Review

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Circadian Rhythm Disruption and Its Association With Type 2 Diabetes Mellitus

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With the accelerated pace of modern life and evolving work patterns, an increasing number of individuals experience circadian rhythm reversal and irregular work-rest schedules. This altered lifestyle profoundly impacts the human metabolic system, particularly by elevating the risk of type 2 diabetes. Alterations in circadian rhythms may heighten this risk of type 2 diabetes through mechanisms such as interference with insulin secretion and glucose metabolism. This study reviewed the circadian rhythm system, behaviors associated with circadian dysregulation and diabetes, circadian rhythm synchronization, and metabolic health to provide scientific evidence for managing type 2 diabetes induced by circadian rhythm disruption.

Keywords: circadian rhythm disruption; type 2 diabetes mellitus; correlation studies; intervention

Introduction

Diabetes, a global metabolic disorder, is steadily increasing in prevalence, placing a heavy burden on society and individuals. Data from the International Diabetes Federation (IDF) indicate that an estimated 589 million adults (20–79 years) worldwide currently live with diabetes, reflecting a global prevalence of 11.1% in 2024 [1]. An international study reported that adult diabetes prevalence rose from 7% to 14% between 1990 and 2022, with global cases doubling to over 800 million [2]. Typical diabetic complications involve impaired function of the kidneys, retina, cardiovascular system, nervous system, and liver, with no current therapies capable of reversing such organ damage [3]. Unhealthy lifestyles, including diets high in calories, sugar, and fat, physical inactivity, smoking, alcohol consumption, and insufficient sleep, are major contributors to the increasing rates of diabetes [4]. A newly recognized risk factor for diabetes is circadian rhythm disruption, often arising from insufficient sleep. With the rapid pace of modern life and the diverse working patterns, circadian rhythm disruption has become an increasingly significant health concern. Inherent in living organisms, the circadian rhythms synchronize cellular processes, behaviors, and physiological functions with the 24-hour cycle, maintaining essential homeostasis in biological systems [5]. Notably, approximately 25% of the global population works in shifts, with healthcare workers comprising the largest subgroup at 15–20% of all shift workers [6]. A large-scale study of 27,399 U.S. adults aged 20 and older from 2005 to 2018 revealed that approximately one-third slept fewer than 6 hours each night [7]. Evidence suggests a strong association between circadian rhythm disruption and the onset of type 2 diabetes mellitus (T2DM) [8]. This paper aimed to review the circadian rhythm system, behaviors leading to circadian rhythm disruption and their associated diabetes risks, circadian rhythm synchronization, and interventions for improving metabolic health. Understanding the interplay between circadian rhythm disruption and diabetes development is critical for establishing effective preventive and therapeutic strategies. Based on the current evidence, the integration of circadian rhythm–related mechanisms into diabetes prevention and management may offer a potentially valuable avenue for improving metabolic health.

Circadian Rhythm System

Components and Functions

Mammalian circadian rhythms are regulated by a central clock in the suprachiasmatic nucleus (SCN) of the hypothalamus, complemented by peripheral clocks in various organs and tissues [9]. The endogenous circadian rhythm system does not precisely align with the external 24-hour cycle and therefore requires daily resetting. It serves as a critical coordinator for aligning internal biological functions with external environmental cues. Light exposure represents the most potent environmental signal for resetting the central clock. Environmental light signals reach the SCN through the retinohypothalamic pathway, enabling the master clock to synchronize with the 24-hour rhythm [10].

Acting as the central circadian conductor, the SCN maintains temporal organization by relaying synchronizing signals to peripheral clocks through neural, hormonal, thermogenic, and behavioral (activity/feeding) pathways. Consequently, peripheral clocks are synchronized, and physiological as well as behavioral processes are regulated in a circadian manner (Fig. 1) [11].

The human biological clock system consists of clock genes and proteins. Through a transcription-translation feedback mechanism, these clock genes regulate their expression and that of critical metabolic genes, sustaining the circadian oscillator function and maintaining biological rhythms. The central clock genes include circadian locomotor output cycles kaput (*CLOCK*), brain and muscle ARNT-like 1 (*BMAL1*), cryptochrome (*CRY*), period (*PER*), reverse-erb (*REV-ERB*), and retinoic acid receptor-related orphan receptors (*RORs*) [12]. CLOCK, as the primary positive regulator of the transcriptional feedback loop, recognizes and binds to E-box motifs within clock gene promoters, thereby activating the transcription of *CRY* and *PER* genes [13]. The CRY and PER proteins function as key repressors within this loop. After synthesis, they accumulate in the cytoplasm, and upon reaching sufficient levels and undergoing specific post-translational modifications (notably phosphorylation), they dimerize, translocate into the nucleus, and directly inhibit the transcriptional activity of the CLOCK-BMAL1 complex bound to E-boxes. Subsequent ubiquitin-dependent proteasomal degradation of CRY and PER proteins relieves this repression on CLOCK-BMAL1, allowing the cycle to restart [14–16].

An auxiliary feedback loop involving reverse-erb alpha (REV-ERBα) and retinoic acid receptor-related orphan receptor alpha (RORα) provides additional regulatory control and stability. Transcription of *REV-ERB*α and *ROR*α is activated by the CLOCK-BMAL1 complex (via E-boxes) but subsequently repressed by accumulating CRY/PER proteins, resulting in their rhythmic expression. REV-ERBα and RORα proteins compete for binding to ROR response elements (ROREs) within the *BMAL1* promoter. Binding of REV-ERBα represses *BMAL1* transcription, while RORα binding activates it (Fig. 2) [17]. This REV-ERB/ROR loop modulates *BMAL1* expression, a key component of the core activator complex, thereby connecting and reinforcing the core negative (CRY/PER) and positive (CLOCK/BMAL1) feedback loops.

Central Clock

Located in the anterior hypothalamus, the SCN serves as the primary circadian clock in mammals, composed of aggregated pacemaker neurons. It represents the starting point of human physiological rhythms and the source of both the generation and transmission of circadian rhythm signals. The SCN autonomously generates and maintains circadian rhythms, and the information it transmits regulates various behavioral and physiological cycles, including locomotion, sleep-wake patterns, thermoregulation, and hormonal secretion [18]. The rhythmicity of the SCN has an intrinsic genetic basis, although it is also strongly influenced by environmental light [19].

