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Metabolic consequences of sleep disorders: a comprehensive analysis of their role in diabetes

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Metabolic consequences of sleep disorders: a comprehensive analysis of their role in diabetes

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Abstract

The prevalence of type 2 diabetes continues to grow globally, and more strategies are needed to combat this public health problem. Considering the link between sleep problems and risk of type 2 diabetes, the objective of this review is to discuss the experimental and epidemiological evidence underlying the link between sleep disturbances (such as insomnia, circadian rhythm disorders, and obstructive sleep apnea), and the development of insulin resistance and glucose intolerance, which are impairments that can eventually result in type 2 diabetes. In order to explore this, PubMed and Google Scholar were utilized to find pertinent peer-reviewed publications, reviews, and clinical studies that have been published in the last four decades. Findings from this literature review suggest an existing relationship between sleep disorders and risk for type 2 diabetes. Potential mechanisms underlying the relationship between sleep disorders and risk for type 2 diabetes include: intermittent hypoxia-induced sympathetic nervous system activation, reactive oxygen species generation, induction of a whole-body pro-inflammatory state, enhanced lipolysis and modified adipokine release in adipose tissue, misalignment between central and peripheral pacemakers, and hypothalamic-pituitary-adrenal axis dysregulation with elevated circulating cortisol levels. The results demonstrate that more thorough evaluation of the roles that sleep, insomnia, and circadian rhythm disturbances play in the treatment of type 2 diabetes is desperately needed.

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Introduction

Historical Background on Sleep

As humans sleep for a third of their lives, it is not astonishing that philosophers, scientists, and medical professionals have been interested in the subject of sleep since antiquity. Since at least the fourth century B.C., there has been debate on the purpose of sleep, its processes of regulation and physiology, and its impact on human mental and physical health (Baker 1985). According to Aristotle, sleep's purpose is to enable wakefulness's sensory awareness and cognitive activities, and an excessive amount of time being causes the bodily "incapacity" (Aristotle). Although modern medicine now understands the underlying cellular and molecular malfunctions that arise due to lack of sleep, the notion that sleep has various health benefits remains the same. This review's objective is to discuss potential mechanisms underlying the experimental and epidemiological data that show sleep disturbances, such as insomnia, circadian rhythm disorders, and obstructive sleep apnea, play a significant role in the development of insulin resistance and glucose intolerance, which are impairments that can eventually result in type 2 diabetes.

With the invention of the electrophysiological instruments required to investigate small-amplitude biopotentials in the 19th century, contemporary scientific investigations into sleep patterns and mechanisms got underway (Baker 1985). It was not until 1929 that human brain biopotentials were discovered, when Berger captured electrical activity from the exposed cortex of individuals whose skulls had been removed (Kirschfeld 2005). In order to characterize the tiny biopotentials originating from brain tissue, Berger created the term electroencephalogram (EEG) and observed that sensory input changed EEG activity (Kirschfeld 2005). His research opened the door for sleep electrophysiological studies and raised awareness on the importance of analyzing sleep and its effects on diverse biological aspects of life.

Human sleep habits have been profoundly altered by modern civilization, which is marked by extensive use of electricity, the need for high performance at work, shift work, lengthy commutes, and a variety of leisure activities. As of 2022, thirty-nine percent of middle-aged Americans report sleeping for less than seven hours a night, a reduction from the average self-reported sleep length of nearly eight hours in the 1960s (Briançon-Marjollet et al. 2015, Donya 2024). Sleep impairment can be caused by a number of factors, including common sleep disorders such as obstructive sleep apnea syndrome (OSA), insomnia and circadian rhythm disorders, in addition to voluntary and work-related sleep limits. Obstructive sleep apnea affects between 9-38% of the American population; insomnia affects approximately 33%; and circadian rhythm disorders affects 3% (Donya 2024).

What is Sleep?

According to current definitions, sleep is based on an individual's behavior when they are asleep as well as associated physiological changes to the electrical patterns of the waking brain during sleep (Chokroverty 2010). A distinctive sleeping posture, a decreased response to external stimuli, an elevated arousal threshold, an increased reaction time, a lack of mobility or slight mobility, cognitive impairment, and a reversible unconscious state are the behavioral criteria of sleep (Chokroverty 2010). Our understanding of the physiological processes involved in sleep has been made possible through modern measures such as electromyography (EMG), electro-oculography (EOG), and electroencephalography (EEG) tests which form the basis of the physiological criteria noted above (Chokroverty 2010).

Based on behavioral and physiological criteria, sleep is classified as having two states: rapid eye movement (REM) sleep and non-REM (NREM) sleep. REM sleep is characterized by desynchronized EEG, muscular atonia, and rapid eye movements. NREM sleep can be

separated into three stages, N1, N2, and N3 (Chokroverty 2010). There are multiple nervous structures that are known to control these sleep states. The so-called master clock, housed in the hypothalamic suprachiasmatic nuclei, regulates the circadian cycle of sleep and wakefulness. The pons is home to the neuroanatomical substrates of REM sleep, while the ventrolateral preoptic nucleus of the hypothalamus is primarily home to those of Non-REM sleep. During sleep, functional changes in the autonomic and somatic nerve systems cause a number of important physiological changes in bodily systems and organs (Chokroverty 2010).

In order to regulate both wake and sleep, the human circadian timing system coordinates humoral, physiological, and behavioral processes. The circadian rhythm that promotes arousal and the homeostatic drive for sleep are two opposing mechanisms that regulate sleep-wakefulness (Reddy et al. 2023). While the circadian component refers to changes in physiological alertness and drowsiness (timing, length, and other features) that fluctuate cyclically with time of day, the homeostatic factor refers to a higher predisposition for sleepiness with longer durations of prior wakefulness (Reddy et al. 2023).

What are Sleep Disorders?

Sleep disorders can be caused by changes in the quantity, quality, and pattern of sleep, and may negatively impact a person's general health (Prabhakar et al. 2012). There are over one hundred recognized sleep/wake disorders, which may be caused by disruptions in the circadian cycle or abnormalities in particular processes during sleep. Individual differences also exist in the capacity to manage disruptions in the circadian cycle (Prabhakar et al. 2012), which can predispose certain individuals to developing sleep disorders.

Sleep problems have been linked to a multitude of health problems and numerous dysfunctions in the majority of physiological systems, including endocrine, metabolic, and

higher cortical systems (Pavlova and Latreille 2019). Furthermore, significant evidence suggests that sleep disturbances have a detrimental effect on cardiovascular systems, increasing morbidity and mortality. In addition, sleep disturbances have been linked to poorer cognitive performance and functioning (Stickgold and Walker 2007, Walker 2009, Punjabi and Beamer 2009, Cappuccio et al. 2010), and cognitive decline (Spira et al. 2015). It has also been acknowledged that sleep is causally linked to appetite control and glucose homeostasis regulation, and that sleep deprivation is a contributing factor to the global increase in obesity and type 2 diabetes mellitus (T2DM).

Insomnia

The most common sleep-related disorder in the general population is insomnia. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR) defines insomnia disorder (i.e., clinical insomnia) as difficulty initiating sleep, difficulty maintaining sleep, or early-morning awakening despite adequate opportunity for sleep, leading to clinically significant distress or impairments in functioning, and with a frequency of three or more nights per week and a duration of three months or longer (APA 2022). This condition can have profound negative effects on and individual’s daytime functioning, causing fatigue, exhaustion, trouble focusing, memory deficits, anxiety about sleep, mood swings, or anger (Ramar and Olson 2013).

Though several neurological and psychological hypotheses have been proposed, the exact pathophysiological mechanisms underlying insomnia have not yet been determined. Behavioral, cognitive, emotional, and genetic characteristics are among the contributing elements (Pavlova and Latreille 2019). What is particularly interesting in insomnia is the observation that some individuals’ perceptions of sleep do not match what is objectively recorded. The disablement of many insomniacs' impression of having slept may be explained

by the elevated alertness level shown in electroencephalogram (EEG) power-spectra investigations (Mahowald and Schenck 2005). This is also related to the fact that adrenocorticotropic hormone (ACTH) and cortisol release are generally elevated in individuals with this condition, which increase sympathetic nervous system activity, leading to heightened arousal and hypervigilance, even when the person is asleep. The underlying physiological anomalies in insomnia are further supported by neuroimaging investigations (Mahowald and Schenck 2005).

According to an article published by Vgontas et al., the most biologically severe phenotype of insomnia is objectively short sleep duration, which is linked to both limbs of the stress system being activated, creating cognitive-emotional and cortical arousal. Risks are increased chances of hypertension, impaired heart rate variability, diabetes, neurocognitive impairment, and premature mortality. Objectively short sleep duration also seems to be a biological indicator of a genetic propensity to chronic insomnia (Vgontzas et al. 2013).

It has also been suggested that a more general hyperarousal disease may be the cause of both the daytime symptoms and poor nocturnal sleep-in individuals with chronic insomnia. The concept of hyperarousal suggests that individuals who focus their cognitive attention on their insomnia and begin to ruminate on their sleep issues are at risk of developing “learned sleep preventing associations” that cause the condition to turn chronic. It is assumed that maladaptive behaviors (such as prolonging bedtime, taking daytime naps, and increasing alcohol consumption) further contribute to the persistence of insomnia. Hyperarousal, that is, heightened autonomic activity, is associated with chronic insomnia (Riemann et al. 2010).

