]

Study/n	Time of assessment	Assessment	Outcomes of interest[a]	Results
Studies utilizing questionnaires				
Qui *et al.*[108] $n = 1290$	Early pregnancy	Sleep duration, snoring	GDM	• Sleeping ≤4 h was associated with increased risk of GDM compared to sleeping 9 h (RR 5.56, with RR 3.23 for lean and 9.83 for overweight women), adjusting for age, race/ethnicity • Women who snored "most or all of the time" had increased risk of GDM compared to those who did not snore (RR 1.86, with RR 6.9 for overweight women who snored)
Bourjeily *et al.*[102] $n = 1000$	Immediate postpartum period	Multivariable Aopnea Prediction index	GDM	• Sleep-disordered breathing (SDB) symptoms were associated with GDM (OR 2.1), adjusting for age, BMI at delivery, multiple pregnancies, and current smoking
Facco *et al.*[106] $n = 189$	Early pregnancy (6–20 weeks) and third trimester	Sleep duration, snoring	GDM, 1-h glucose values from 50-g OGTTT	• Women sleeping <7 h had higher glucose values and higher incidence of GDM (OR 11.7) than those who slept ≥7 h adjusting for age, race/ethnicity, BMI, and frequent snoring • Women who snored ≥3 times/week had higher glucose values and higher incidence of GDM (OR 6.9), adjusting for age, race/ethnicity, BMI, and sleeping <7 h
Ugur *et al.*[110] $n = 465$	During pregnancy or admission for labor	Berlin Questionnaire	GDM	• More women with increased OSA risk had GDM, but not after adjusting for BMI and maternal medical disorders
Reutrakul *et al.*[111] $n = 169$	Second trimester (26 weeks)	Pittsburg Sleep Quality Index, Berlin Questionnaires, Epworth Sleepiness Scale	GDM, 1-h glucose values from 50-g OGTT	• Each hour of reduced sleep time was associated with 4% increase in glucose levels • Increased OSA risk was associated with GDM (OR 3.0) • Sleeping < 7 h was associated with GDM (OR 2.4) • Combination of increased OSA risk and sleeping <7 h was associated with GDM (OR 3.4) • Frequent snoring (>3–4 days/week) was associated with GDM (OR 3.4)
O'Brien *et al.*[101] $n = 1719$	Third trimester	Snoring	GDM	• No association between chronic snoring (3–4 times/week) or pregnancy-onset snoring with GDM
Bourjeily *et al.*[109] $n = 1000$	Immediate postpartum period	Epworth Sleepiness Scale	GDM	• No association with GDM in those with score >10. • Significant association with GDM was found in those with score >16 after adjusting for age, BMI at delivery, and current smoking. The authors cautioned that the number of women with score >16 was small.
O'Brien *et al.*[107] $n = 1211$	Second to third trimester	Sleep duration	Maternal hyperglycemia (1-h glucose value after 50-g OGTT ≥140 mg/dL)	• No differences in glucose values between short sleepers (≤ 6 h/night), normal sleepers (7–9 h/night), or long sleepers (≥10 h/night)