The SCN can influence peripheral tissues (e.g., liver, pancreas, adipose) through the autonomic nervous system to regulate glucose metabolism and meet glucose demands during activity [8]. A study in rats demonstrated that liver glucose production follows circadian patterns controlled by the SCN. The impact of the SCN on liver glucose production is minimal at the start of the light phase (Zeitgeber 2, ZT2), when plasma glucose concentrations are lower and glucose tolerance is reduced. In contrast, at the end of the light phase (Zeitgeber 11, ZT11), the SCN exerts its greatest influence on liver glucose production, corresponding to higher plasma glucose concentrations and improved glucose tolerance. This rhythmic regulation enables the body to prepare for both rest and activity, adapting to regular environmental changes [20].

Additionally, the SCN regulates the release of key endocrine hormones (melatonin, cortisol, growth hormone, leptin), ensuring the body operates in sync with the predetermined rhythm. Study indicates that SCN damage eliminates daily oscillations in both physiological processes and behaviors, underscoring its central role in maintaining biological rhythms [21]. Clock genes expressed in the SCN include *CLOCK*, *BMAL1*, *PER*, and *CRY*. Research indicates that specific damage to the bilateral SCN in mice leads to the loss of circadian rhythmicity in clock gene expression in specific peripheral organs [22]. Thus, the SCN functions as an essential phase coordinator, not merely a pacemaker, whose integrity prevents metabolic desynchronization among peripheral clocks, directly linking circadian coherence to systemic insulin sensitivity.

Peripheral Clocks

Peripheral clocks are present in most tissues outside the SCN, including the heart, liver, pancreas, and kidneys. However, peripheral biological clocks cannot autonomously generate rhythms. Instead, they are regulated by various neural, humoral, and other signaling factors modulated by the central biological clock, thereby adjusting the rhythm of effector tissues [23].

Muscle Clock Genes: Muscle glycogen serves as the storage form of glucose in muscle tissue, and a functional biological clock is essential for maintaining the balance between muscle glycogen synthesis and breakdown. Harfmann *et al.* [24] reported that skeletal muscle fiber types were altered in *Bmal1* gene knockout mice, showing abnormal myofibrillar structure, reduced mitochondrial respiration, and disrupted glucose metabolism, primarily manifested as defective glucose disposal and insulin resistance. Dyar *et al.* [25] further confirmed that skeletal muscle glucose transporter 4 (GLUT4) expression was downregulated, and insulin-stimulated muscle glucose uptake was impaired

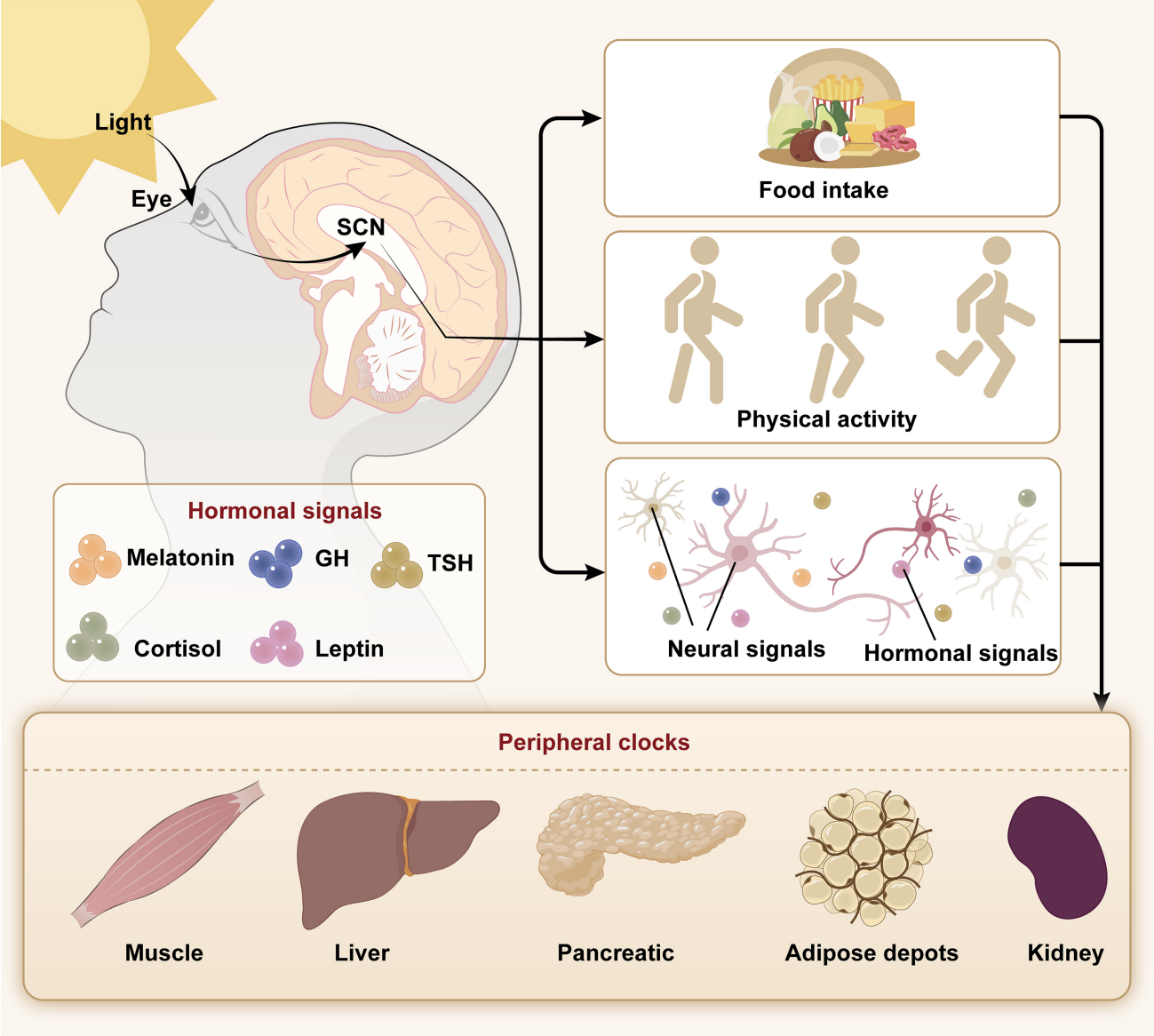

Fig. 1. The circadian rhythm system. The circadian rhythm system comprises a central clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus and peripheral clocks distributed across various peripheral tissues. Light signals, transmitted via the retina and the retinohypothalamic tract to the SCN, act as the primary zeitgeber for the central clock. The SCN synchronizes peripheral clocks through neural, endocrine, activity-related, and feeding-related cues. Peripheral clocks are present in most tissues outside the SCN, including muscle, liver, pancreas, adipose tissue and kidney. The figure was created by the authors using Adobe Illustrator 2024 v28.0 (Adobe Inc., San Jose, CA, USA). GH, growth hormone; TSH, thyroid-stimulating hormone.

in *Bmal1* gene knockout rats. Simultaneously, reduced pyruvate dehydrogenase (PDH) activity contributed to abnormal glucose metabolism. These findings demonstrate that physiological levels of muscular *Bmal1* are critical for maintaining glucose homeostasis. Dysregulated *Bmal1* gene expression in muscles modifies glucose metabolism, causing impaired glucose tolerance and insulin resistance, potentially contributing to diabetes pathogenesis.