Treatment for Insomnia

Treatments that combine behavioral and pharmaceutical approaches are frequently successful, for example, hypnotic drugs and cognitive behavior therapy (Ramar and Olson 2013). According to recent studies, cognitive behavioral therapy may be just as effective as pharmaceutical treatment for insomnia, if not more so, and its effects may persists for longer (Pavlova and Latreille 2019). Sleep restriction and relaxation-based therapy are examples of further behavioral treatment techniques. Pharmacological therapy may be used in conjunction with behavioral treatments or when treatment is expected to be brief (for example, insomnia during stressful situations) (Pavlova and Latreille 2019). The following factors should be considered when selecting a treatment: the primary complaint type, such as sleep initiation or maintenance; the frequency of insomnia symptoms (nightly vs. intermittent); the expected duration of treatment; and the patient's age and comorbidities (Pavlova and Latreille 2019).

Benzodiazepines and the more recent non-benzodiazepines are the two groups of drugs that are FDA-authorized to treat insomnia (Mahowald and Schenck 2005). Despite their affordability and widespread use, benzodiazepines have a number of drawbacks, including excessive sedation, a high risk of falls (because of the nonselective effects of gammaaminobutyric acid), hypotension, a propensity to lose effectiveness with prolonged use, muscle relaxant effects, and significant cognitive effects (Pavlova and Latreille 2019). Other non-benzodiazepine hypnotics include: zolpidem, zolpidem CR, Intermezzo (Purdue Pharma, Stamford, CT; zolpidem ultrashort acting, 1.75-3 mg), zaleplon, and eszopiclone. Certain hypnotics have the advantage of being FDA-approved for the treatment of chronic insomnia (eszopiclone, zolpidem CR) and having relatively short half-lives (Intermezzo, zaleplon). Nevertheless, common side effects include over-sedation and parasomnia, and some medications may lose their effectiveness with prolonged use (Pavlova and Latreille 2019).

Obstructive Sleep Apnea

Obstructive sleep apnea occurs when the upper airway collapses during sleep, causing a halt in airflow for at least ten seconds. The number of respiratory episodes per hour of sleep is used to measure the severity of sleep apnea, which can be identified during polysomnography, a diagnostic test used to evaluate sleep disorders by monitoring various physiological parameters during sleep, including brain waves, heart rate, breathing, and eye and leg movements (Ramar and Olson 2013). A diagnosis of sleep apnea requires at least five episodes per hour (Apnea-Hypopnea Index ≥ 5) in addition to clinical symptoms. The most common criteria state that mild sleep apnea is defined as an Apnea-Hypopnea Index of five to fourteen, moderate sleep apnea as one between fifteen and twenty-nine, and severe sleep apnea as more than thirty occurrences per hour (Ramar and Olson 2013). Excessive daytime sleepiness, obesity, treatment-refractory hypertension, the necessity for bariatric surgery, atrial fibrillation, congestive heart failure, stroke, nocturnal cardiac dysrhythmias, type 2 diabetes mellitus, and pulmonary hypertension are among the conditions that might trigger an OSA examination (Ramar and Olson 2013). Polysomnography should be referred if obstructive sleep apnea is suspected.

Between 9-38% of the American population suffers from obstructive sleep apnea (OSA), one of the most prevalent medical conditions that contribute to daytime hypersomnia (Sonya 2024). Although middle-aged and overweight men are more likely to have OSA, individuals of normal weight and children can also have it (Prabhakar et al. 2012). Repetitive arousals (up to one hundred per hour of sleep) are necessary to restore upper airway airflow after this collapse, which may be linked to a drop in blood oxygen levels (Mahowald and Schenck 2005). Although the person typically is not aware of these fleeting arousals, the sleep disturbances cause excessive daytime drowsiness. The most common clinical signs are loud snoring, gasping or choking, apneas that the bed partner witnesses, excessive weariness and

lethargy, and headaches in the morning (Pavlova and Latreille 2019). The quality of life for both the patient and their family is severely impacted by sleep apnea. Sleep apnea also raises the risk of cardiovascular disease, type 2 diabetes, and hypertension, all of which can have serious negative health effects if addressed (Pavlova and Latreille 2019).

There are numerous alternatives for treatment. Conservative treatments include losing weight and avoiding the supine posture (for positional sleep apnea), which can be beneficial for mild cases of obstructive sleep apnea (Pavlova and Latreille 2019). Continuous positive airway pressure (CPAP) therapy is now the most popular and first-line treatment for obstructive sleep apnea. A constant flow of air into the nose is known as continuous positive airway pressure, whereas bilevel treatment produces a higher pressure during inspiration and a lower pressure during expiration (Pavlova and Latreille 2019). CPAP lowers blood pressure in OSA patients, particularly in those with severe OSA and excessive daytime sleepiness (Ramar and Olson 2013).

Another alternative is an autotitrating CPAP machine, which responds to apneas, hypopneas, snoring, or flow limitation by automatically adjusting the pressure within a predetermined range (Ramar and Olson 2013). However, many patients find it difficult to adhere to CPAP therapy, so weight loss, positional therapy, surgery, oral appliances, and Provent therapy—a nasal device with an expiratory valve that generates positive end-expiratory pressure to maintain an open upper airway—are other treatment possibilities (Ramar and Olson 2013). Furthermore, the most prevalent surgical therapy options are maxillomandibular, nasal, and soft palate surgeries. While they usually fail to cure sleep apnea, they might lessen its severity (Pavlova and Latreille 2019).

Circadian Rhythm Disorders

The light-dark cycle is the most influential regulator of the human circadian rhythm. Homeostatic mechanisms and the endogenous circadian system maintain times of sleep and waking. The circadian rhythm's sleep phase typically starts two hours after melatonin secretion begins. It might happen earlier or later than the socially prescribed sleep period, leading to an accelerated or delayed sleep-wake phase problem (Pavlova and Latreille 2019). Circadian rhythm sleep problems are the result of a mis-match between the body's endogenous circadian clock and the social sleep period (Crowley 2023). There are two types of sleep-wake schedule disorders: primary, which occurs when the biological clock itself malfunctions, and secondary, which happens when environmental factors affect the underlying clock (Mahowald and Schenck 2005). The two most prevalent primary circadian rhythm abnormalities are advanced sleep-phase disorder (ASWPD) and delayed sleep-phase disorder (DSWPD) (Crowley 2023).

In DSPS, the sleep period is significantly later than an individual's desired sleep onset and wake time. In ASPS, there is a significant phase advance of the sleep–wake cycle where onset of sleep may occur extremely early in the evening (sometimes as early as 6pm) and morning wake time may be set in between 2 a.m. and 5 a.m. (Crowley 2023). However, the length of sleep is typical in both situations, and if the individual's social and occupational schedule allows them to go to bed at the time their body prefers, they can feel rested (Pavlova and Latreille 2019).

Without a precise assessment of the patient's circadian phase, diagnosing and treating sleep-wake problems related to the circadian rhythm can be challenging. Melatonin plasma levels and core body temperature are frequently measured in research settings (Pavlova and Latreille 2019). However, these are not feasible for regular clinic usage since they are costly, time-consuming, and require specific environments. Melatonin levels in the urine and saliva

are more practical evaluation criteria. Circadian rhythm sleep-wake problems are very common, yet they are frequently misinterpreted as insomnia or, in certain cases, hypersomnia (Pavlova and Latreille 2019).

Phototherapy and chronotherapy are the cornerstones of the treatment for individuals with circadian rhythm disorders. In chronotherapy, sleep logs taken during a "free-running" phase are used to calculate the ideal overall length of sleep (Mahowald and Schenck 2005). Until sleep onset reaches the desired time, the patient advances or delays sleep onset by a few hours each day and only sleeps during the pre-established period. The patient subsequently makes an effort to stick to their sleep routine over that period (Prabhakar et al. 2012). Regarding phototherapy (exposure to bright daytime-mimicking light), the biological clock can be strongly impacted by this treatment, and the underlying rhythm is altered when exposure occurs at specific points during the sleep/wake cycle. For example, in individuals with ASWPD, evening exposure to bright light treatment (BLT) may help shift their circadian phase to a later hour, whereas in individuals with DSWPD, morning BLT is recommended (Gooley 2008). These insights have made it possible to efficiently treat circadian dysrhythmias (Mahowald and Schenck 2005). During phototherapy, the patient sits a certain distance away from a bright light source that emits 2,500 lux when it reaches them. The way light affects human rhythms depends on its intensity, wavelength, exposure time, and duration (Prabhakar et al. 2012).

Melatonin (one hour before the required bedtime in delayed phase disorder) and timed bright or blue light (morning for delayed and afternoon for advanced phase disorders) are other treatment options for circadian rhythm sleep disorders (Pavlova and Latreille 2019). Patients should be advised that the successful treatment of delayed sleep-wake phase disorder may depend on the precise timing of any therapies. For instance, the spectrum or wavelength of light, intensity, previous exposure to light, and—above all—timing all influence the effect

of light (Pavlova and Latreille 2019). The same amount of light can either advance or delay the circadian cycle's sleep phase depending on whether it is administered before or after the core body temperature low point. The circadian phase should also be used to time the delivery of exogenous melatonin for the same reasons (Pavlova and Latreille 2019).

Diabetes

A major concern to public health in the twenty-first century is diabetes, a severe and economically debilitating disease that is becoming epidemic in both industrialized and developing nations. Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia mainly due to insulin resistance. Glucose is a monosaccharide that acts as the primary energy source for cells, and it is metabolized via glycolysis, producing pyruvate and adenine triphosphate (ATP) (Roglic 2016). In the bloodstream, glucose levels are tightly regulated, typically ranging between 70–100 mg/dL in a fasting state. Dysregulation of this balance is a hallmark of diabetes; with a fasting blood sugar level 100-125 mg/dL (5.6-6.9 mmol/L) being considered prediabetes, and 126 mg/dL or higher defined as diabetes (Roglic 2016). Type 2 diabetes is more prevalent in older adults and members of specific racial groups, including Hispanics, African Americans, American Indians, and Alaskan Natives. However, the main culprit in the prevalence of diabetes are lifestyle choices, such as physical inactivity and diet (Winer ans Sowers 2013).