Continued

Table 1. *Continued*

Study/n	Time of assessment	Assessment	Outcomes of interest[a]	Results
Studies utilizing objective measurements of sleep				
Facco *et al.*[105] $n = 143$ (women who had both PSG and delivery records)	PSG: 46% before and 54% after delivery	PSG; mild (AHI 5–14.9) and moderate-to-severe OSA (AHI ≥ 15)	GDM	• 34 women with mild and 26 with moderate-to-severe OSA. Six women had GDM • None of the women without OSA had GDM, while 5.9% of those with mild OSA, and 11.5% of those with moderate-to-severe OSA had GDM ($P = 0.004$)
Chen *et al.*[112] 791 with OSA and 3955 age-matched women presumed without OSA	Women with OSA had PSG within 1 year before index deliveries. Matched control did not have PSG.	PSG; diagnosis of OSA	GDM	• 167 women diagnosed with GDM • OSA was significantly associated with GDM (OR 1.63) after adjusting for education, marital status, gestational hypertension, anemia, coronary heart disease, hyperlipidemia, obesity, geographic region, paternal age, infant's sex, and parity.
Izci- Balserak *et al.* [113] $n = 104$	First trimester, 83 had repeated PSG in third trimester	PSG Pittsburg Sleep Quality Index, Multivariable Apnea Prediction Index	Maternal hyperglycemia defined as 1-h glucose value after 50-g OGTT ≥ 135 mg/dL	• 11 Women had hyperglycemia • Self-reported loud snoring, snorting/gasping, and apneas were associated with maternal hyperglycemia (OR 3.37) after adjusting for age, race, neck circumference, and shift work • Self-reported nap duration was associated with hyperglycemia (OR 1.64) after adjusting for age, race, and neck circumference • First trimester AHI, self-reported sleep duration, sleep duration, and efficiency by PSG were not associated with hyperglycemia
Herring *et al.*[114] $n = 76$	21 weeks	Actigraphy for 6 days; sleep duration	1-h glucose after 50-g OGTT	• Each hour of reduced sleep time was associated with 8.2 mg/dL increase in glucose levels • Shorter night-time sleep was associated with hyperglycemia (glucose ≥ 130 mg/dL) after adjusting for age and BMI, OR 0.2
Facco *et al.*[104] $n = 75$ (high-risk group for preeclampsia)	17 weeks	Portable monitor (WPAT200); Diagnosis of OSA	GDM	• OSA was significantly associated with GDM (OR 3.7) after adjusting for maternal age, BMI, history of chronic hypertension
Reutrakul *et al.*[115] $n = 45$ (15 GDM, 15 pregnant NGT,[b] and 15 nonpregnant NGT; matched for age and ethnicity)	Late 2nd–early 3rd trimester in pregnant women	PSG; Diagnosis of OSA	Risk of OSA in GDM women	• 11 GDM women (73%) had OSA • GDM was significantly associated with OSA (OR 6.6) after adjusting for pre-pregnancy BMI • In NGT women, pregnancy was associated with higher AHI, microarousal index, and wake time after sleep onset.

[a]Many studies had other outcomes of interest, but only outcomes related to glucose metabolism are summarized here.
[b]NGT, normal glucose tolerant.

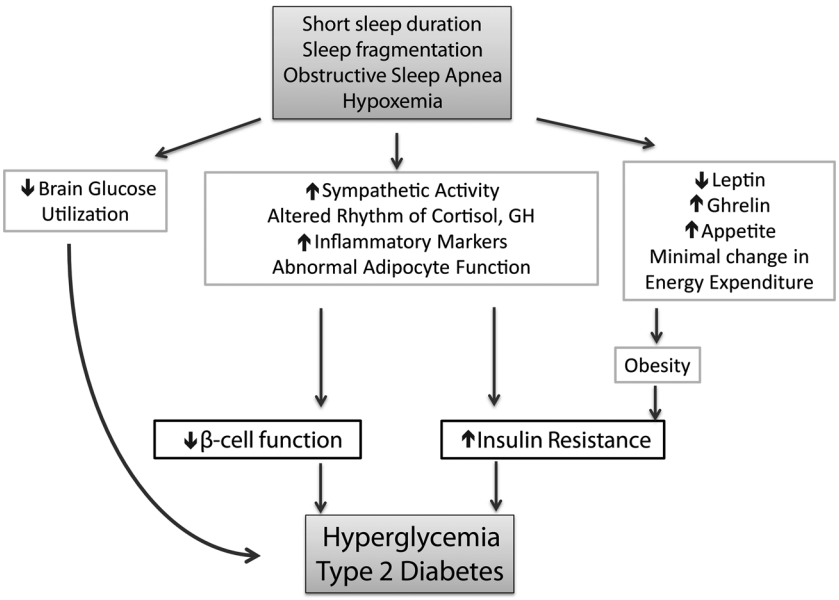

Figure 3. Pathways linking sleep insufficiency, fragmentation, obstructive sleep apnea, and hypoxemia to abnormal glucose metabolism and type 2 diabetes.