Liver Clock Genes: The liver stores glucose primarily in the form of glycogen, and a properly functioning biological clock is fundamental for balancing glycogen synthesis and breakdown. Zhang *et al.* [26] observed a marked upregulation of the liver clock gene *Cry1* in mice with T2DM and insulin resistance. These mice exhibited hyperglycemia and decreased insulin sensitivity. Another study suggested that the circadian gene *Cry2* enhances lipid storage while restricting glucose synthesis in liver metabolism [27]. Consequently, normal *Cry1* and *Cry2* expression in hepatocytes is essential for coordinating glycogen production and insulin response in the liver. Dysregulation of hepatic circadian genes may induce insulin resistance and impair glucose homeostasis, potentially triggering diabetes development.

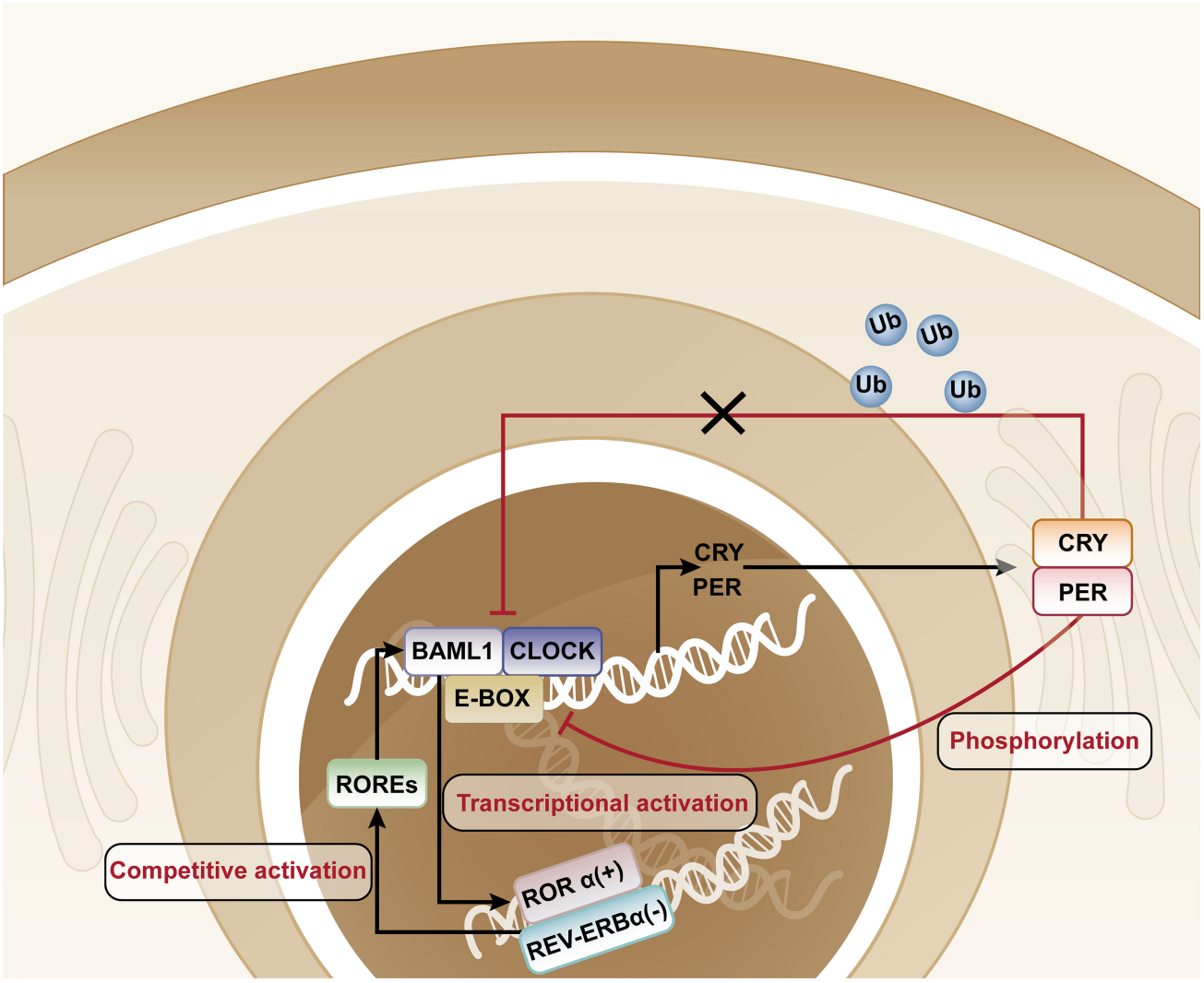

Fig. 2. Core regulatory mechanism of the mammalian circadian clock. CLOCK, a core transcriptional activator, binds E-box elements to initiate *CRY* and *PER* gene expression. Newly synthesized CRY and PER proteins undergo sequential phosphorylation in the cytoplasm, enabling their dimerization and nuclear translocation. Phosphorylated CRY/PER complexes inhibit the transcriptional activity of the CLOCK-BMAL1 complex bound to E-boxes, while ubiquitination targets them for proteasomal degradation, thereby resetting the cycle. The CLOCK-BMAL1 complex also activates transcription of *REV-ERBα* and *RORα* genes (via E-boxes). The REV-ERBα/RORα auxiliary loop regulates *BMAL1* expression through ROREs, with REV-ERBα binding repressing *BMAL1* transcription, while RORα binding activates it. The symbols in the figure represent the main interactions among circadian regulatory factors. Solid arrows (→) indicate activation or directional processes; T-shaped lines (⊥) represent inhibition; plus sign (+) denotes positive regulation; minus sign (–) indicates inhibitory effects; and cross mark (X) represents blockage, referring to the termination or inactivation of specific processes or complexes. The figure was created by the authors using Adobe Illustrator 2024 v28.0 (Adobe Inc., San Jose, CA, USA). *CLOCK*, circadian locomotor output cycles kaput; *BMAL1*, brain and muscle ARNT-like 1; *CRY*, cryptochrome; *PER*, period; *REV-ERBα*, reverse-erb alpha; *RORα*, retinoic acid receptor-related orphan receptor alpha; E-BOX, enhancer box; ROREs, ROR response elements; Ub, ubiquitin.