There are diverse pathophysiological and biochemical mechanisms involved in the pathophysiology of T2DM. One of these may be neurotransmitter dysfunction. The central nervous system, particularly the hypothalamus, plays a key role in energy homeostasis. Neurotransmitters, such as dopamine and serotonin, are involved in regulating appetite, satiety, and glucose metabolism (Astrup et al. 2008). In T2DM, altered neurotransmitter signaling can affect the autonomic nervous system, leading to increased hepatic glucose

production through sympathetic nervous stimulation and altered pancreatic hormone secretion, which contribute to systemic insulin resistance. Moreover, in T2DM, there is upregulation of SGLT2 (Sodium-Glucose Cotransporter 2) in the kidneys' proximal tubules, enhancing glucose reabsorption. This reduces glucose excretion in urine, maintaining hyperglycemia. Additionally, in the intestines, higher expression of SGLT1 can increase postprandial glucose absorption, exacerbating spikes in blood glucose after meals (Astrup et al. 2008).

Type 2 diabetes is also associated with a decreased incretin effect. Incretins are gut-derived hormones, primarily GLP-1 (glucagon-like peptide-1) and GIP (gastric inhibitory polypeptide), that enhance glucose-dependent insulin secretion and inhibit glucagon release (Toft-Nielsen et al. 2006, Holst et al. 1987). In T2DM, there is a blunted incretin effect, leading to insufficient insulin secretion post-meal. Reduced GLP-1 levels contribute to delayed gastric emptying, diminished insulin secretion, and reduced satiety signaling to the brain, aggravating hyperglycemia and insulin resistance (Meier et al. 2003, Zander et al. 2002). Hyperglycemia is also worsened by increased glucagon secretion, stimulating glycogenolysis and gluconeogenesis in the liver and, therefore, increasing blood glucose levels. In T2DM, α-cells in the pancreas secrete excess glucagon even in the presence of hyperglycemia, leading to elevated hepatic glucose output. This paradoxical glucagon secretion is partly due to defective glucose sensing by the pancreas and decreased inhibitory effects from insulin and incretins (Chia and Egan 2020).

Insulin is another major hormone that is dysregulated during T2DM. Insulin is a peptide hormone synthesized in the β-cells of the pancreatic islets of Langerhans. It binds to the insulin receptor, a tyrosine kinase receptor, activating the PI3K-AKT signaling pathway (Saltiel and Kahn 2001). This pathway promotes glucose uptake by regulating GLUT4 trafficking from storage compartments to the plasma membrane, stimulates glycogen

synthesis via glycogen synthase, and inhibits gluconeogenesis in the liver (Taylor 1999). Over time, chronic hyperglycemia (glucotoxicity) and high free fatty acids (lipotoxicity) impair pancreatic β-cell function. This results in decreased insulin secretion due to oxidative stress, inflammation, and amyloid deposition in the islets. β-cell dysfunction leads to an impaired first-phase insulin response, which normally suppresses hepatic glucose production, and a reduced second-phase insulin release needed for postprandial glucose clearance (Saltiel and Kahn 2001).

A defining feature of T2DM is insulin resistance, where peripheral tissues, particularly skeletal muscle and adipose tissue, have a reduced response to insulin. In skeletal muscle, this is due to defects in the insulin receptor substrate (IRS) signaling pathway, leading to impaired GLUT4 translocation (Taylor 2012). Decreased muscle glucose uptake exacerbates hyperglycemia. Additionally, adipose tissue insulin resistance results in increased lipolysis, raising free fatty acid levels, which further impair insulin signaling through mechanisms like serine phosphorylation of insulin receptor substrates (Roy 2012).

In insulin-resistant individuals, the liver fails to inhibit gluconeogenesis and glycogenolysis despite high insulin levels (Petersen 2006). This results in increased hepatic glucose production through enhanced activity of key enzymes like phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase. Insulin resistance disrupts normal suppression of hepatic glucose output, contributing significantly to fasting and postprandial hyperglycemia (Petersen 2006).

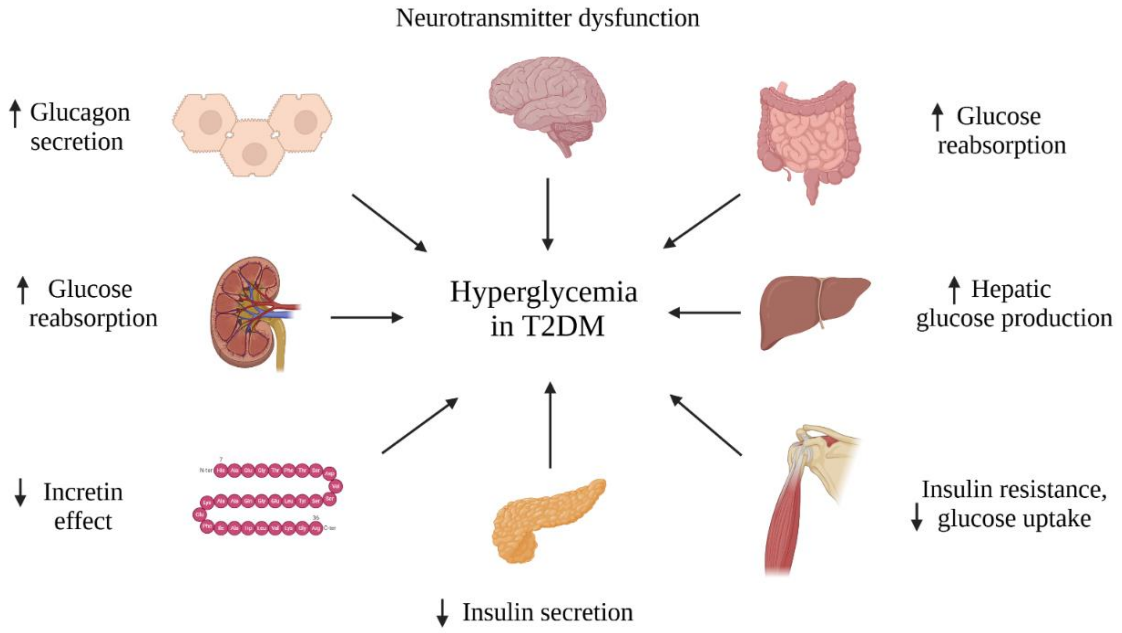

Fig. 1. *Factors leading to hyperglycemia in type 2 diabetes mellitus. Image created in BioRender.*

T2DM patients exhibit certain traditional and uncommon symptoms at first. Polyphagia, polydipsia, and polyuria are the traditional signs of type 2 diabetes. Other traditional symptoms include nocturia, dry mouth, easy fatigability, increased appetite, and exhaustion. The following symptoms are less common: pruritus, chronic infections, recurring fungal infections, unclear weight loss, and blurred vision (Olgun et al. 2011). Additionally, urinary tract infections, dry skin, weakness, numbness, tingling, or burning sensations in the feet are possible symptoms for these patients (Olgun et al. 2011). Microvascular problems such as retinopathy, nephropathy, and peripheral and autonomic neuropathy are brought on by uncontrolled hyperglycemia. Additionally, hyperglycemia may cause peripheral artery disease, cerebrovascular disease, and coronary heart disease to develop earlier (Mollaoğlu and Beyazıt 2009).

The prevalence of type 2 diabetes continues to grow, and more strategies are needed to combat this public health problem. Considering the link between sleep problems and risk of type 2 diabetes, the objective of this review is to discuss the experimental and

epidemiological evidence underlying the link between sleep disturbances (such as insomnia, circadian rhythm disorders, and obstructive sleep apnea), and the development of insulin resistance and glucose intolerance, which are impairments that can eventually result in type 2 diabetes. Not only does poor sleep increase the chances of developing type 2 diabetes, but it also has an effect on diverse aspects of metabolic health. Public policies should be implemented to increase individuals' consciousness on this topic, and also more resources should be devoted to developing treatment options that can offer the population better sleep conditions.

Methods

A thorough assessment of the current literature was conducted in order to investigate how sleep disorders affect metabolic health and how they are related to diseases including diabetes. In order to achieve this, PubMed and Google Scholar, two of the largest online databases, were utilized to find pertinent peer-reviewed publications, reviews, and clinical studies that have been published in the last four decades. The selected articles were first assessed for relevancy based on their titles and abstracts. If full-text articles satisfied the inclusion requirements, they were reviewed.

The goal of the search approach was to identify research that looked into the connections between metabolic health outcomes and sleep disorders, such as insomnia and sleep apnea. Terms like "sleep disorders," "metabolism," and "diabetes," as well as combinations of these terms (for example, "sleep disorders AND diabetes," "insomnia AND diabetes," "sleep apnea AND diabetes") were employed to refine the search. The search results were expanded and refined using Boolean operators (AND/OR). The following inclusion criteria were used to choose articles: research articles published in journals with

peer review; studies that concentrate on adult human populations; and research examining how sleep disorders affect metabolic health, with a focus on diabetes.

