Metabolic consequences of sleep and circadian disorders

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Abstract

Sleep and circadian rhythms modulate or control daily physiological patterns with importance for normal metabolic health. Sleep deficiencies associated with insufficient sleep schedules, insomnia with short-sleep duration, sleep apnea, narcolepsy, circadian misalignment, shift work, night eating syndrome and sleep-related eating disorder may all contribute to metabolic dysregulation. Sleep deficiencies and circadian disruption associated with metabolic dysregulation may contribute to weight gain, obesity, and type 2 diabetes potentially by altering timing and amount of food intake, disrupting energy balance, inflammation, impairing glucose tolerance and insulin sensitivity. Given the rapidly increasing prevalence of metabolic diseases, it is important to recognize the role of sleep and circadian disruption in the development, progression, and morbidity of metabolic disease. Some findings indicate sleep treatments and countermeasures improve metabolic health, but future clinical research investigating prevention and treatment of chronic metabolic disorders through treatment of sleep and circadian disruption is needed.

Keywords

sleep; circadian misalignment; insufficient sleep; sleep deficiency; insulin sensitivity; energy balance; shift work; type 2 diabetes; metabolic syndrome; obesity; glucose tolerance; circadian disruption; sleep apnea

Introduction

The prevalence of chronic metabolic disorders such as obesity and Type 2 diabetes (T2D) has increased rapidly over the past 30 years reaching world-wide epidemic proportions (1).

As such, diseases of metabolic dysregulation are now a major public health burden. In parallel with the increased prevalence of obesity and metabolic disorders, nightly sleep duration in the United States has decreased with reports of over 50% of Americans sleeping 7 hours/night (2). Furthermore, U shaped associations between body mass index and sleep duration have been reported (3). These findings have brought to light the hypothesis that sleep deficiencies may have causal mechanisms contributing, at least in part, to the rapidly increasing prevalence of metabolic disorders.

Supporting this hypothesis, sleep and circadian rhythms are known to modulate or control daily patterns in human physiology with importance for normal metabolic function. Daily patterns of energy expenditure (4), hormones, and lipids involved in energy metabolism (e.g., leptin, ghrelin, PYY, glucose, insulin, glucocorticoids, catecholamines, fatty acids, triglycerides) are regulated by sleep and circadian rhythms (4-8). Disruption of sleep and circadian rhythms is increasingly evident as a contributing factor to impaired physiological function and disease processes, especially with respect to metabolic dysregulation (9-12). Sleep deficiency occurs as a result of a number of untreated sleep problems including insufficient sleep schedules, insomnia, sleep apnea, periodic limb movement disorder, narcolepsy, shift work and shift work disorder, night eating syndrome and sleep-related eating disorder (13-15). Metabolic disorders associated with sleep deficiency include unwanted weight gain, obesity, and T2D (Fig. 1) (16-19). We are now beginning to understand how sleep and circadian disruption contributes to metabolic dysregulation and how treatment of sleep and circadian problems may improve metabolic treatment outcomes.

Insufficient Sleep

More than 50% of Americans report regularly sleeping less than 7h per night (2). The International Classification of Sleep Disorders, 3rd edition (ICSD-3)(20), describes insufficient sleep syndrome as failure to obtain sufficient nocturnal sleep necessary to maintain alert wakefulness. Symptoms include daytime sleepiness with uncontrolled need for sleep or lapses into sleep, short sleep duration for the age, need of an alarm clock or being awakened by another, and longer sleep duration without such measures on free days (e.g., weekends or vacation). The sleep pattern is persistent for at least three months and reversal of the sleep problem occurs with sleep extension. Insufficient sleep is associated with the risk of multiple health problems including inflammation, depression, stress, anxiety, obesity, diabetes, cardiovascular disease and fatigue related accidents (18, 21-23).

With regards to metabolic disruption, findings from a meta-analysis (24), indicated the relative risk of developing T2D increased 2% for every year of follow-up in subjects reporting insufficient sleep. Similarly, findings from a meta-analysis including 603,519 adults and 29,502 children, showed an increased risk of obesity in adults who sleep less than 5h per night and children who sleep less than 10h per night (25). Although these reports indicate an association between insufficient sleep and metabolic diseases, causal directionality cannot be inferred based on such cross-sectional designs.