Pancreatic Clock Genes: The pancreas regulates blood glucose homeostasis by secreting insulin and glucagon into circulation, and circadian regulation modulates the pancreatic output of insulin and glucagon. Marcheva *et al.* [28] reported that *Clock*/*Bmal1* mutant mice displayed impaired glucose metabolism, reduced glucose tolerance, and diminished insulin secretion. Age-related declines were also observed in pancreatic cell proliferation, glucose tolerance, and insulin secretion capacity. Perelis *et al.* [29] further reported that *Bmal1* knockout in adult mouse β-cells via tamoxifen treatment triggered pronounced hyperglycemia, diminished glucose tolerance, and inadequate insulin production, ultimately progressing to diabetes.

Central Clock Regulates Peripheral Clocks Through Neural and Hormonal Signals

The central and peripheral clocks require tight temporal synchronization and functional coordination. The central clock regulates peripheral clocks by generating neural and hormonal signals that ensure their rhythms remain aligned. This synchronization and coordination are essential for maintaining normal physiological functions in the body [18].

The SCN establishes direct neural fiber connections with several brain regions, enabling it to convert light signals into neural impulses and transmit them through neural pathways to other brain regions and peripheral tissues, thereby regulating circadian rhythmic activities [30]. The central clock also indirectly influences peripheral clocks by modulating behavior, for example, synchronizing feeding and sleep patterns with ambient light-dark cycles. Additionally, the SCN influences other hypothalamic regions to secrete hormones that, once released into the bloodstream, act on receptors in peripheral tissues, thereby regulating peripheral clocks [31].

Melatonin (MT), produced primarily in the pineal gland, is ubiquitously present in organisms and undergoes SCN-mediated regulation to maintain synchronization with light-dark cycles. Plasma melatonin concentrations peak 3–5 hours following the lights-off phase and remain at low levels under light exposure [32]. Research indicates that MT can significantly downregulate pro-inflammatory transcript production (e.g., interleukin-1β (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6), interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α)) and attenuate mitochondrial superoxide generation. Additionally, MT enhances endothelial function, reduces inflammatory responses, and maintains the redox balance of pancreatic β-cells, thereby preventing β-cell damage and regulating glucose metabolism and insulin secretion [33]. Conversely, circadian disruption from nocturnal light exposure substantially decreases melatonin production, promoting insulin resistance and increasing the risk of T2DM [34].

Cortisol, secreted by the adrenal cortex, exerts the strongest influence on glucose metabolism. Its release is primarily controlled by the hypothalamic-pituitary-adrenal (HPA) axis. Study indicates that cortisol is regulated by the SCN, and in humans, cortisol secretion peaks in the early morning and gradually decreases, reaching a trough at night [35]. By comparing circadian rhythms of salivary cortisol levels between diabetic patients and healthy individuals, Lederbogen *et al.* [36] observed significant alterations in the salivary cortisol circadian rhythm among T2DM patients, showing decreased morning levels alongside increased afternoon and evening values. A prospective cohort study measuring salivary cortisol in a community population suggested that abnormally elevated nighttime cortisol levels significantly increased the risk of incident T2DM (odds ratio [OR] = 1.18; 95% confidence interval [CI]: 1.01–1.37; p = 0.035) [37]. Mechanistically, cortisol raises blood glucose by inducing lipolysis, promoting the release of free fatty acids into the bloodstream, and increasing triglyceride levels. Additionally, cortisol binds to glucocorticoid receptors on pancreatic β-cells, reducing insulin secretion and lowering insulin sensitivity [37].

Growth hormone (GH), a peptide hormone, plays a critical role in protein synthesis and glucose metabolism. GH secretion peaks shortly after sleep onset and significantly increases during sleep, particularly during slow-wave sleep [38]. Its intermittent secretion during sleep may be linked to the periodic nature of slow-wave sleep. Declines in GH and its mediator, insulin-like growth factor-1 (IGF-1), elevate liver free fatty acids, resulting in abnormal fat accumulation that potently triggers liver insulin resistance [39,40]. Furthermore, GH deficiency weakens the regulatory effects of IGF-1 on insulin, inhibiting lipolysis and thereby increasing the risk of android obesity and insulin insensitivity [41].

Thyroid-stimulating hormone (TSH) secretion exhibits circadian variation. TSH levels begin to rise in the evening before sleep onset, peak during the early part of the night shortly after sleep begins, then gradually decline throughout the remainder of the sleep, returning to lower daytime levels upon waking [42]. The study has shown that elevated TSH levels, along with decreased FT3 and FT4 levels, are significantly associated with an increased risk of type 2 diabetes mellitus (T2DM). TSH indirectly influences blood glucose levels by regulating the synthesis and secretion of thyroid hormones. Thyroid hormones can elevate blood glucose through mechanisms such as promoting hepatic gluconeogenesis and modulating pancreatic endocrine function, specifically by inhibiting insulin secretion and enhancing glucagon secretion [43].

Leptin suppresses glucagon and cortisol secretion while enhancing glucose utilization and inhibiting hepatic glucose production, collectively contributing to reduced blood glucose [44]. Under normal conditions, baseline plasma leptin levels peak during the dark phase. However, chronic light cycle disruption alters the leptin signaling pathway, reducing energy expenditure and impairing glucose regulation [45].

Circadian Rhythm of Glucose Metabolism

Proper blood glucose levels are essential for maintaining normal physiological functions. However, these levels are not constant and exhibit circadian fluctuations. Typically, glucose levels demonstrate diurnal variation, lower at night and elevated during the day, primarily linked to eating behavior and physical activity [46]. Such oscillations result from diurnal changes in glucose metabolism and systemic insulin responsiveness, coordinated by the hypothalamic SCN and peripheral clocks. For instance, the circadian clock of the liver regulates glucose production and release,

while the pancreatic circadian clock moderates insulin secretion over time, thereby maintaining blood glucose stability [47].

Substantial evidence further indicates that mature erythrocytes exhibit significant circadian variations in glucose metabolism despite their anuclearity and consequent inability to perform transcription and translation. Specifically, glucose metabolism primarily occurs via the pentose phosphate pathway during the day, whereas glycolysis predominates at night [48]. This circadian variation may be associated with changes in redox reactions and energy demands [48]. This discovery not only reveals a previously unrecognized transcription-independent mechanism regulating circadian glucose metabolism but also underscores that the inherently oscillatory nature of metabolic pathways constitutes a fundamental strategy for aligning physiological functions with circadian rhythms, establishing it as a foundational element of the broader biological timing system.