Results

Metabolic Consequences of Sleep Disorders

In addition to affecting cognitive function, sleep disturbances are linked to higher rates of morbidity and premature mortality (Walker 2009, Chien et al. 2010). Recent experimental and epidemiological research has shown that both the quantity and quality of sleep are significant factors in determining whole-body metabolism, and that sleep deprivation may be a direct cause of the obesity and type 2 diabetes epidemics. Large-scale cross-sectional epidemiological studies have consistently and convincingly shown that self-reported sleep duration is linked to a roughly doubled prevalence of type 2 diabetes or impaired glucose tolerance. These studies have been conducted in a variety of populations, including adolescents, middle-aged and older subjects, hypertensive patients, and pregnant women (Gottlieb et al. 2005, Tuomilehto et al. 2008, Najafian et al. 2013, Fiorentini et al. 2007).

The relationship between T2DM and sleep deprivation is still prevalent when other conventional risk factors for diabetes are not taken into consideration, which means that the connection is not due to those components. Additionally, a number of pre-diabetic characteristics, including fasting hyperglycemia, higher postprandial glucose and insulin levels, or indicators of whole-body insulin resistance, are linked to subjectively reported inadequate, poor, or brief sleep (Jennings et al. 2007, Flint et al. 2007, Hung et al. 2013). Lastly, it has also been demonstrated that people with diabetes already suffer from insufficient sleep, as it impairs glycemic control. Experiments showing that healthy human volunteers exposed to a harsh paradigm of complete sleep deprivation lasting one to five days develop insulin resistance and β-cell malfunction have further supported the epidemiological evidence

(González-Ortiz et al. 2000). Insulin resistance and insulin secretion abnormalities led to elevated fasting and postprandial glucose levels after sleep deprivation (Wehrens et al. 2010, Reynolds et al. 2012).

Sleep Apnea and Diabetes

OSA prevalence is higher in individuals who are overweight and obese. Regardless of obesity, there is currently strong evidence linking OSA to insulin resistance, glucose intolerance, and the risk of type 2 diabetes (Pamidi et al. 2010). Studies suggest that up to 83% of individuals with type 2 diabetes likely have undiagnosed OSA, and worse glucose management is independently correlated with the severity of OSA (Pamidi et al. 2010). Metabolic syndrome is 9.1 times more common in OSA subjects than in non-OSA subjects (Coughlin et al. 2004). Being a complex syndrome associated with central obesity, metabolic syndrome raises the risk of type 2 diabetes (De et al. 2009). In addition to obesity's role, OSA has been linked independently to further neuro-endocrine-metabolic alterations that may promote the onset of type 2 diabetes (Shaw et al. 2008). This point is further supported by the fact that OSA is known to impact insulin sensitivity, glucose metabolism, pancreatic beta-cell function, and the quality of sleep at night. These factors can lead to daytime fatigue and drowsiness, which may encourage physical inactivity and thereby predispose individuals to the development of obesity and type 2 diabetes (Punjabi and Beamer 2009, Ip et al. 2002, Punjabi and Polotsky 2005). According to research by Punjabi and Beamer, individuals with mild, moderate, and severe sleep-disordered breathing (SDB) showed decreased insulin sensitivity by 26.7%, 36.5%, and 43.7%, respectively, as compared to normal subjects (AHI <5 events/h).

In a study conducted by Aronsohn, the major objective was to determine the impact of OSA on hemoglobin A1c (HbA1c), which is a relevant clinical indicator of glycemic control,

in patients with type 2 diabetes. After adjusting for age, sex, race, BMI, number of diabetes medications, exercise level, years of diabetes, and total sleep time on PSG, the results demonstrated that worse glucose management was linked to greater OSA severity ($P < 0.0001$ for linear trend) (Aronsohn et al. 2010). For patients with mild OSA, the adjusted mean HbA1c was higher than that of patients without OSA by 1.49% ($P = 0.0028$), 1.93% ($P = 0.0033$) for those with moderate OSA, and 3.69% ($P < 0.0001$) for those with severe OSA ($P < 0.0001$ for linear trend) (Aronsohn et al. 2010). When "number of diabetes medications" was substituted in the regression model with "oral hypoglycemic medication use" ($P < 0.0001$ for linear trend) or "insulin use" ($P = 0.0002$ for linear trend), the associations between OSA severity and HbA1c levels remained strong (Aronsohn et al. 2010). When diabetic comorbidities were included in the regression model, similar correlations between the severity of OSA and glycemic control were discovered ($P < 0.0001$ for linear trend) (Aronsohn et al. 2010).

After adjusting for the degree of adiposity and several other potential confounders, the same study by Aronsohn and colleagues shows that OSA is very common in patients with type 2 diabetes and suggests, for the first time, a distinct, graded, inverse relationship between OSA severity and glucose control in patients with type 2 diabetes (2010). The majority of individuals with type 2 diabetes have undiagnosed OSA, and untreated OSA is linked to worse glucose control, which may necessitate more intensive medication (Aronsohn et al. 2010).

Similar results were observed in a study performed by Ronksley, which also had the objective of studying the association between OSA and type 2 diabetes mellitus. The results showed that, as the severity of OSA increased, so did the prevalence of T2DM ($p<0.001$). After controlling for patient demographics, weight, and neck circumference, severe OSA was linked to DM (odds ratio (OR) 2.18; 95% CI 1.22 to 3.89; $p<0.01$) (Ronksley et al. 2009).

This association was only seen in patients who were drowsy after a stratified analysis (OR 2.59 (95% CI 1.35 to 4.97) as compared to 1.16 (95% CI 0.31 to 4.37) in patients who were not sleepy). DM is independently linked to severe OSA in patients who report being very sleepy (Ronksley et al. 2009).

Remarkably, in this correlation, OSA appears to be impacted by T2DM in addition to raising the risk for this endocrine-metabolic condition. After examining 941 men, West et al. came to the conclusion that T2DM might significantly increase the risk of OSA on its own. According to their data, OSA is prevalent in 23% of people with type 2 diabetes. Diabetes accounted for an additional 8% of the variation in OSA after controlling for BMI, which accounted for 13% (West et al. 2006).

One of the most well-understood effects of stressful events, including OSA and other sleep disorders, is the activation of the sympathetic nervous system (SNS) (Leproult et al. 2014). Through chemoreceptor reflexes and other mechanisms, the hypoxemia and hypercapnia that ensue from OSA contribute to sympathetic activity (Smith et al. 1996) (Narkiewicz and Somers 2003, Leuenberger et al. 2007). These sympathetic-drive alterations in OSA patients continue throughout the day, presumably as a result of hypoxia (Narkiewicz and Somers 2003, Leuenberger et al. 2007). Similar to hypoxia, hypercapnia causes SNS activation, although it has no long-term effects (Leuenberger et al. 2007).

One of the most well-known pathways through which SNS activation is likely to predispose patients to obesity, glucose impairment, metabolic syndrome, and type 2 diabetes is the stimulation of the hypothalamic–pituitary–adrenal axis (HPA), which results in excessive cortisol secretion that disrupts glucose homeostasis and the inhibition of leptin secretion (Sandoval and Davis 2003, Balbo et al. 2010). As previously stated, sleep deprivation activates the SNS, which in turn activates the HPA axis. Some of the effects of cortisol, a glucocorticoid released as a result of HPA activity, are closely linked to peripheral

tissue metabolism. By increasing glucose output and lipogenesis, decreasing glucose utilization, and preventing lipid mobilization in the presence of insulin, particularly from the visceral adipose tissue, exposure to high glucocorticoid levels causes insulin resistance, weight gain, and metabolic syndrome (Balbo et al. 2010, Qi and Rodrigues 2007). Leproult et al. discovered variations in cortisol levels in the evening after a sleep-deprived night, despite the fact that cortisol levels do not appear to vary after twenty-four hours without sleep. Following either complete or partial sleep deprivation, the initiation of cortisol secretion was delayed by at least one hour, and plasma cortisol levels were greater on day two than on day one (37 and 45% increases, $p = 0.03$ and 0.003, respectively) (Leproult et al. 1997).

Spiegel et al. also found that higher evening cortisol levels ($p = 0.0001$) and sympathetic nervous system activation ($p < 0.02$) were associated with worse glucose tolerance in the sleep-debt condition compared to the totally rested condition ($p < 0.02$). Apart from sleep deprivation, OSA was also linked to elevated cortisol and catecholamine levels (Punjabi and Beamer 2009, Punjabi et al. 2003). Thus, it is feasible to draw the conclusion that sleep apnea influences the HPA axis as well as the SNS, impairing the metabolism of carbohydrates and encouraging the emergence of glucose intolerance, which may result in type 2 diabetes.

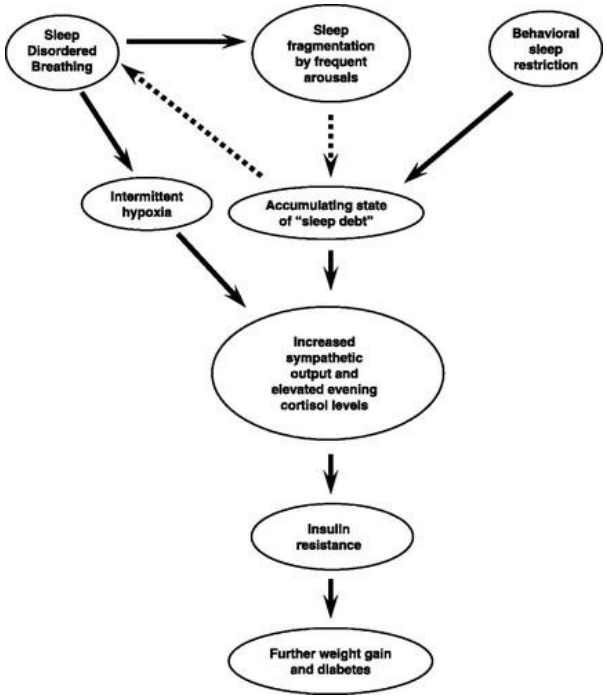

Fig. 2. *Potential mechanisms underlying the development of insulin resistance and diabetes in patients with sleep disordered breathing (Spiegel et al. 2005).*

In addition to the effects cause by over-activation of the HPA axis, insulin resistance is exacerbated by the release of adrenal adrenaline during sympathetic activation, which causes glucose synthesis and inhibits insulin secretion (Deibert and DeFronzo 1980). Numerous β-adrenoceptor subtypes allow adrenaline and, to a lesser extent, norepinephrine to operate as essential mediators of adipose tissue lipolysis (Bartness et al. 2010, Prigge and Grande 1971). Thus, it is possible to hypothesize that chronic stimulation of the sympathetic nervous system may facilitate IH-induced lipolysis and insulin resistance.