Several controlled laboratory intervention studies have investigated mechanisms of how insufficient sleep may contribute to metabolic dysregulation. With respect to weight gain,

Spiegel et al. (26) reported that two nights of 4h versus 10h sleep opportunities increased daytime ghrelin and reduced daytime leptin levels in 12 healthy young men. These hormonal changes were associated with increased hunger and appetite. Importantly, food intake was kept the same between conditions in this study, thus the impact of insufficient sleep on food intake was not determined. Recently, Markwald et al. (4) reported that 5 nights of insufficient sleep (5h per night), modeling a 5 day work-week, increased food intake and total daily energy expenditure. Increased food intake during the insufficient sleep schedule exceeded energy expenditure contributing to weight gain. Women showed more eating restraint when sleep was adequate, whereas both men and women overate during insufficient sleep. In this study, 24h leptin and Peptide-YY (PYY) levels increased and 24h ghrelin levels decreased. As food intake was *ad-libitum*, changes in appetitive hormones likely reflected the increased food intake during insufficient sleep. Comparable findings of increased food intake and altered appetitive hormones during insufficient sleep have been reported (27, 28). Together, these studies identified increased hunger and food intake associated with increased energy expenditure as potential mechanisms by which insufficient sleep contributes to obesity.

Glucose metabolism is also disturbed during insufficient sleep. Findings from a seminal study on this topic showed that six nights of a 4h per night sleep opportunity reduced glucose clearance by 40% and the acute insulin response to glucose by 30% during an intravenous glucose tolerance test (IVGTT) (29). This outcome is similar to differences between young glucose tolerant and older glucose intolerant adults. Findings from a similar study (16) indicated that seven nights of 5h sleep opportunity in healthy men decreased insulin sensitivity assessed by the hyperinsulinemic euglycemic clamp. In a longer duration study (30), 14 days of a 5.5h per night sleep opportunity reduced oral glucose tolerance and IVGTT insulin sensitivity (S_i) in healthy subjects. Insufficient sleep of four nights of a 4h per night sleep opportunity has also been shown to decrease cellular adipose insulin signaling (30%) and whole body S_i (16%) (31). Collectively, these controlled laboratory studies support the hypothesis that insufficient sleep can contribute to impaired metabolism. If persistent, such metabolic changes could contribute to or worsen T2D. Additional research is needed to improve our understanding of potential mechanisms underlying impaired metabolism associated with insufficient sleep and to investigate the potential benefit of increasing sleep in short sleepers with metabolic disorders.

Circadian Misalignment

Altering the timing of sleep and wakefulness such that sleep occurs during the daytime and wakefulness occurs at night results in circadian misalignment. One common cause of circadian misalignment is shift work in which shifts occur during the biological night, a time normally reserved for sleeping. Other common causes include insufficient sleep, social jet-lag, and night time light exposure. Circadian misalignment has been shown to alter neuroendocrine physiology with the potential for negative health consequences such as obesity and diabetes (5, 8, 9). Findings from several studies suggest that circadian misalignment may contribute to impaired glucose tolerance and reduced insulin sensitivity (8, 32, 33). In studies where meals occur during the biological night, findings show increased glucose or insulin levels (8, 33).

Research findings have shown that short-term circadian misalignment in humans to elevate postprandial blood glucose levels. These findings likely resulted from reduced pancreatic β-cell compensation or reduced insulin sensitivity (8). Long-term blood glucose dysregulation from chronic circadian misalignment may be due to differences in the circadian timing of central and peripheral circadian clocks (8, 33), which has been demonstrated in animals (34, 35), but has yet to be tested in humans. Findings from a genome wide association study indicate a possible link between circadian rhythm regulation, glucose homeostasis and melatonin signaling in the pancreas, supporting the idea that uncoupling of peripheral circadian clocks may contribute to metabolic dysregulation in humans (36). Furthermore, altered cortisol secretion relative to the feeding-fasting, wakefulness-sleep cycle during circadian misalignment may contribute to insulin resistance (8).