decreased, especially in several cortical and subcortical areas.[120] This is in agreement with the findings of a sleep debt study that revealed a 30% reduction in glucose effectiveness, an index of insulin-independent glucose disposal.[1]

Increased sympathetic nervous system activity. It is well documented that sleep deprivation and sleep fragmentation lead to a shift in sympathovagal balance toward an increase in sympathetic nervous system activity, as reflected by lower heart-rate variability.[1,25] Increased sympathetic nervous system activity has inhibitory effects on insulin secretion and promotes insulin resistance and the development of the metabolic syndrome.[121,122] In addition, some studies have documented increased serum and urine norepinephrine and epinephrine concentrations following sleep deprivation.[4,5,123] These hormones promote gluconeogenesis.

Alterations in the hypothalamic–pituitary–adrenal (HPA) axis and growth hormone (GH). Several studies observed an increase in salivary and serum cortisol levels following sleep deprivation, particularly in the evening and early part of the night, at the time when the levels are normally very low following the normal circadian pattern.[1,5,124,125] In one study, there was no change in corticotropin (ACTH) level, suggesting an enhanced adrenal reactivity.[124] Evening elevations of cortisol may promote morning insulin resistance.[126] An increase in morning serum cortisol levels was also reported after sleep fragmentation.[25] In a sleep debt study, GH secretion was found to increase before sleep onset and to limit the amplitude of postsleep onset GH release.[2] Prolonged night-time exposure to GH may promote hyperglycemia.

Increase in systemic inflammatory response. Inflammatory responses to sleep deprivation have been reviewed in detail.[127] Multiple studies demonstrated increases in leukocyte and monocyte counts[128–130] and elevations in the levels of proinflammatory cytokines including IL-1β, IL-6, IL-17, TNF-α, and hsCRP.[131–134] Increased proinflammatory cytokines have been linked to insulin resistance.[135] Some studies, however, did not observe alterations in the circulating levels of some of these cytokines, possibly partly due to variability of baseline levels within the population as well as the timing of specimen collection relative to the circadian cycle.[127]

Alterations in appetite-regulating hormones and increased obesity risk. Appetite-regulating hormones including leptin, which is one of the

satiety hormones, and ghrelin, which is a hunger hormone, have been studied in the context of sleep restriction experiments. The first study that assessed these changes involved two nights of 4 h in bed versus two nights of 10 h in bed in healthy, normal-weight young men.[136] During sleep restriction, leptin decreased by 18% and ghrelin increased by 28%. These changes were associated with a 23% increase in hunger ratings and a 33% increase in appetite for carbohydrate-rich foods. More than 10 subsequent studies have explored these hormonal changes in response to sleep restriction with some variations in participants' characteristics (i.e., adiposity and sex distribution), severity of sleep restriction, blood sampling methodology, and dietary protocols (*ad libitum* food access or controlled caloric consumption).[137,138] Not surprisingly, since leptin levels are highly sensitive to energy balance and modulated by sex and adiposity, the findings have been inconsistent, with decreased,[136,139–141] unchanged, or increased[6,142–144] concentrations. However, the studies that used multiple blood samplings in normal weight men under conditions of controlled food intake consistently revealed a reduction in leptin amplitude or mean levels, suggesting that the discrepancies may at least be in part due to modulation of leptin secretion by obesity, sex, and food intake. Whether the results obtained in short-term laboratory studies may be extrapolated to real-life conditions is debatable. In a field study of 80 obese adults, no associations were found between leptin levels and sleep duration or quality.[145]

Multiple studies documented increased ghrelin levels along with increased hunger in response to partial sleep restriction[136,142,144] and increased caloric intake,[146–149] notably from snacks and saturated fat. However, similar to the findings regarding leptin levels, not all studies observed increased ghrelin levels.[4,147,150] Recently, two studies utilizing functional magnetic resonance imaging revealed increased neuronal activity in certain brain areas involved in the reward system in response to presentation of food stimuli after total and partial sleep restriction.[151,152]