The results of a study by Aronhson et al., which had the objective of understanding the impact of untreated obstructive sleep apnea on glucose control in T2DM, showed that, when age, sex, race, BMI, number of diabetes medications, exercise level, years of diabetes, and total sleep time on PSG were taken into account, patients with OSA had more diabetic complications than those without OSA, and the severity of OSA was linked to worse glucose control ($P < 0.0001$ for linear trend). For patients with mild OSA, the adjusted mean HbA1c was higher than that of patients without OSA by 1.49% ($P = 0.0028$), 1.93% ($P = 0.0033$) for those with moderate OSA, and 3.69% ($P < 0.0001$) for those with severe OSA ($P < 0.0001$ for linear trend) (Aronhson et al. 2010). After adjusting for the degree of adiposity and several other potential confounders, the study showed that OSA is very common in patients with type 2 diabetes and that there is a distinct, graded, inverse relationship between OSA severity and glucose control in these patients. According to the available data, OSA and its underlying features—such as intermittent hypoxia, increased sympathetic nerve activity, fragmented sleep, low slow wave sleep, and cumulative sleep loss—have a negative impact on glucose tolerance (Aronhson et al. 2010).

Insulin resistance was linked to the severity of nocturnal hypoxia in non-obese OSA patients, indicating that the hypoxia-reoxygenation sequences associated with OSA are a significant contributor to this metabolic dysfunction (Borel et al. 2013). Intermittent hypoxia exposure has been shown to increase sympathetic nervous system activity (Tamisier et al. 2011). Oxidative stress, increased HIF-1α signaling, decreased HIF-2 signaling, as well as endothelin-1 have been proposed as key mechanisms in IH-induced SNS activation (Prabhakar et al. 2012).

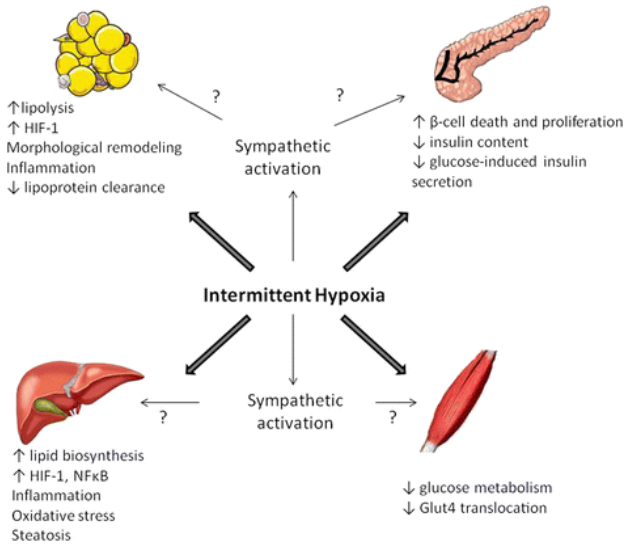

Fig. 3. *Mechanisms relating poor glucose metabolism and intermittent hypoxia. Insulin target organs like skeletal muscle, liver, and adipose tissue are all impacted by intermittent hypoxia, as is the generation and release of insulin by the pancreas (Briançon-Marjollet et al. 2015). Insulin resistance, dyslipidemia, and reduced glucose tolerance are the results of these combined impacts. The sympathetic nervous system may be directly or indirectly involved in the effects of intermittent hypoxia. GLUT4 (glucose transporter type 4), NF-κB (nuclear factor-κB), and HIF-1α (hypoxia inducible factor 1-alpha) (Briançon-Marjollet et al. 2015).*

According to Aronhson's study, many people with type 2 diabetes may also have undiagnosed OSA, and untreated OSA is linked to worse glucose control, which may necessitate more aggressive medication (Aronhson et al. 2010). On the other hand, managing

OSA may improve glucose regulation in a clinically meaningful way and lower the number of medications required and/or their dosage schedule. Weight-gain-promoting medications used to treat type 2 diabetes may have the unintended side effect of accelerating the onset of OSA or making pre-existing OSA worse, which would impair glycemic management and increase cardiovascular risk. The high incidence of OSA and associated cardiovascular repercussions in people with type 2 diabetes may play a role in causing the potential side effects of antidiabetic medication (Aronhson et al.).

Sleep apnea can also cause sleep fragmentation with slow-wave sleep duration, which in turn may also cause poor glucose metabolism. It has been suggested that slow-wave sleep is especially crucial for maintaining metabolic homeostasis since selectively suppressing slow-wave sleep (SWS) without affecting overall sleep duration led to reduced β-cell activity, insulin resistance, and glucose intolerance (Tasali et al. 2008). In healthy men, selective SWS suppression (but not REM sleep suppression) also resulted in poor post-prandial glucose homeostasis and increased morning insulin and glucose levels (Herzog et al. 2013). Cross-sectional research showing that SWS length is a powerful predictor of glucose-induced insulin release in obese individuals and studies showing shorter SWS in T2DM participants compared to nondiabetic subjects, further underscore the significance of SWS in glucose homeostasis (Koren et al. 2011, Pallayova et al. 2010). Significantly, SWS length was inversely correlated with HbA1c levels in T1DM patients as well, indicating a general role for SWS in controlling glucose metabolism that is unrelated to obesity or the etiology of T2DM (Feupe et al. 2013).

Additional evidence of the relationship of sleep apnea and type 2 diabetes is found in research developed by Barceló et al., where patients with excessive daytime sleepiness (EDS), caused by sleep apnea, showed greater plasma levels of insulin ($p<0.01$) and glucose ($p<0.05$), as well as signs of insulin resistance ($p<0.01$), than patients without EDS or healthy

controls, even if age, BMI, and AHI were equal. In patients with EDS, CPAP treatment raised IGF-1 levels and decreased insulin, cholesterol, and the HOMA index; in those without EDS, it had no effect on any of these factors. IR is linked to EDS in OSAS, regardless of BMI (Barceló et al.). As a result, EDS might be a helpful clinical indicator for determining which OSAS patients are at risk for metabolic syndrome (Barceló et al. 2008).

In their study, Keckeis et al. showed that, compared to healthy controls, OSA patients were nearly five times more likely to have impaired glucose tolerance. Furthermore, the rate of values above the reference level in both HbA1c and fasting plasma glucose levels suggested a twenty-fold increased risk of diabetes in patients with OSA, and mean HbA1c values were higher in both diagnostic groups when compared to controls (Keckeis et al. 2010). Repeated arousals may be a common mechanism of poor glucose tolerance in this sleep disorder, as evidenced by the positive link between 2h-plasma glucose levels and quantitative measurements of sleep disruptions (apnea-arousal-index). By changing the nature of sleep, specifically by avoiding SWS, repeated arousals may have an impact on glucose metabolism (Keckeis et al. 2010). However, by the subsequent activation of the sympathetic nervous system, repeated sleep arousals may potentially directly impact glucose metabolism.

Insomnia and Diabetes

Short duration of sleep and difficulty in initiating sleep are associated with a greater risk of developing type 2 diabetes, usually with a larger effect on men compared to women (Cappuccio et. al. 2010). A number of pre-diabetic characteristics, including fasting hyperglycemia, higher postprandial glucose and insulin levels, or indicators of whole-body insulin resistance, are linked to perceived inadequate, poor, or short duration sleep. Since it impairs glycemic control, inadequate sleep has also been demonstrated to be harmful in

patients who have already developed diabetes (Jennings et al. 2007, Flint et al. 2007, Hung et al. 2013).

Aforementioned experiments showing that healthy human volunteers exposed to a regimen of complete sleep deprivation of one to five days develop insulin resistance and β-cell malfunction have further supported the epidemiological evidence (Gonzalez-Ortiz 2000). Fasting and postprandial glucose levels rose after sleep deprivation due to insulin resistance and insulin secretion abnormalities (Benedict et al. 2011). Studies employing gentler paradigms, such as limiting sleep to four to five hours per night for multiple consecutive nights, more closely resemble chronic sleep loss found in modern lifestyles, even if studies involving complete sleep deprivation have offered significant insights into the role of sleep in metabolic controls. Despite the variety of research methods, subjects who were somewhat sleep deprived likewise showed deficits in a number of insulin sensitivity and glucose tolerance metrics (Spiegel et al. 2004, Buxton et al. 2010, van Leeuwen et al. 2010).

It is interesting to note that the metabolic profile following sleep restriction has some characteristics in common with type 2 diabetes, such as increased liver glucose production, decreased muscle glucose absorption, and pancreatic β-cell dysfunction. According to studies, administering melatonin (or melatonin receptor agonist) improved glucose homeostasis in a number of animal models by increasing glucose uptake, increasing glucose-induced insulin secretion, improving insulin sensitivity, or reducing liver gluconeogenesis (Buxton et al. 2010) (Donga et al. 2010).