Weight gain in shift workers has been implicated as one potential mechanism contributing to T2D development (37). One mechanism through which this could occur is through changes in appetitive hormones reported to occur during circadian misalignment. In humans, leptin levels are typically low during wakefulness and higher during sleep. Circadian misalignment has been reported to reduce circulating leptin levels (8, 33), potentially contributing to increased appetite and weight gain. Additionally, the circadian timing of food intake can contribute to weight gain. Findings from a study that fed mice a high-fat diet (60% fat) exclusively during either the light or dark phase showed that mice fed during the light phase when they would normally be sleeping gained significantly more weight than mice fed during the dark phase when they would normally be awake (38). Similarly, mice fed a high-fat diet but with restricted feeding to their habitual wake time (dark cycle) were protected from obesity and hyperinsulinemia as compared to mice that freely consumed a similar amount of high-fat calories at unrestricted times (39). Findings from another study investigating circadian disruption in mice showed exposure to constant light increased the duration of food intake and increased the respiratory exchange ratio during habitual sleep time, indicating a higher relative carbohydrate to fat oxidation ratio (40). Such findings suggest that food consumption during inappropriate circadian times can contribute to weight gain (38). Thus, the metabolic effect of calories consumed is dependent upon the biological time of food intake. Such findings have important implications for risk of weight gain and obesity in shift workers who tend to consume more calorie-dense (41) and carbohydrate-rich (42) foods at night during the typical sleep time.

Insomnia

The prevalence of insomnia in the general population varies widely raging from ~8 to 40% (43-45). Such findings are complicated by the definition of insomnia used. For example, about 8 to 10% of the population suffers from chronic insomnia whereas about 20 to 30% suffer from symptoms of insomnia (43-45). Insomnia is defined in the ICSD-3 (20) as a complaint of difficulty three or more times per week, for three or more months, of initiating or maintaining sleep, or earlier awakening than desired, with associated daytime functioning complaints (e.g. fatigue or daytime sleepiness, cognitive impairment and accidents, mood or behavioral problems, dissatisfaction with sleep). Findings from studies investigating associations between insomnia and metabolic dysregulation are mixed (46-50). Most that did not show associations between insomnia and blood glucose regulation did not

investigate insomnia with short sleep duration or did not stratify on sleep duration (46, 48, 50). Instead, findings from the Penn Sleep Study indicated that subjects with insomnia and short sleep duration (6h per night) had the highest odds ratio (2.95 [1.2-7.0 95% CI]) of developing T2D (47). Supporting this outcome, findings from another study (49) showed insomnia with fragmented sleep in diabetic patients was associated with increased fasting insulin and reduced insulin sensitivity assessed by Homeostasis Model Assessment (HOMA). Contradictory findings from one observational study showed increased insulin sensitivity assessed by HOMA in patients with insomnia who were short-sleepers compared to patients with insomnia with 6-h sleep/night (51). But, this increased insulin sensitivity was accompanied by reduced beta-cell function assessed by HOMA-B. Chronically, reduced beta-cell function could contribute to increased T2D risk. Small sample sizes and use of only one single overnight PSG to define short-sleep limit these findings. Together, these outcomes highlight the importance of differentiating insomnia with and without short sleep duration as insomnia with short sleep duration may negatively impact glycolytic regulation. It has been proposed that different diagnoses and treatments be identified for insomnia with and without short sleep duration as these two conditions may have different causal mechanisms (44). Thus, those with short-sleep duration may particularly benefit metabolically from insomnia treatment (44). In all, the efficacy of treating patients diagnosed with insomnia with short sleep duration for metabolic outcomes remains to be established and prospective interventional studies are needed.

Obstructive Sleep Apnea (OSA)

Over 18 million Americans are affected by the respiratory sleep disorder OSA. Symptoms of OSA include daytime sleepiness and fatigue, and sleep related loud snoring or gasping for air, and reduced or cessation of airflow during sleep. The number of hypopneas (shallow breathing) and apneas (cessation of breathing), and the number of respiratory effort related arousals that occur per hour define the severity of the disorder (20). Apnea events typically last between 10-30 seconds but can extend to minutes (52). Apneas often result in reduced arterial oxygen saturation and frequent arousals from sleep. Obesity is a risk factor for both OSA and diabetes. With respect to OSA, approximately 50% of obese patients are thought to have apnea. Continuous positive airway pressure (CPAP), oral appliances and surgery are commonly used OSA therapies. Unfortunately, poor compliance is common for OSA therapies and likely contributes to deterioration of OSA associated sleep and metabolic problems.

Findings from studies consistently show an association between OSA and T2D severity independent of obesity and other potential confounding factors (53-56). Overall, data supporting an association between OSA and disturbed glycemic regulation is strong. Importantly, many patients may not present with clinical symptoms of OSA (56). Thus undiagnosed OSA may be a contributing factor to metabolic dysregulation.