Circadian Metabolic Rhythm of Glucose Tolerance

Human glucose tolerance exhibits a pronounced circadian rhythm, progressively declining from morning to evening under constant metabolic conditions [49]. Studies demonstrate that this characteristic, superior morning glucose tolerance compared to evening in healthy individuals, is independent of feeding and activity cycles [8,50]. This intrinsic rhythmicity is governed by the endogenous circadian clock, as demonstrated by experiments utilizing forced desynchrony (FD) protocols to separate the effects of behavioral cycles from those of the circadian clock [51].

At the molecular level, core clock genes (e.g., *CLOCK*, *BMAL1*) directly regulate key physiological processes, including insulin secretion from pancreatic β-cells and hepatic glucose production [52]. In T2DM, this diurnal pattern of glucose tolerance is often attenuated, phase-delayed, or even reversed, with individuals exhibiting the dawn phenomenon (DP) showing markedly elevated postprandial glucose levels after breakfast [49,53]. Overall, human glucose tolerance demonstrates an inherent circadian rhythm, higher in the morning and lower in the evening, regulated by the endogenous circadian clock. Maintenance or disruption (e.g., attenuation, delay, or reversal) of this rhythm is critically linked to glycemic control in T2DM.

Circadian Rhythm of Insulin Sensitivity

In mammals, insulin produced by pancreatic β-cells is released into the bloodstream in response to elevated glucose levels. Elevated insulin enhances glucose uptake in responsive tissues (e.g., muscle and adipose) while suppressing hepatic glucose production, establishing insulin as the key regulator of glycemia [54].

The liver, adipose tissue, and skeletal muscle contain abundant insulin receptors, serving as principal regulators of systemic glucose and lipid homeostasis. These organs have intrinsic molecular clocks. The liver exhibits distinct circadian patterns in which its biological clock contributes to the daily modulation of glycogen levels and insulin sensitivity in healthy individuals. Feeding rhythms significantly influence the diurnal variations in hepatic insulin responsiveness. Properly timed feeding can synchronize with the liver clock, allowing the liver to respond more effectively to insulin signals after food intake, thereby promoting glucose uptake and metabolism. Diurnal variations in insulin sensitivity peak in the morning and reach their lowest levels at night. Notably, meal timing modulates rhythmic hepatic gene expression and may desynchronize the liver clock from the SCN master clock by altering feeding patterns, thereby modifying hepatic insulin sensitivity rhythms [55,56].

Human skeletal muscle possesses an autonomous molecular clock that remains synchronized with the SCN. Muscular insulin sensitivity is modulated by circadian mechanisms, with the rhythmic expression and activity of glucose transporter 4 (GLUT4) directly determining diurnal fluctuations in insulin sensitivity. Normally, muscle tissue pre-upregulates GLUT4 prior to activity or feeding, ensuring efficient glucose utilization, with peak intrinsic insulin sensitivity occurring in the morning hours [25,57]. Ill-timed activity or feeding disrupts synchronization between skeletal muscle circadian oscillators and the SCN, potentially inducing insulin resistance.

White adipose tissue (WAT) also contains autonomous biological clocks similar to those of skeletal muscle, which synchronize through SCN-derived signals and feeding cues. In human WAT, nearly 25% of transcribed genes exhibit circadian fluctuations, including those regulating glucose uptake [58]. Carrasco-Benso *et al*. [59] reported that protein kinase B (AKT) phosphorylation establishes the endogenous circadian rhythm of insulin action in subcutaneous adipose tissue of obese subjects, with the highest sensitivity observed around noon. While assessing insulin sensitivity at 4-hour intervals can reveal general circadian rhythms, it may overlook finer variations, especially during periods of rapid changes. For example, faster physiological fluctuations may occur between early morning (shortly after waking) and midnight, which such sampling intervals fail to capture. Continuous monitoring technologies would provide more detailed dynamic data, improving the detection of subtle insulin responses and their temporal relationships.

The circadian coordination of insulin sensitivity across multiple target organs optimizes glucose metabolism. In contrast, mistimed feeding or clock dysfunction disrupts this homeostatic equilibrium, leading to systemic insulin resistance.

Behaviors Causing Circadian Rhythm Disruption and Their Diabetes-Related Risks

Shift Work

Shift work involves employees rotating through different work periods (morning, afternoon, and night) based on a fixed schedule, with night shifts being a common form. The unconventional work hours in shift work require abrupt adjustments to both sleep routines and photoperiod exposure. These alterations disrupt circadian rhythms, creating desynchronization with external environmental cues [60].

Retinol binding protein 4 (RBP4) functions as a potential inducer of insulin resistance across species, including rodents and humans. RBP4 is predominantly produced by hepatocytes, forming complexes with retinol for subsequent delivery to peripheral tissues. The retinol-RBP4 complex (holo-RBP) mediates its biological effects through stimulated by retinoic acid 6 (STRA6) receptor binding, influencing insulin receptor phosphorylation, downstream gene expression, and maintaining glucose homeostasis via the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. The RBP4-STRA6 signaling axis exhibits circadian rhythmicity, with STRA6 playing a critical role in the circadian variation of insulin sensitivity. Shift work disrupts the circadian rhythm of the RBP4-STRA6 signaling axis, thereby impairing glucose regulation [61]. Furthermore, altered *CLOCK* gene expression in peripheral blood mononuclear cells (PBMCs) of night-shift workers compared with day-shift counterparts provides additional molecular evidence of circadian dysregulation [62].

Shift work represents a major occupational hazard contributing to T2DM. A large cohort study revealed a 19% [95% confidence interval (CI): 3–37%] higher diabetes risk among shift workers compared to day workers, even after adjusting for confounders [63]. Another study reported that exclusive night shift work in the preceding year was linked to elevated T2DM risk versus daytime-only shifts (hazard ratio (HR) = 1.59; 95% CI: 1.02–2.43). Elevated T2DM incidence was also associated with frequent consecutive night shifts ($\geq$3 consecutive night shifts) and longer durations of exclusive night-shift work compared to mixed schedules [64]. A meta-analysis of 12 longitudinal studies indicated that shift work was linked to elevated diabetes risk (relative risk (RR) = 1.14; 95% CI: 1.10–1.19; I^2 = 38.9%; p = 0.028), showing a linear exposure-response relationship with years of shift work [65]. This exposure-response relationship underscores the likelihood of irreversible metabolic damage from sustained circadian disruption, highlighting the need for workplace interventions to optimize shift rotation patterns.