Since sleep restriction provides more wake time, it has been suggested that the caloric need of extended wakefulness may counterbalance the increase in hunger and food intake. Several recent studies have addressed changes in energy expenditure following sleep restriction. Surprisingly, three independent studies failed to detect an increase in energy expenditure assessed by the doubly labeled water method in individuals who were submitted to partial sleep restriction.[146–148] However, when the subjects were confined to a calorimetry room in order to monitor minute-to-minute energy expenditure during normal sleep and total sleep deprivation,[153] the caloric cost per hour of wakefulness under sedentary conditions as compared to sleep averaged only 17 kcal, suggesting that the stimulation of hunger and food intake far exceeds the caloric needs of extended wakefulness. A recent study involving 5 days of partial sleep restriction, similar to a work week, under controlled laboratory conditions indeed observed that the approximate 5% increase in daily energy expenditure was overcompensated by energy intake, particularly at night, resulting in significant weight gain.[154] Additionally, there is evidence that the sleepiness and fatigue associated with insufficient sleep may result in a reduction in voluntary physical activity.[155,156]

Collectively, these changes in appetite regulation in favor of increased hunger and food intake without commensurate increase in energy expenditure place individuals at risk for obesity. These results are supported by multiple prospective studies that found a significant association between short sleep and greater weight gain in both adults and children.[157–160]

Abnormal adipocyte function. Adipocytes play a pivotal role in the regulation of energy balance and appear to play an important role in the changes in energy balance in response to sleep restriction.[161] Leptin is released primarily from subcutaneous fat depot in direct proportion to insulin-stimulated glucose uptake and total subcutaneous fat mass.[162] Increased sympathetic nervous activity leads to stimulation of lipolysis and increased free fatty acids, which could lead to insulin resistance.[163] In addition, it is well known that elevated levels of glucocorticoids facilitate visceral fat accumulation, increased lipolysis, and insulin resistance. Molecular mechanisms involved in insulin signaling in adipocytes collected from individuals who were sleep restricted were recently examined by Broussard *et al.*[3] Seven healthy adults participated in a randomized crossover study of 4 days with 4.5 h in bed or 8.5 h in bed under controlled conditions of caloric intake and physical activity. Subcutaneous

fat biopsy under restricted sleep conditions revealed a 30% reduction in the ability of insulin to increase levels of phosphorylated Akt, a crucial early step in the insulin-signaling pathway, compared to during normal sleep conditions. This impaired cellular insulin sensitivity paralleled the decrease in total body insulin sensitivity as assessed by IVGTT.

Pathways involved in the adverse metabolic impact of long sleep duration

The mechanisms linking long sleep duration and abnormal glucose metabolism are poorly understood. One of the limitations is that most, if not all, studies documenting an adverse metabolic impact of long sleep (typically >8–9 h/night) have been based on self-reported sleep duration. It has been speculated that long sleepers are actually poor sleepers who extend their time in bed to try to compensate for poor sleep quality.[164] Another possibility is that long sleepers suffer from fatigue resulting from an undiagnosed preclinical condition. In a study of type 2 diabetes patients, long sleepers (≥8.5 h/night) were more likely to have depressive symptoms and to be more physically inactive compared to those who reported sleeping 6.5–7.4 h/night.[22] Increased sedentarity, a correlate of long sleep, could also have adverse cardio-metabolic effects. A prerequisite to the identification of putative mechanisms that could mediate adverse effects of long sleep is the demonstration that these effects are still present when sleep duration is assessed objectively, rather than by self-report.