Adequate treatment of OSA appears to improve glycemic regulation. For example, findings from a study of newly diagnosed OSA patients showed improvements in glycated hemoglobin (HbA1c) in subjects that used CPAP for 4 nights per week for six months, highlighting the importance of CPAP compliance (57). Findings from another study,

utilizing CPAP versus sham in patients with impaired glucose tolerance, but not T2D, showed CPAP did not improve results of an oral glucose tolerance test (OGTT) (58). More than eight weeks of CPAP may thus be needed to induce OGTT improvements in non-diabetic patients. However, with each hour of use, CPAP improved the insulin sensitivity index by 4.2% from baseline, further implicating CPAP compliance for improving glycemic regulation. In a CPAP versus sham trial (59), three months of CPAP in Metabolic Syndrome (MetS) patients improved cholesterol, triglycerides, HbA1c, and resolved MetS in 20% of the patients. Interestingly, resolution of MetS did not result from a single common MetS component. In contrast to most studies, CPAP use lead to reduced body mass index (BMI), likely contributing to resolution of MetS in this study. Whereas some trials provide evidence that CPAP therapy may improve blood glucose regulation (57, 59-61), findings are mixed (58, 62-64). Variable study populations and protocols (i.e. severity/duration of OSA and T2D diagnosis, CPAP versus sham, and CPAP duration/compliance) are likely major contributors to differing outcomes on the effectiveness of CPAP to improve blood glucose regulation.

Importantly, findings from an epidemiological study indicated that diabetes is also associated with central sleep apnea (cessation of respiratory effort) and periodic Cheyne Stokes breathing (65). Central sleep apnea and periodic breathing may be associated with diabetic autonomic neuropathy in diabetic patients (66). Like obstructive sleep apnea, central sleep apnea and periodic breathing may contribute to metabolic dysregulation in diabetic patients.

Dual therapy with CPAP and T2D medications has been investigated in a few studies with respect to treatment outcomes. A retrospective analysis of T2D patients taking a variety of blood glucose regulating medications while using CPAP (61) showed that HbA1c decreased by 0.5% over an average of 134 days of treatment. This clinically significant improvement indicates that CPAP has the potential to further benefit blood glucose regulation beyond treatment with T2D medications. Alternatively, findings from a study of T2D patients with newly diagnosed OSA and taking blood glucose medications showed 41 days of CPAP did not benefit HbA1c (62). The relatively short CPAP treatment duration may have been too short to observe benefits in glycemic regulation as measured by HbA1c. In a more controlled trial, men with established T2D on various treatment regimens underwent three months of CPAP or sham in addition to their T2D therapies (63). Findings showed HbA1c and insulin sensitivity were similar between treatment conditions suggesting CPAP may not improve blood glucose regulation over and above T2D treatment regimens in men with established T2D. However, low CPAP compliance potentially reduced its efficacy in this study, but as noted by the authors, analysis of only good compliers did not change the outcome. As the authors suggested, in patients with established T2D as in this study, β-cell function may be too impaired for CPAP to benefit blood glucose regulation on top of T2D treatments. Thus, patients with higher functioning β-cells may be most responsive to the addition of CPAP. In all, the findings from the few studies examining dual CPAP and T2D therapies for improved glycemic regulation are mixed. The studies done to date are limited and more research is required to determine the metabolic benefits of combined medication and apnea treatment.

Narcolepsy

Narcolepsy occurs in 1 out 2000 people and is defined in the ICSD-3 (20) as (a) Type 1, daytime sleepiness with uncontrolled need for sleep or lapses into sleep, cataplexy and cerebral spinal fluid (CSF) hypocretin-1 deficiency, or as (b) Type 2, daytime sleepiness with uncontrolled need for sleep or lapses into sleep, without cataplexy or CSF hypocretin-1 deficiency, but with two or more sleep onset REM periods on a daytime Multiple Sleep Latency Test performed in a sleep disorders center.

Findings from a retrospective study at the Max-Planck Institute demonstrated patients with narcolepsy had higher BMI compared to the general population (67) and such findings are supported by others (68-70). As treated and untreated patients had similar BMI, it was hypothesized that elevated BMI resulted from the pathophysiology of narcolepsy itself (e.g., loss of orexin peptide) or disease behavior such as reduced physical activity. More recently, blood glucose regulation and T2D was investigated in two studies of patients with narcolepsy using BMI matched controls (71, 72). Findings from both of these studies showed that narcoleptic patients did not have elevated risk of developing T2D or blood glucose dysregulation independent of BMI. Given that associations between narcolepsy and elevated BMI and morbidity have been reported (67-70, 73), weight gain and metabolic regulation in narcoleptic patients should be monitored. Future research is needed to understand mechanisms and test prevention of weight gain in patients with narcolepsy.