Social Jetlag

Social jetlag refers to the discrepancy between an individual's circadian rhythm and externally imposed social schedules [66]. This misalignment typically arises between sleep patterns on workdays and weekends, where individuals follow a relatively strict wake-sleep schedule during the workweek but stay up late and sleep on weekends or days off, resulting in social jetlag. Compared to individuals with a preference for morning activities, those with an evening preference tend to have poorer blood glucose control, partly due to increased nighttime food intake. Study suggests that persistent circadian desynchronization promotes excessive feeding, weight gain, and disturbances in carbohydrate metabolism [67]. A cross-sectional study demonstrated that among individuals aged <61 years, social jetlag (particularly when exceeding 2 hours) was associated with a 75% higher risk of T2DM or prediabetes (prevalence ratio (PR) = 1.75; 95% CI: 1.2–2.5) [68]. Maintaining regular sleep schedules may therefore represent a key strategy for preventing metabolic disorders in younger populations.

Irregular Meal Timing

Busy modern lifestyles frequently lead to irregular meal timing, and delayed eating patterns can cause significant circadian rhythm imbalance. Consuming dinner too late (within 2 hours before bedtime) reduces glucose tolerance and negatively affects glucose metabolism and weight control [69].

Late dinners impair glucose metabolism through multiple mechanisms. At the genetic level, late-night meals disrupt circadian rhythm regulation, altering clock gene expression patterns. At the hormonal level, late dinners disrupt insulin secretion rhythms. In the evening, insulin secretion normally decreases as the body prepares for rest. Eating late increases insulin secretion, but its glucose-lowering effect is blunted due to self-regulatory mechanisms, impairing glucose metabolism and preventing effective blood glucose control. Additionally, gastrointestinal motility and gastric emptying are significantly reduced at night, prolonging food retention in the digestive tract and sustaining stimulation of gut hormone release (e.g., glucagon-like peptide-1 (GLP-1)), thereby altering their physiological secretion patterns. Abnormal gastrointestinal hormone secretion interferes with normal insulin production and action, leading to inadequate blood glucose regulation, thus indirectly affecting glucose metabolism [69,70].

Moreover, delaying lunch impacts glucose metabolism, resulting in decreased glucose tolerance. The cortisol curve after a delayed lunch shows a flatter pattern, resembling that seen under acute stress conditions, indicating a disrupted metabolic rhythm [71]. Garaulet *et al*. [72] reported that late dinner timing elevates melatonin levels, thereby inhibiting insulin secretion and significantly elevating postprandial glucose. Another study observed that individuals consuming dinner after 22:00 exhibited a higher risk of T2DM (HR = 1.44; 95% CI: 1.00–2.09) compared to those finishing dinner before 19:00 [73]. Collectively, delayed meals disrupt circadian rhythms at genetic and hormonal levels, impair insulin secretion and

action, and alter gut hormone profiles, leading to reduced glucose tolerance and metabolic dysregulation.

The Impact of Light

Light serves as a critical regulator for resetting the central circadian clock. The liver, adipose tissue, and skeletal muscles contain autonomous circadian regulators that integrate metabolic information to adjust glucose-handling capacity. When these biological clocks are inconsistent with the body's light-dark cycle, they can be inhibited or resynchronized by environmental factors such as light exposure. Glucose metabolism is influenced by differences in light intensity and wavelength across the day-night cycle. Photosensitive retinal neurons relay ambient illumination data to the suprachiasmatic nucleus, which modulates glycemic regulation via neuroendocrine pathways and autonomic signaling [10]. Consequently, nocturnal light exposure disrupts normal circadian rhythms, leading to dysregulation of glucose metabolism.

A nationwide cross-sectional study in the Chinese adult population examined the association between artificial light at night (ALAN) exposure and diabetes prevalence by estimating outdoor nighttime ALAN intensity using satellite imagery. The results revealed that high-intensity ALAN exposure was strongly associated with elevated diabetes occurrence (PR = 1.28, 95% CI: 1.03–1.60) [74]. Furthermore, external light input also synchronizes with daily variations in skeletal muscle insulin responsiveness. Diminished light perception functionality can promote insulin resistance in skeletal muscle tissue, substantially increasing the risk of T2DM [75]. Notably, with societal advancements, exposure to electronic device screens (e.g., mobile phones, tablets, computers, and televisions) has increased, making blue light exposure an increasingly prominent concern. Daytime blue spectrum illumination inhibits melatonin production, promoting wakefulness and cognitive function. However, low-intensity blue light exposure at night may impair sleep quality and profoundly disrupt circadian rhythms and cycles [76]. In summary, light synchronizes central and peripheral circadian clocks that regulate glucose metabolism. In contrast, nocturnal exposure, especially high-intensity ALAN and screen-emitted blue light, disrupts this integration, elevates diabetes risk through interference with insulin pathways, and impairs melatonin-mediated metabolic rhythms.

Sleep Deprivation

Extended work hours, academic pressure, and excessive use of electronic devices often lead to insufficient sleep. Sleep deprivation triggers a series of physiological changes, such as hypoxia and hypercapnia, which can stimulate abnormal activation and disruption of body chemoreceptors, including the sympathetic nervous system, the stress system, hormones, and the hypothalamic-pituitary-adrenal (HPA) axis [77]. The heightened sympathetic activity induced by sleep disorders suppresses insulin secretion, reducing the capacity of the body to take up glucose, leading to chronic hyperglycemia and ultimately promoting T2DM [78]. Sleep loss, particularly reduced slow-wave sleep (SWS), directly activates the HPA axis. This involves increased release of corticotropin-releasing hormone (CRH) from the hypothalamus, with subsequent elevation of adrenocorticotropic hormone (ACTH) and cortisol levels. Chronic sleep disruption impairs HPA axis negative feedback, sustains glucocorticoid excess, and disrupts the normal diurnal cortisol rhythm. This hyperactivation promotes metabolic dysregulation, including insulin resistance and visceral adiposity, partly via amplified tissue cortisol action [79].

Sleep loss also alters the production of multiple metabolic regulators, such as insulin, glucagon, leptin, and orexins. A decrease in serum leptin levels can stimulate foraging behavior, increase appetite, and elevate food intake, while simultaneously decreasing the liver's capacity to counteract serum insulin antagonists, leading to enhanced anaerobic metabolism [80]. Additionally, irregular sleep patterns impair circadian rhythm regulation and biological clock function, including melatonin secretion, which regulates sleep. Insufficient melatonin secretion affects sleep quality and circadian rhythms, impairs insulin activity and sensitivity, and elevates susceptibility to T2DM, metabolic disorders, obesity, and cardiovascular conditions [81]. Furthermore, this disruption can impair normal pancreatic β-cell function, leading to insufficient insulin secretion, inability to timely break down excess glucose in a timely manner, and enhanced hepatic conversion of glucose into fat, resulting in insulin resistance and obesity [82].