Pathways involved in the adverse metabolic impact of OSA

Besides sleep fragmentation and reduced total sleep time, the component of oxygen desaturation is unique to OSA. There is no study addressing mechanisms linking hypoxia during sleep to abnormal glucose metabolism in humans, but mechanistic links have been well documented in the rodent model of IH. IH induces acute insulin resistance in mice through several mechanisms, including activation of hepatic lipid synthesis leading to hepatic insulin resistance, activation of sympathetic nervous system and HPA axis, and alterations of adipokines.[165] In addition, IH was shown to increase oxidative stress and lead to increased β cell proliferation and cell death.[166]

In summary, there is a large body of evidence in support of a causal relationship between sleep disturbances (duration, quality, and OSA) and alterations in multiple physiologic pathways resulting in abnormal glucose metabolism, increased diabetes

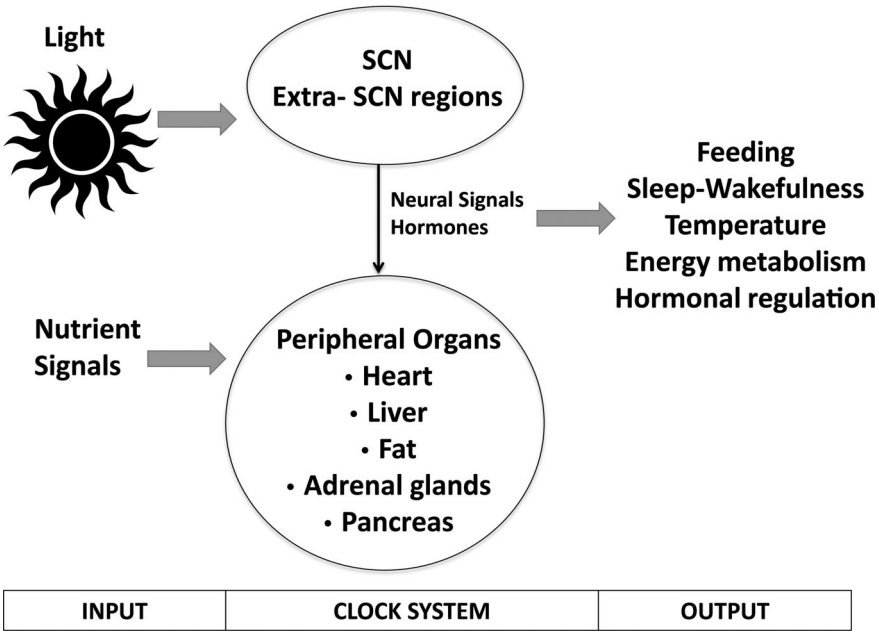

Figure 4. Illustration of the circadian system regulation.

risk, and possibly contributing to poor glycemic control in individuals who are prediabetic or diabetic. Further research studies should explore whether optimizing sleep duration and quality will in the long term result in decreased diabetes risk or improved glycemic control in patients with established type 2 diabetes.

The circadian system and glucose metabolism

The circadian system, controlled by the master circadian clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus, plays a major role in regulating daily rhythms of sleep/wake cycle, feeding behavior, central and peripheral tissue metabolism, and hormonal secretions.[167] The clock in the SCN is synchronized to the 24-h day primarily by light signals conducted via the retinohypothalamic tract. It then relays the information via hormonal and neuronal pathways to the rest of the brain, and to peripheral organs such as the heart, liver, adipose tissue, muscle, adrenals, and pancreas, which all possess "peripheral clocks," leading to coordinated rhythms and behaviors[168] (Fig. 4). The central clock mechanism consists of a transcription–translation negative feedback loop involving several core clock genes, including *Clock* (circadian locomotor output cycles kaput), *Bmal1* (brain and muscle arnt-like protein-1), *Per 1–3* (Period 1–3), and *Cry1–2 (*Cryptochrome 1–2), as well as feedback signals from nutrient intake.[167]

There is evidence that circadian disruption has detrimental effects on energy metabolism. It was first shown that *Clock* mutant mice shift their feeding and activity behavior to their normally inactive phase and develop obesity and the metabolic syndrome (hyperlipidemia, hepatic steatosis, hyperglycemia, and hypoinsulinemia).[169] Habitual sleep duration in this mutant animal is about 1 h shorter than in the wild type, thus resulting in a condition of lifelong insufficient sleep.[169] In another study, wild-type mice exposed to dim light during their usual biological night were shown to shift their food intake into the inactive phase. This was associated with reduced glucose tolerance and a greater gain in body mass, suggesting that eating at an adverse circadian time contributed to metabolic dysfunction in these animals.[170]