Periodic Limb Movement Disorder

Periodic Limb Movement Disorder (PLMD) is a sleep related movement disorder that affects more than 10 million American adults. The disorder is characterized by stereotypic movements of the limbs during sleep often associated with brief arousals and therefore sleep disturbance. Daytime consequences include impaired cognition, behavioral and physical functioning (20). Patients with Restless Legs Syndrome (RLS) present with PLMD, and RLS and PLMD appear to be common in patients with diabetes (74-77). Little is known about whether PLMD is associated with metabolic dysregulation in the absence of frank diabetes and therefore this represents an important research need. Also, it is unknown whether treatment of PLMD in patients with diabetes improves metabolic function.

Shift Work and Shift Work Disorder

Shift work refers to work schedules that occur during times typically reserved for sleep. Such schedules are especially common in health care, transportation, manufacturing and public services (78). In industrialized countries, shift workers make up 20-25% of the total work force (79). Findings consistently show years of shift work negatively impact sleep duration, sleep quality, performance and health outcomes (78). Shift Work Disorder (SWD) is defined in the ICSD-3 (20) as excessive sleepiness or insomnia accompanied by a reduction of total sleep time, which is associated with a recurring work schedule that overlaps the usual time for sleep during the previous three months. The prevalence of SWD is estimated at 10-38% of shift workers (15, 80, 81).

Findings from epidemiological studies consistently show shift work is associated with obesity (82-85) and T2D (86). However, findings from studies controlling for sleep duration indicate shift work is not consistently associated with MetS (87). Based on self-reported T2D, and controlling for gender and BMI, findings indicate shift workers have increased odds of developing T2D relative to individuals having never worked shift work (88). Similar findings were reported in another study that controlled for education, smoking, physical activity, alcohol consumption and insomnia symptoms (89). Findings from a study comparing rotating shift work versus day work controls indicated rotating shift work is an independent risk factor for developing T2D (90). Overall, the current literature indicates that shift workers are at increased risk of developing T2D. Whereas some studies have investigated specific causal mechanisms including circadian misalignment, this and the effectiveness of treatments for shift workers represents an important research area requiring further investigation.

Night Eating Syndrome and Sleep-Related Eating Disorder

Two eating disorders that are associated with sleep or altered circadian timing and may contribute to metabolic dysfunction are night eating syndrome and sleep-related eating disorder. Night eating syndrome is defined by consumption of a large part of the total daily caloric intake in the evening and nighttime hours (at least 25% of caloric intake after the evening meal or nocturnal awakenings with food ingestion   two time per week) and a reduction of caloric intake in the morning, for at least three months (91, 92). This eating pattern is associated with a later timing of the internal clock (93), which may contribute to the later eating pattern which is also observed during insufficient sleep schedules (4). Later sleep schedules are also reported to be associated with greater evening food intake and higher BMI (94, 95). Sleep-related eating disorder is defined in the ICSD-3 (20) by dysfunctional eating after an arousal from the primary sleep episode. This disorder is thought to be a form of sleep-walking (96-98) with partial or complete arousal from sleep and consumption of food or inedible or toxic substances (e.g., cleaning fluids). Patients are often not aware of their eating behavior until the next morning upon seeing a mess in the kitchen or on their bed clothes. Obesity is often, but not always, associated with night eating syndrome and sleep-related eating disorder (99). Limited research has been conducted to determine whether these disorders are associated with metabolic dysfunction beyond obesity. However, night eating syndrome does appear to be more prevalent than other eating disorders (e.g., binge eating disorder) in patients with T2D (100).