Insomnia and sleep deprivation may direct or indirectly contribute to the development of insulin resistance and type 2 diabetes by negatively affecting glucose regulation components or by dysregulating appetite, which results in weight gain and obesity, a significant risk factor for both conditions (Spiegel et al. 2005). Spiegel et al. conducted the first study in 1999 to examine the hormonal and metabolic effects of recurring partial sleep

restriction, a far more prevalent condition, in which males were subjected to four-hour sleep restrictions for six days. A 30–40% drop in glucose effectiveness, a gauge of non-insulin-dependent glucose consumption, was seen when the glucose and insulin responses were analyzed using the minimum model (Spiegel et al. 1999).

There are probably several routes involved in the detrimental effects of sleep deprivation on glucose tolerance. According to PET studies that have demonstrated decreased brain glucose utilization in sleep-deprived subjects, the decrease in glucose effectiveness is likely to reflect decreased brain glucose utilization because the brain is a major site of non-insulin-dependent glucose uptake (Thomas et al. 1998, Spiegel et al. 1999). Autonomic nerve activity affects the function of pancreatic β-cells; parasympathetic activation promotes the release of insulin, whereas sympathetic stimulation inhibits it. Therefore, the change in sympathovagal balance may be linked to the decrease in the acute insulin response to intravenous glucose. Heart rate variability recordings from the study do, in fact, show a change toward greater sympathovagal balance when patients were sleep-restricted as opposed to fully rested (Spiegel et al. 1999). The modifications in glucose regulation components observed after sleep loss may also be caused by disturbances in the secretory patterns of the counterregulatory hormones, cortisol and growth hormone. A rise in evening cortisol levels and a prolonged period of elevated overnight growth hormone concentrations are linked to six days of sleep restriction (Spiegel et al. 1999). Increased nighttime cortisol concentrations are expected to cause decreased insulin sensitivity the next morning, and prolonged exposure of peripheral tissues to increased GH levels may negatively impact glucose homeostasis by causing a sharp decline in muscle glucose uptake (Spiegel et al. 1999, Plat et al. 1999).

In 2004, Spiegel et al. conducted a follow-up study utilizing a randomized crossover design to validate the detrimental effects of sleep deprivation on glucose metabolism. Following two nights of ten hours in bed and two nights of four hours in bed, twelve healthy

males were examined. To prevent variations in hunger and appetite associated with meal consumption, an intravenous glucose infusion was administered at a steady rate to replace calorie intake after the second night of each bedtime condition (Spiegel et al. 2004). Following two days of short bedtimes, insulin levels were lower and glucose levels were higher in the morning than they were following two days of extended bedtimes. When subjects slept for shorter periods of time as opposed to longer periods, their appetite for items high in calories and carbohydrates increased by more than 30% (Spiegel et al. 2004). The ratio of ghrelin to leptin was more than 70%. Crucially, there was a strong correlation between the rise in the ghrelin to leptin ratio and the increase in hunger after sleep restriction (Spiegel et al. 2004). According to an analysis of variance, changes in hunger were more strongly predicted by a reduction in leptin than by an increase in ghrelin.

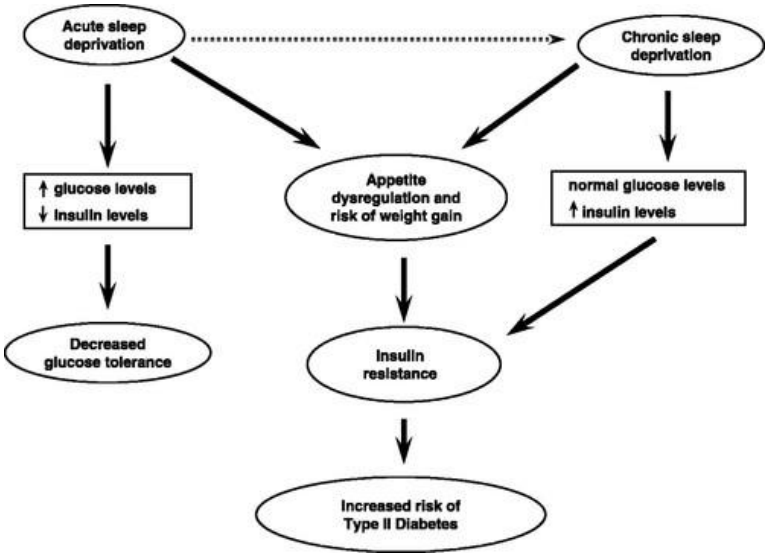

Fig. 4. *Putative mechanisms by which sleep deprivation may result to weight gain, altered glucose metabolism, and Type 2 diabetes (Spiegel et al. 2005).*

LeBlanc et al. developed a cohort study to determine the association between insomnia and the risk of type 2 diabetes mellitus. It showed that hyperglycemia caused by experimentally induced sleep loss was reversed in short-term laboratory experiments by

normal sleep restoration (LeBlanc et al. 2018). According to epidemiologic research, the amount and quality of sleep significantly predicts the likelihood of type 2 diabetes mellitus (T2DM). This study, by establishing a correlation between the risk of type 2 diabetes and clinically recognized insomnia, has broadened the group of people at risk to include those with clinically diagnosed insomnia (LeBlanc et al. 2018).

Even after controlling for conventional risk factors such age, BMI, race, ethnicity, and cardiovascular risk factors, individuals with insomnia had a roughly 30% higher chance of acquiring type 2 diabetes in this study of 81,233 people with pre-diabetes (LeBlanc et al. 2018). The study contributes significant information to the expanding body of research indicating the potentially significant impact of sleep disturbance on elevated risk for type 2 diabetes due to its scale and the fact that it was carried out in an actual healthcare system (LeBlanc et al. 2018).

Due to low participant motivation, high dropout rates, and, in the case of weight loss programs, an often delayed effect of the intervention and a high risk of returning to excess weight, current interventions, such as weight loss and/or exercise interventions, to address conventional T2DM risk factors like high BMI or sedentary lifestyle can be successful, but they are frequently challenging to implement (Riemann et al. 2017). Treatments for behavioral insomnia, on the other hand, are quick, easy, and show positive results right away (Brasure et al. 2016). Furthermore, because getting regular sleep again is inherently satisfying, people who are sleep deprived are usually very motivated to follow the regimen.

The results are in line with experiments where researchers cause healthy participants to miss sleep. According to these studies, when sleep returns to normal, hyperglycemia and insulin resistance are reversed. Inadequate sleep duration (usually four to five hours per night for a period of one to fourteen days) and disruption of sleep architecture (due to circadian misalignment with resulting changes in rapid eye movement [REM] distribution) cause these

effects (Stamatakis and Punjabi 2010). The results of LeBlanc's study are also in line with earlier epidemiologic research that revealed those who had trouble sleeping or had short sleep duration had a 28%–84% higher risk of type 2 diabetes (St-Onge et al. 2016, Kowal et al. 2016).

Sleep deprivation may raise the risk of type 2 diabetes for a number of reasons. According to epidemiologic research and experimental sleep deprivation, short-term or disturbed sleep may alter the profile of peptides that mediate energy homeostasis, such as adiponectin, ghrelin, and leptin. This could result in an increase in appetite, including cravings for foods high in calories and carbohydrates, and eventually insulin resistance (Spiegel et al. 2005). According to other research, individuals who experience short-term experimental sleep deprivation, long-term short-sleep duration, or sleep disorders have higher levels of salivary and serum cortisol, especially in the evening when levels are typically relatively low (Leproult et al 2014). Increased central fat distribution is linked to elevated cortisol levels and is closely linked to insulin resistance (Champaneri et al. 2013).

The link between sleep disturbance and the risk of diabetes may possibly be attributed to elevated inflammation and sympathetic activation. Sleep disturbance triggers both systems, and it has been linked to insulin resistance and ultimately type 2 diabetes (T2DM) (Wieser et al. 2013, Zinman et al. 1999). In laboratory models, insomnia has also been demonstrated to enhance β-cell apoptosis and hasten loss of β-cell function with higher β-cell mass loss (Spiegel et al. 2004). Lastly, the weariness brought on by sleep deprivation may result in decreased physical activity, both in terms of quantity and intensity, which may lead to the development of type 2 diabetes (Bromley et al. 2012).

The aim of a prospective cohort study by Green et al. was to determine if the incidence of type 2 diabetes is causally impacted by cumulative exposure to insomnia symptoms. A community-based sample of individuals without diabetes who were tracked from roughly

thirty-six to fifty-seven years of age was used to examine the relationship between insomnia symptoms and the incidence of type 2 diabetes (Green et al. 2017). By efficiently controlling for time-varying confounders with marginal structural models (MSMs) and comparing the results with more conventional regression models, this study attempted to determine if relationships between insomnia symptoms and the risk of type 2 diabetes are likely to be causative (Green et al. 2017). The study demonstrates that the risk for type 2 diabetes rises as exposure to insomnia symptoms accumulates over several years, even while other studies have found links with type 2 diabetes for shorter-term measures of insomnia (Cappuccio et al. 2010, Vgontzas et al. 2009, Green et al. 2017). Conventional logistic regression revealed a correlation between the incidence of type 2 diabetes and insomnia symptoms, which would be quite significant if compounded by prolonged exposure (Green et al. 2017).