A large cohort study of 247,867 participants revealed that habitually short sleep duration is associated with an increased risk of developing T2DM. Cox regression analysis, adjusted for confounding variables, demonstrated a significant increase in T2DM risk among participants with $\leq$5 hours of daily sleep. Individuals sleeping 5 hours per day exhibited an adjusted HR of 1.16 (95% CI: 1.05–1.28), and those sleeping 3–4 hours per day exhibited an adjusted HR of 1.41 (95% CI: 1.19–1.68) compared with individuals with normal sleep duration [83].

In summary, sleep deprivation induces multi-system dysregulation, spanning sympathetic hyperactivity, HPA axis disruption, hormonal imbalance (leptin/insulin/melatonin), and circadian misalignment, culminating in impaired glucose metabolism, insulin resistance, β-cell dysfunction, and elevated T2DM risk.

Collectively, the behaviors discussed above (shift work, social jetlag, irregular meal timing, inappropriate light exposure, and sleep deprivation) converge to disrupt circadian rhythms. As summarized in Fig. 3, this circadian disruption is a key driver in the pathogenesis and progression of type 2 diabetes.

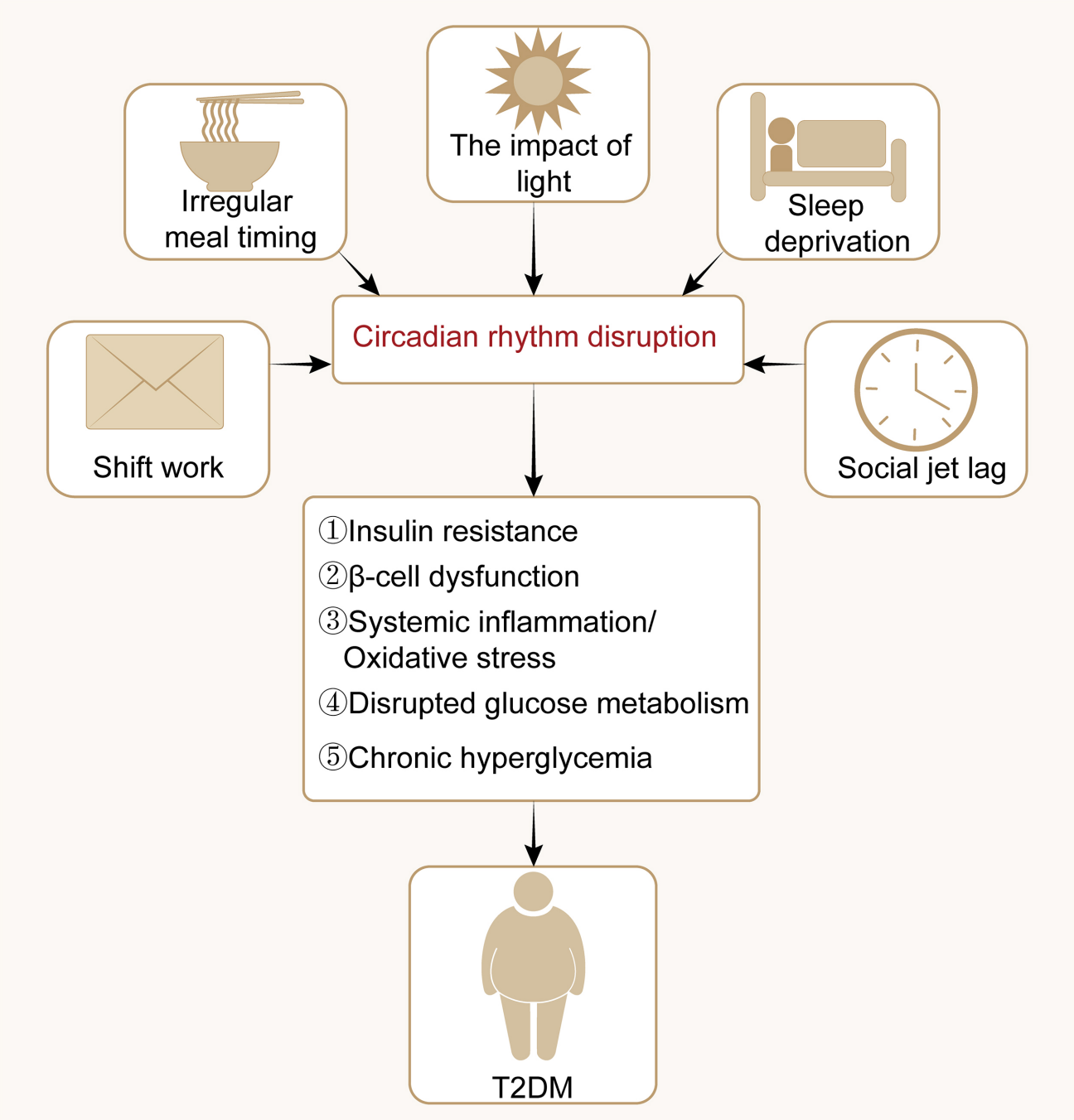

Fig. 3. Circadian rhythm disruption contributes to the pathogenesis and progression of type 2 diabetes. External factors, including shift work, social jetlag, irregular meal timing, light exposure at inappropriate times, and sleep deprivation, perturb the synchronization between the SCN and peripheral clocks. This circadian disruption contributes to insulin resistance, pancreatic β-cell dysfunction, systemic inflammation and oxidative stress, and impaired glucose homeostasis, culminating in chronic hyperglycemia and an increased risk of type 2 diabetes mellitus (T2DM). The figure was created by the authors using Adobe Illustrator 2024 v28.0 (Adobe Inc., San Jose, CA, USA).

The Effect of T2DM on Circadian Disruption

Hyperglycemia, particularly in individuals with diabetes, disrupts circadian rhythms through multiple pathways, leading to dysregulation of normal physiological processes. Most directly, diabetes-related symptoms induced by hyperglycemia, such as nocturia and polydipsia, cause sleep fragmentation, thereby disturbing the sleep-wake rhythm. Furthermore, nocturnal hyperglycemic or hypoglycemic episodes often trigger awakenings, interrupting deep sleep [84]. Diabetic complications and comorbidities further exacerbate circadian disruption. For ex-

ample, peripheral neuropathy may cause pain or discomfort (e.g., restless legs syndrome), impairing sleep onset [85]. Obstructive sleep apnea (OSA) independently promotes diabetes onset and progression via intermittent hypoxia, heightened sympathetic activity, systemic inflammation, and sleep fragmentation [86].