Conclusion

Several common sleep problems including insufficient sleep schedules, insomnia, sleep apnea, narcolepsy, shift work and shift work disorder are known to cause sleep deficiencies that likely contribute to metabolic diseases (Fig. 1). Importantly, bi-directional relationships exist between metabolic dysfunction and some of these sleep problems, most notably for OSA and obesity and T2D. Evidence for the treatment of sleep and circadian problems to improve metabolic health is emerging, with treatment of sleep apnea showing the most evidence thus far. To optimize public health recommendations based around sleep deficiency and metabolic dysfunction, a better understanding of the physiological

mechanisms by which sleep problems contribute to metabolic disorders is needed. While the metabolic consequences of some sleep disorders like OSA have been more thoroughly investigated, less is known about others. Notably, associations of circadian misalignment, PLMD, Night Eating Syndrome, and Sleep-Related Eating Disorder with T2D represent important unmet research needs. Additionally, the metabolic consequence of circadian disruption represents an emerging clinically relevant area of investigation. For example, how the circadian timing of food intake in humans influences metabolic health in patients with primary circadian rhythm sleep-wake disorders such as delayed sleep phase is unknown. Specific gaps in our understanding of physiological mechanisms by which sleep and circadian disruption contribute to metabolic dysregulation include: 1) How does insufficient sleep and circadian misalignment contribute to reduced insulin sensitivity at a tissue specific level?; 2) What are the causal mechanisms and metabolic consequences of insomnia with short-sleep duration?; 3) What are specific causal mechanisms of weight gain in narcolepsy?; 4) Are the mechanisms of circadian misalignment that lead to reduced insulin sensitivity different from the mechanisms of insufficient sleep at a whole body and tissue specific level? 5) Do sleep and circadian treatments improve metabolic health when combined with other lifestyle and treatment regimens? Given the low success of current recommendations and lifestyle interventions focusing on diet and physical activity, future treatment approaches should include new and combined approaches including those focusing on optimal sleep and treatment of sleep disorders. Healthy sleep and circadian function are increasingly becoming recognized as important for metabolic health as are sufficient physical activity and good nutrition.

Acknowledgments

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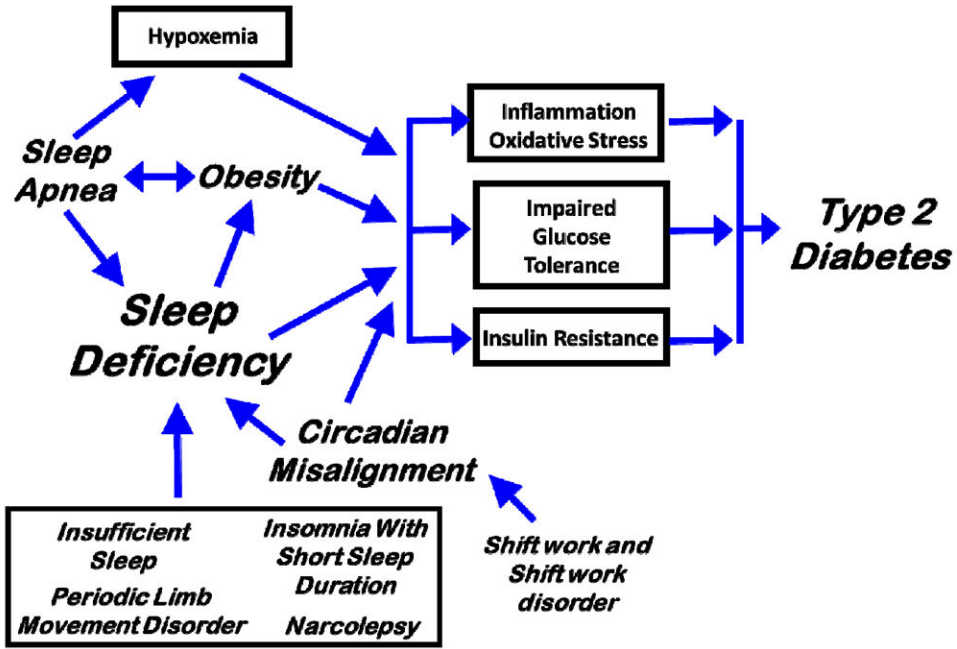
Figure 1.

Model of the hypothesized relationships between sleep and circadian disorders and type 2 diabetes. Sleep deficiency can result from several sleep and circadian disorders including insufficient sleep, periodic limb movement disorder (PLMD), insomnia and narcolepsy. By working at times that overlap with the normal sleep opportunity, shift work and shiftwork disorder can induce circadian misalignment contributing to sleep deficiency. There is a bidirectional relationship between obesity and sleep apnea and apnea results in both hypoxemia and sleep deficiency. Sleep deficiency is also associated with increased risk of obesity. Sleep deficiency, circadian misalignment, obesity and hypoxia are associated with increased inflammation, oxidative stress, impaired glucose tolerance and insulin resistance. Thus, sleep problems likely increase type 2 diabetes risk through multiple pathways.