In humans, living in modern industrialized societies with 24-h access to light coupled with work/social obligations often leads to behaviors that are inappropriately timed relative to endogenous circadian rhythms. This mismatch in timing is termed *circadian misalignment*. Night-shift work is an example of severe circadian misalignment, as workers are awake, active, and eating during their biological night and trying to sleep and fast during their biological day. Several prospective studies demonstrated that shift work is associated with an increased risk of developing diabetes. The Nurses' Health Study followed 177,184 participants for 18–20 years and found that those who worked rotating night shifts had increased hazard ratios for diabetes between 1.03 and 1.24, after adjusting for traditional diabetes risk factors as well as BMI, with higher risk in those who had a longer duration of shift work compared to those reporting no shift work.[171] Although the magnitude of the increased risk associated with shift work was modest when other risk factors were controlled for, the findings suggest that shift work may compound the risk imparted by traditional risk factors. Another 10-year longitudinal study in 2426 alternating-shift workers and 3203 day-shift workers found that alternating-shift work was associated with a significantly increased risk for development of diabetes, with OR of 1.35.[172]

Human experiments in controlled laboratory settings have provided insights into metabolic alterations under experimentally induced circadian misalignment. Ten healthy adults underwent a 10-day laboratory protocol that involved sleeping and eating on a 28-h day. Circadian misalignment, when the participants ate and slept 12 h out of phase from their habitual times, was associated with a 6% increase in glucose levels despite a 22% increase in insulin concentration. Further, leptin levels were decreased. Three subjects had postprandial glucose responses in a prediabetic range.[173] Another carefully conducted experiment combined sleep restriction with circadian disruption and involved 24 participants studied for more than 5 weeks in a controlled laboratory setting.[174] After 3 weeks of sleep restriction to 5.6 h/day and recurring 28-h days, fasting and postprandial glucose levels were increased by 8 and 14%, respectively. These changes were apparently caused by decreased β cell function as plasma insulin decreased by 12% during fasting and 27% after meals. The metabolic derangements returned to baseline levels after 9 days of sleep recovery.

Many individuals in modern society experience a form of mild circadian misalignment, especially during the work or school week, as they follow social rhythms imposed by professional obligations, school schedules, family, and other commitments rather than their own biological rhythms.[175] The degree of misalignment is dependent on the individual's *chronotype.*[175] Chronotype is a construct that captures an individual's preference for being a "morning" or "evening" person. Late chronotype is typically associated with a greater degree of misalignment between social rhythms and the circadian clock.[175] Chronotype can be evaluated in several ways. In 1976, Horne and Ostberg developed the Morningness–Eveningness questionnaire, which categorizes respondents into five types (definitely morning, moderately morning, neither morning nor evening, moderately evening, and definitely evening). These chronotypes correlate with the participants' circadian peak time of body temperature.[176] Subsequently, Roenneberg and colleagues proposed the mid-sleep time on free days (MSF) as a metric of chronotype. MSF is derived from mid-sleep time on weekend nights, with further correction for calculated sleep debt with the assumption being that sleep timing on days when unconstrained by the social clock would more accurately reflect the underlying phase of the circadian system.[177,178] Recently, a large cross-sectional study in Finland involving 4589 participants found that those who were evening types had a 2.5-fold odds ratio for type 2 diabetes, as compared to morning types. This association was independent of sleep duration and sleep sufficiency.[179] Two separate cohorts (1244 and 483 participants, respectively) provided similar findings where eveningness was associated with increased risk of metabolic syndrome (OR 1.4 and 2.2, respectively)[180,181] and diabetes (OR 2.0)[181]. In addition, several genetic studies have shown that individuals carrying specific variants of the canonical circadian genes *Clock* and *Bmal-1* had evening preference, resistance to weight loss, metabolic syndrome and susceptibility to type 2 diabetes.[182–184]

Furthermore, evening chronotype in nondiabetic individuals was found to be associated with unfavorable cardiometabolic profiles.[185] A study involving 119 obese short sleepers ($\leq$6.5 h/night) revealed that eveningness was associated with eating later and a larger food portion size, an increase in BMI, and a lower HDL cholesterol level. Evening types were also found to have more sleep apnea and higher stress hormones. These results are suggestive of a higher risk of cardiovascular disease in this population.