Vgontzas et al.'s study showed that a clinically relevant risk factor for type 2 diabetes is persistent insomnia linked to objectively assessed short sleep duration. Comorbid factors like age, race, obesity, alcohol use, smoking, SDB, periodic limb movements, or depression that are commonly linked to insomnia or diabetes do not affect this elevated risk (Vgontzas et al. 2013). Additionally, their results imply that objective measurements of sleep duration in cases of insomnia could indicate the disorder's biological severity and its medical consequences. In the basic adjusted model, there was a significant correlation between greater odds of diabetes and more severe insomnia (defined as having complained of sleeplessness for at least a year) (Vgontzas et al. 2013). Most significantly, a 300% increased risk of diabetes was linked to severe insomnia and an objective sleep duration of less than five hours, in comparison with the subjects who did not have a sleep complaint and slept for ≥6 h (Vgontzas et al. 2013).

Circadian Rhythm Disorders and Diabetes

Long-distance travel, shift work, and circadian rhythm disorders all pose challenges to the balance between pacemakers in the SCN and peripheral tissues and their synchronization with behavioral and environmental cycles, including the cycles of light and dark, sleep and wakefulness, food intake, and physical activity (Briançon-Marjollet et al. 2015). A major misalignment between biological pacemakers and the living environment arises from incomplete adaptation to irregular sleep patterns. Environmental stimuli, such as food and exercise, are received by metabolically active tissues at improper "central" times or at unsuitable points in their own pacemaker cycle (Briançon-Marjollet et al. 2015). An organism's life and general needs depend on the central and peripheral pacemakers being in alignment, yet desynchrony is prevalent and has major repercussions, such as an increased risk of type 2 diabetes and cardiovascular mortality and morbidity (Buijs et al. 2013, Vyas et al. 2012) (Ha et al. 2011).

Circadian misalignment and shift work significantly disrupt glucose homeostasis and metabolic function. Shift workers who experience circadian rhythm problems are more likely to have type 2 diabetes, glucose intolerance, insulin resistance, and metabolic syndrome, according to cross-sectional and retrospective research (Mikuni et al. 1983, Puttonen et al. 2012, Esquirol et al. 2009). Numerous prospective studies involving both men and women who worked shifts have confirmed the causal relationship between shift work and the development of metabolic disorders. T2DM and metabolic syndrome were observed to be more likely to develop in the studies (Kawada and Otsuka 2014, De et al. 2009, Eriksson et al. 2013). Patients who already have diabetes appear to be most affected by the deleterious impacts of shift employment, as seen by all of the aforementioned symptoms. Diabetics who worked shifts reported having elevated HbA1C values, and the length of time they worked

shifts and the number of hours they worked per shift were associated with inadequate diabetes control (Kawada and Otsuka 2014, Monk and Buysse 2013, Morikawa et al. 2005)

The vital role of central and peripheral pacemakers in controlling glucose levels, glucose tolerance, insulin sensitivity, insulin secretion, and food intake has been shown in studies employing mice with whole-body or organ-selective mutations in pacemaker genes (Kennaway et al. 2013, Sadacca et al. 2011, Doi et al. 2010). For instance, deletion of the *Bmal* gene in β-cells causes hyperglycemia and impaired glucose-induced insulin secretion due to excessive production of reactive oxygen species, whereas loss of the *Bmal* gene in the liver causes hypoglycemia and changes the expression of genes involved in glucose metabolism (Marcheva et al. 2010, Lamia et al. 2008). Mice fed with central and peripheral pacemaker misalignment also acquired insulin resistance and increased in weight (Sherman et al. 2012). Furthermore, even though their overall sleep duration was maintained, healthy human volunteers exposed to circadian misalignment showed elevated CRP (C-reactive protein), reduced insulin sensitivity, and impaired compensatory insulin production (Leproult et al. 2014). Subjects who worked shifts showed the same results, with insulin and plasma glucose responses to a test meal being considerably higher when the same food was given at night than during the day (Lund et al. 2001). Simultaneously, shift workers with circadian rhythm abnormalities showed signs of insulin resistance and hyperinsulinemia (Lund et al. 2001).

According to recent research, endocrine mechanisms that may contribute to the development of insulin resistance and β-cell dysfunction following circadian disturbance include higher FFA levels, decreased leptin levels, and a disturbed cortisol cycle. Moreover, mice with circadian disruption have shown increased release of pro-inflammatory cytokines by macrophages, indicating a potential mechanism for the general pro-inflammatory activation characteristic of type 2 diabetes (Lee et al. 2013, Castanon-Cervantes et al. 2010).

Studies have shown that the circadian clock plays a direct role in regulating glucose levels. By generating circadian oscillations of rate-limiting enzymes involved in tissue metabolism throughout the day and night, the molecular clock preserves energy constancy (Green et al. 2017). The central oscillator in the hypothalamus and even in peripheral tissues of mammals is driven by the transcription factors BMAL1 and CLOCK (Marcheva et al. 2010). The daily fluctuation of insulin sensitivity and glucose tolerance over the twenty-four-hour day is one of the most noticeable rhythmic features of physiology. Crucially, type 2 diabetes is characterized by a disruption of the circadian oscillation of glucose metabolism (Polonsky et al. 1998). In addition, genomic analyses have shown that both neural and peripheral clocks control the 24-hour periodicity of RNAs that mediate rate-limiting steps in glycolysis, fatty acid oxidation, and oxidative phosphorylation, suggesting that metabolic and circadian systems are interconnected at the transcriptional level. This suggests that these processes are primed to occur at the ideal time during glucose and fatty acid utilization cycles (Marcheva et al. 2010).

Pancreatic islets release insulin to maintain glucose homeostasis throughout eating times; individuals with diabetes are known to have dysregulated insulin release. Marcheva et al. examined twenty-four-hour glucose and insulin profiles in 8-month-old *Clock*$^{\Delta 19/\Delta 19}$ mutant mice and their wild-type (WT) littermates during ad lib feeding in order to ascertain whether molecular disruption of the pancreatic clock correlates with abnormalities in the temporal control of glucose metabolism. In WT animals, insulin levels rise at the start of the feeding period, but in *Clock*$^{\Delta 19/\Delta 19}$ mutants, glucose levels were high throughout the light-dark (LD) cycle without an increase in insulin levels (Marcheva et al. 2010). Additionally, *Clock*$^{\Delta 19/\Delta 19}$ mutant mice showed markedly higher fasting glucose levels, and glucose tolerance tests showed a 50% decrease in insulin release, which corresponded to higher glucose excursion, especially at the start of the dark period (Marcheva et al. 2010). The observation that

Clock$^{\Delta 19/\Delta 19}$ mutant mice had normal insulin tolerance further reinforces the hypothesis that reduced glucose tolerance in these animals is due to a fundamental impairment in pancreatic function.

Marcheva et al. investigated glucose-stimulated insulin secretion (GSIS) in isolated size-matched pancreatic islets from eight-month-old mice in order to gain a better understanding of the effect of the circadian gene mutation on pancreatic function. GSIS was ~50% lower in the islets of *Clock*$^{\Delta 19/\Delta 19}$ mice. In contrast to WT islets, the researchers found that the *Clock*$^{\Delta 19/\Delta 19}$ mutant showed normal calcium flow in response to 12 mM glucose, which is consistent with a major impairment in insulin release rather than glucose metabolism (Marcheva et al. 2010). The decreased function of *Clock*$^{\Delta 19/\Delta 19}$ mutant islets was also localized to a late stage in stimulus-secretion coupling, as islets from these mice showed reduced insulin secretory responses to the cyclase activators forskolin and exendin-4, as well as 8-Bromo-cyclic AMP (Marcheva et al. 2010). This work elucidates the potential molecular mechanism involving cyclic AMP and calcium.

In addition to this, Marcheva et al. examined both GSIS and islet size in *Bmal1−/−* mutant mice to ascertain if the abnormalities in islet function and size are specific to the *Clock*$^{\Delta 19/\Delta 19}$ animal or rather represent a widespread function of the core circadian network in islet function. In response to glucose, KCl, exendin4, forskolin, and 8-Br-cAMP, the insulin production of *Bmal1−/−* islets was reduced by up to 60% as compared to littermate controls. Additionally, compared to their WT littermates, *Bmal1−/−* mice had a two-fold lower percentage of big islets (Marcheva et al. 2010). Defects in the islets of *Bmal1−/−* and *Clock*$^{\Delta 19/\Delta 19}$ mutant mice are similar, indicating that several key circadian genes influence β-cell formation and function.

This study demonstrates that the transcription factors CLOCK and BMAL1 exhibit self-sustaining circadian gene and protein oscillations in pancreatic islets. Both *Clock* and

Bmal mutants show reduced insulin secretion, impaired glucose tolerance, and defects in the size and proliferation of pancreatic islets that worsen with age (Turek et al. 2005, Marcheva et al. 2010). Circadian mutant mice also show a delayed phase of oscillation of islet genes involved in growth, glucose metabolism, and insulin signaling. The expression of islet genes involved in growth, survival, and synaptic vesicle assembly changes transcriptome-wide when clock disruption occurs. Diabetes mellitus is brought on by conditional excision of the pancreatic clock because it impairs β-cell function at the most recent stage of stimulus-secretion coupling. These findings show that the β-cell clock plays a part in regulating insulin secretion in relation to the sleep-wake cycle and that the development of diabetes mellitus can be triggered by disruption of the pancreatic clock (Marcheva et al. 2010).