The first study to address the contribution of chronotype in patients with type 2 diabetes involved comprehensive questionnaires to assess sleep and eating habits in 194 nonshift worker participants who all had an established diagnosis of diabetes.[186] After adjusting for age, sex, race, BMI, insulin use, depressed mood, diabetes complications, and perceived sleep debt, chronotype, as assessed by MSF, was significantly associated with glycemic control (Fig. 5). The difference in median HbA1c between participants in the fourth quartile of MSF

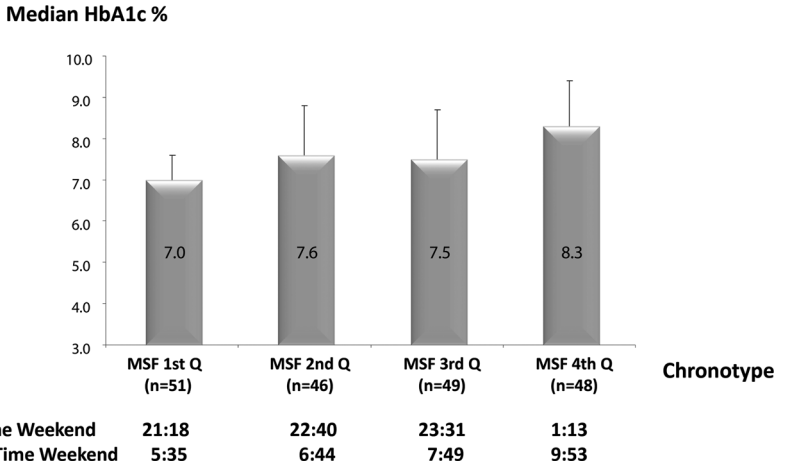

Figure 5. HbA1c levels across quartiles of mid-sleep time on free days (MSF), an indicator of chronotype. Later chronotypes had significantly higher HbA1C levels and later bedtimes/wake times than those with earlier chronotypes.

compared to the first quartile was approximately 1.3%, a remarkably strong effect size. Besides having significant later bedtime/wake time and poorer glycemic control, participants with later chronotype were more depressed, had a higher BMI, and were significantly more likely to require insulin. This suggested that patients with type 2 diabetes who have a late chronotype may be more hypoinsulinemic, consistent with the findings in the *Clock* mutant mice.

Another neurohormone, which plays an important role in circadian regulation, is melatonin, secreted by the pineal gland. Its secretion is modulated by light signals through the SCN and the sympathetic nervous system.[187] Melatonin secretion follows a diurnal pattern with low levels during the day, an abrupt increase 1–2 h before habitual bedtime, high levels throughout the night, and a progressive decrease initiated before habitual wake-up time.[188,189] Melatonin exerts its effects through membrane receptors belonging to the class of G protein-coupled receptors.[190] In mammals, there are two receptor isoforms: MT1 and MT2 (found in the brain, SCN, retina, and peripheral tissues).[191] Melatonin can entrain circadian rhythms because of its effect on the SCN.[192] In addition, both isoforms of melatonin receptors are found in the pancreatic β cells and α cells,[190] and melatonin has been shown to modulate insulin secretion through rather complex cascades involving several secondary messengers and possibly through α cell stimulation.[190,193] Therefore, melatonin may act as a mediator between the central circadian regulation and peripheral metabolism as well as an internal signal synchronizing the central circadian clock and clocks in peripheral tissues. A recent review has suggested that the increased duration of exposure to light that is common in modern society may inhibit melatonin release and disrupt seasonal cycles. The authors further suggest that these factors could be involved in causing metabolic disturbances.[194]

Recently, genetic studies have linked the gene encoding MT2, *MTNR1B,* to abnormal glucose metabolism and diabetes risks.[195–198] In a study involving 19,605 Europeans, the MTRN1B intronic variant, rs 10830963, was associated with a significantly increased risk of impaired fasting glucose, with an OR of 1.6.[195] In addition, analyses in subgroups of this population revealed an association of this genetic variant with increased type 2 diabetes risk, with ORs of 1.19 (French case-control study) and 1.23 (Danish case-control study). This allele was associated with decreased insulin secretion after oral and intravenous glucose challenges. Another study in 1276 healthy individuals of European ancestry revealed that this MTNR1B variant was associated with higher fasting glucose levels, decreased early insulin response, and decreased β cell glucose sensitivity, as evaluated by an OGTT and a euglycemic–hyperinsulinemic clamp.[196] Because the effect of this allele on diabetes risk was modest, a large-scale exon resequencing was conducted in 7632 Europeans (including 2186 type 2 diabetes individuals).[199] This identified 40 nonsynonymous variants, including 36 very rare variants, which were associated with a much higher increased risk for type 2 diabetes (OR 3.31). Among the rare variants, those with partial or total loss of function (i.e., complete loss of melatonin binding and signaling capabilities), but not the neutral ones, significantly contributed to diabetes risk (OR 5.67).

A recent well-documented epidemiologic study demonstrated a link between low nocturnal melatonin secretion and development of diabetes.[200] In this case-control study nested within the nurses' Health Study Cohort, 370 women who developed type 2 diabetes during a follow-up of 10–12 years were matched with 370 controls. Women with the lowest baseline urine secretion of 6-sulfatoxymelatonin, a major metabolite of melatonin, had an increased risk of subsequent diabetes development, with an OR of 2.16 compared to those with the highest levels, after adjusting for demographics, lifestyle habits, sleep duration, snoring, and biomarkers of inflammation and endothelial dysfunction. The authors postulated several mechanisms by which low melatonin may be associated with diabetes. These include reduced sleep duration and sleep apnea, which are known to be associated with low melatonin levels[201,202] but could not be accurately captured by the study questionnaires.

Increasing melatonin level by exogenous supplementation in patients with diabetes was conducted in a randomized, double-blinded, crossover study involving 36 type 2 diabetes patients with insomnia.[203] Prolonged-release melatonin administration significantly improved sleep efficiency and reduced wake time after sleep onset, as assessed by actigraphy at 3 weeks, but without changes in glucose levels. However, HbA1c improved significantly at 5 months during the open labeled phase (−0.6%

compared to baseline) without changes in C-peptide levels, but the magnitude of this improvement was not predicted by sleep improvements as assessed by actigraphy. The study was limited by the lack of assessment of the circadian system.

Taken together, these human experimental studies, results from cross-sectional studies, and genetic data support the contribution of the circadian system and sleep timing in metabolic regulation. Prospective and interventional studies are required to evaluate the role of the circadian system in the development and severity of type 2 diabetes.

Conclusion

Disturbances of different aspects of sleep, including sleep duration, quality, respiratory function during sleep, and circadian timing have all been linked to abnormal glucose metabolism. Well-controlled in-laboratory experiments have provided some evidence for causal effects. As the prevalence and costs of care for metabolic syndrome, type 2 diabetes, and gestational diabetes show no signs of decline, the efficacy and effectiveness of interventions optimizing sleep to prevent the development or reduce the severity of these metabolic disorders need to be urgently evaluated.

Conflicts of interest

S.R. has no potential conflicts of interest. E.V.C. receives grant support from Philips/Respironics, the ResMed Foundation, and Amylin/Bristol-Meyers-Squibb; is a consultant for Pfizer Inc., Viropharma, and Vanda Pharmaceuticals; is an associate editor for the journal *SLEEP*, and for a volume entitled *Sleep Loss and Obesity: Intersecting Epidemics* published by Springer Science & Business, LLC; and serves as an expert witness for Lamson, Dugan and Murray, LLP (Omaha, NE).

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