Sleep disorder	Genes	Proteins	Hormones	Others
Sleep apnea	Increased gene expression of gluconeogenic enzymes	Elevated HbA1c Elevated cytokines Increased protein levels of gluconeogenic enzymes Elevated HIF-1α levels Low HIF-2 levels Low endothelin levels Decreased lipoprotein clearance	Insulin resistance Elevated catecholamines Elevated epinephrine Decreased insulin sensitivity Increased cortisol secretion Elevated adrenaline levels Decreased insulin secretion	Elevated glucose synthesis Elevated BMI Hypoxemia Hipercapnia Increased sympathetic activity Increased activity of the HPA axis Dyslipidemia Physical inactivity due to fatigue Low glucose control Increased lipogenesis Decreased lipid mobilization Increased oxidative stress Increased β-cell death SWS suppression EDS presence

Insomnia		Elevated HbA1c Elevated cytokines	Insulin resistance Low leptin levels Elevated ghrelin levels Elevated cortisol levels Elevated overnight growth hormone levels Decreased insulin sensitivity Decreased insulin secretion	Elevated glucose synthesis Increased appetite Elevated central fat distribution Increased sympathetic activation Decreased β-cell function Elevated β-cell apoptosis Decreased muscle glucose absorption Decreased brain glucose utilization Greater sympathovagal balance Physical inactivity due to fatigue
Circadian Rhythm Disorders	Elevated liver-specific *Bmal* Decreased β-cell specific *Bmal* Decreased pancreatic *Clock*	Elevated CRP Elevated cytokines Elevated HbA1c	Insulin resistance Decreased leptin levels Elevated cortisol levels Decreased insulin sensitivity Decreased insulin secretion	Elevated glucose synthesis Central and peripheral pacemakers Elevated free fatty acids Physical inactivity due to fatigue

Fig. 5. *Genes, proteins, hormones, and other factors that lead to the development of type 2 diabetes mellitus in individuals with sleep apnea, insomnia, and circadian rhythm disorders.*

Conclusions

This study summarizes the molecular and endocrine mechanisms that underlie the independent and potentially causative relationships between sleep apnea, insomnia, and abnormalities of the circadian rhythm with glucose intolerance, insulin resistance, decreased insulin secretion, and ultimately type 2 diabetes. The most likely mediators, according to the literature, are the following: intermittent hypoxia-induced sympathetic nervous system

activation, reactive oxygen species generation, induction of a whole-body pro-inflammatory state, enhanced lipolysis and modified adipokine release in adipose tissue, misalignment between central and peripheral pacemakers, and hypothalamic-pituitary-adrenal axis activation with elevated circulating cortisol levels. There are multiple genes, proteins and hormones that act as mediators, all of which are interconnected, as well as relevant in explaining the relationship between type 2 diabetes and sleep disorders.

The diversity of factors that are caused by sleep disorders might make medical drug treatment difficult, as there is not a factor determining the relationship between diabetes and these sleep conditions that can be used as a target. Treatment methods would need to utilize a holistic approach to address underlying issues. Furthermore, the current knowledge in the field about each of these factors varies depending on the specific sleep disorder that is being addressed; for instance, the majority of circadian rhythm disorders' studies that look at the connection with type 2 diabetes focus on genes, while diabetes has not been a fully studied topic in insomnia and sleep apnea studies. Future research is necessary to ascertain if addressing the aforementioned molecular regulators will yield metabolic benefits in people with improper sleep, even though several of these pathways represent prospective therapeutic targets.

This review limits the scope to address type 2 diabetes, but it is relevant to note that metabolic health in general is affected by insufficient or poor quality of sleep, and other metabolic diseases can occur (Cedernaes et al. 2015). Additionally, there are other metabolic components that can influence diabetes and sleep (Ogilvie and Patel 2017). For example, weight that has a detrimental effect on both type 2 diabetes and sleep disorders, but it was not explored in this review. This review can be used to expand future research and to understand sleep and its relationship with metabolic health.

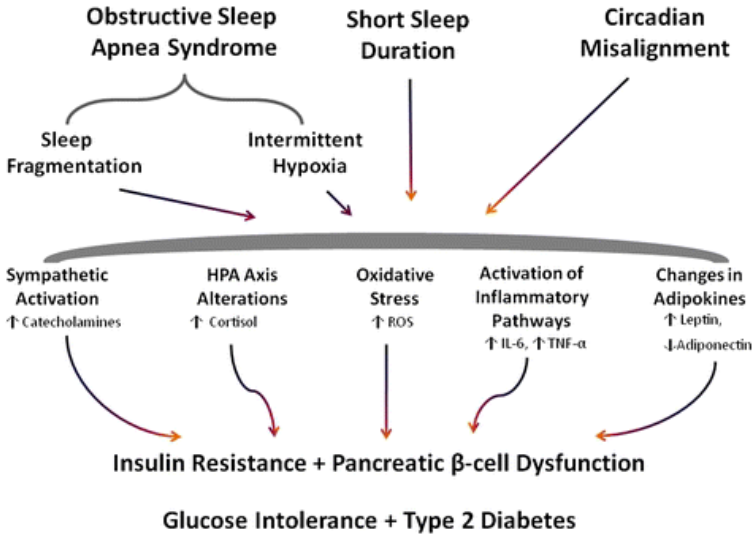

Fig. 6. *Metabolic pathways linking sleep disorders with the development of Type 2 diabetes. HPA (hypothalamic-pituitary-adrenal axis), ROS (reactive oxygen species), IL-6 (Interleukin-6), TNF-α (tumor necrosis factor-α) (Briançon-Marjollet et al. 2015).*

Future Research Directions

The roles of insomnia, circadian rhythm disorders and sleep apnea in the management of type 2 diabetes and prediabetes are in urgent need of further rigorous assessment. The question of whether these disorders represent independent risks for the development of prediabetes and type 2 diabetes over time, remains to be investigated by prospective studies of sufficient duration and power. Large scale randomized controlled trials of the previously mentioned sleep disorders with well-validated assessments of insulin sensitivity and glucose tolerance are needed. This research should be done with a special focus on insomnia and circadian rhythm disorders, as there have been fewer studies conducted for those sleep disorders in comparison to sleep apnea.

Interdisciplinary teams should be established to develop these future research studies, as there are multiple factors involved in the relationship between type 2 diabetes and insomnia as well as between sleep apnea and circadian rhythm disorders. Including a diverse group of

individuals from different specialties and fields of expertise, and with distinct perspectives, would allow for more creative, comprehensive and integral lines of inquiry. In addition, more meta-analyses should be conducted to observe the general patterns that emerge from primary research on the relationship between type 2 diabetes and the three sleep disorders discussed in this review. These large-scale meta-analyses would lead to improved understanding of what has already been explored in this particular field, as well as the overall results obtained from existing investigations.

Furthermore, the vast majority of studies of the relationship between insomnia, circadian rhythm disorders and/ or sleep apnea and glucose regulation have been conducted in males. There is a need to evaluate this relationship in women, in whom these conditions may be underdiagnosed and undertreated. Moreover, focusing on women would be relevant because estrogen is related to cortisol levels, and high cortisol levels and sympathetic nervous system activation are associated with worse glucose tolerance (Punjabi and Beamer 2009). A study by Edwards and Mills shows that estrogen increases cortisol levels, so looking at the relationship between cortisol levels and type 2 diabetes in women would be important to expand the knowledge on this field.

Relevance

Type 2 diabetes is steadily rising around the world. Careful glucose management is necessary to stop or postpone the emergence of potentially fatal consequences. Poorer glucose control is linked to untreated sleep apnea, insomnia, and circadian rhythm abnormalities, which may necessitate more rigorous medication. On the other hand, addressing the aforementioned sleep problems may improve glucose regulation in a clinically meaningful way and lower the number of medications required and/or their dosage schedule. Using medications that encourage weight gain to treat type 2 diabetes may have the unintended side

effect of accelerating the onset of certain sleep disorders or making them worse if they already present, which would impair glycemic control and increase the risk of cardiovascular disease. The potential side effects of antidiabetic medication may be aided by the high prevalence of sleep apnea, insomnia, and circadian rhythm abnormalities as well as their cardiovascular implications in type 2 diabetes.

As sleep quality and duration have declined in the past years, there is a need to raise awareness on the importance of sleep. Not only does poor sleep increase the chances of developing type 2 diabetes, but it also has an effect on diverse aspects of metabolic health. Public policies should be implemented to increase individuals' consciousness on this topic, and more resources need to be devoted to developing treatment options that can offer the population better sleep conditions. In addition, as this review shows the existing relationship between type 2 diabetes mellitus and insomnia, sleep apnea, and circadian rhythm disorders, it would be relevant to explore treatment options that could tackle this connection. It would be advantageous to explore if people who have type 2 diabetes and one of the previously mentioned sleep disorders benefit from already existing treatments. This would imply treating the person for their sleep disorder, and analyzing if their glucose levels improve; in treating diabetes, it would be useful to consider the patient's sleep patterns and conditions.

The findings of this study show that more thorough evaluation of the roles that OSA, insomnia, and circadian rhythm disturbances play in the treatment of type 2 diabetes is desperately needed. The discovery of the current association between these sleep disorders and type 2 diabetes has significant clinical ramifications because it suggests that the treatments currently available to address the aforementioned sleep disorders may significantly impact glucose control in patients with these sleep conditions and type 2 diabetes. In contrast to unmodifiable risk variables like age, race, and ethnicity, these results point to new risk factors that may be able to be changed and might be the focus of efforts to prevent diabetes.

The aforementioned sleep disturbances in individuals with type 2 diabetes should be systematically evaluated and treated as part of updated current practice approaches. Millions of people's health could be enhanced if sleep therapy could be included in the arsenal for preventing the debilitating condition known as type 2 diabetes.

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