Type 2 diabetes mellitus (T2DM) also causes significant structural and functional damage to the circadian timing system, impairing the molecular clock. Pathological investigations reveal a significant reduction in key neuronal and glial cell populations within the suprachiasmatic nucleus (SCN), the central circadian pacemaker, including decreases in arginine vasopressin-immunoreactive (AVP-ir) neurons, vasoactive intestinal polypeptide-immunoreactive (VIP-ir) neurons, and glial fibrillary acidic protein-immunoreactive (GFAP-ir) astroglial cells [8]. Such structural degeneration of the SCN likely underpins circadian clock dysfunction in T2DM. The hyperglycemic milieu further exacerbates circadian disruption via multiple mechanisms. Gut dysbiosis induces systemic inflammation, characterized by elevated plasma levels of TNF-α and IL-6, thereby inhibiting insulin signaling pathways. Oxidative stress impairs the activity of sirtuin 1 (SIRT1), an nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase which is crucial for sustaining CLOCK-BMAL1 transcriptional activity. The impairment of rhythmic secretion of short-chain fatty acids (SCFAs) and bile acids (BAs) diminishes their synchronizing influence on clock genes such as *PER2* and *BMAL1* [87].

Chronic hyperglycemia also impairs circadian rhythmicity in peripheral clock genes within adipose tissues and the pancreas. This suppresses diurnal variations in subcutaneous adipose tissue insulin sensitivity (with peak sensitivity reduced by 54%) and attenuates β-cell function in the evening, leading to abnormal diurnal patterns of glucose tolerance. Moreover, it may promote behavioral rhythm misalignment, such as delayed, high-calorie evening meals, causing desynchrony between the central SCN clock and peripheral clocks in organs, including the liver and gut [88].

Consequently, a bidirectional relationship exists between circadian rhythm disruption and T2DM. Circadian misalignment reduces insulin sensitivity and impairs β-cell function, while poor glycemic control further exacerbates circadian abnormalities. This mechanistic link highlights the clinical necessity of integrating circadian rhythm regulation strategies into therapeutic approaches to interrupt the vicious cycle of "hyperglycemia-circadian disruption-metabolic deterioration".

Circadian Rhythm Synchronization and Metabolic Health

Adjusting Light Exposure

Optimizing daily light exposure can help restore circadian rhythm synchronization and improve metabolic health. Exposure to natural light is a practical therapeutic approach for regulating circadian phases and maintaining glucose homeostasis, as well as other metabolic processes [89]. Morning light serves as the primary environmental cue for synchronizing the 24-hour biological clock. However, most office workers have limited exposure to high-intensity natural light, with time spent under indoor lighting greater than 1000 lux averaging only about 16 minutes daily. Therefore, recommending patients spend more time outdoors may have practical limitations. A potential research direction involves developing indoor artificial lighting systems that dynamically adjust light intensity and color temperature based on biological rhythms [90]. Adoption of such dynamic lighting systems may help overcome natural light accessibility constraints and represent a promising avenue for future investigation.

Light therapy is a convenient, safe, and non-pharmacological intervention designed to simulate the natural light spectrum by exposing individuals to appropriate levels of light for therapeutic purposes [91]. Early light therapy devices include lightboxes and light panels, but recent developments have introduced portable devices, such as wearable light therapy helmets and glasses [91]. Light therapy acts by influencing SCN circadian pacemakers, regulating melatonin release, and consequently modulating circadian rhythms, thereby improving sleep, mood, and cognitive function [92]. A meta-analysis indicates that light therapy significantly improves sleep disorders. Compared with controls, the light therapy group showed significant improvements in both objective and subjective Wake After Sleep Onset (WASO) indicators. For objective results, the standardized mean difference (SMD) was –0.61 [–1.11, –0.11] ($p = 0.017$), with a weighted difference of 11.2 minutes (SD = 11.5); for subjective outcomes, the SMD was –1.09 [–1.43, –0.74] ($p < 0.001$), with a weighted difference of –36.4 minutes (SD = 15.05). Most of the interventions were delivered in the morning or daytime, using light intensities typically exceeding 2500 lux, with treatment sessions lasting from 0.5 to 2 hours over periods ranging from several days to weeks [93]. Research also suggests that light therapy can lower glucose levels and ameliorate insulin resistance. However, most such studies have been conducted in animal models [94–96]. Only Powner and Jeffery [97] have conducted human trial, demonstrating that during an oral glucose tolerance test (OGTT) test, participants in the light therapy group (670 nm red light for 15 minutes) exhibited a 27.7% overall reduction in blood glucose elevation ($p = 0.0002$) and an approximately 7.5% decrease in peak glucose levels ($p = 0.0054$). However, the study was limited to healthy individuals and had a relatively small sample size, underscoring that research on glucose regulation in this context remains at an early stage.

Regarding blue light restriction and its sleep-related consequences, it is recommended that patients avoid using electronic devices at least 30 minutes before bedtime and

upon nocturnal awakening. A recent synthesis of six randomized controlled trials (RCTs) suggested that blue-light filtering eyewear does not adequately substitute for direct blue light reduction, and its sleep-enhancing benefits remain unconfirmed [98]. Thus, the adverse impact of blue light on sleep warrants continued caution.

Adjusting Daily Rhythm

Improving Sleep

Healthy sleep patterns are essential for physical and psychological well-being and contribute significantly to improved glucose regulation. Evidence synthesis from RCTs shows that sleep restriction, circadian rhythm disruption, and suppression of slow-wave sleep negatively affect insulin sensitivity [99]. Increasingly, evidence suggests that improving sleep may regulate insulin response, alleviate insulin insensitivity, and consequently enhance glycemic control. One study demonstrated that increasing sleep duration, even by just 1 hour and 2 minutes per night for one week, significantly improved insulin sensitivity, with 84% of participants showing a 20% increase in insulin sensitivity [100]. Additionally, emphasizing the importance of sleep education is critical. Research has shown that educating individuals about the significance of sleep and optimal duration can improve sleep quality, fasting blood glucose, and HbA1c levels in the short term [101]. A two-way feedback approach with personalized education is more readily accepted by patients. For individuals with sleep disorders, oral melatonin supplementation before bedtime may be considered to improve sleep quality. Meta-analyses have shown that melatonin supplementation effectively improves fasting blood glucose, insulin resistance, and HbA1c levels, with doses of 10 mg/day or higher yielding greater benefits compared to lower doses [102]. Thus, through behavioral interventions or melatonin supplementation, insulin sensitivity and glycemic control can be significantly improved.

Many individuals with T2DM also experience OSA, which disrupts circadian rhythms and worsens glycemic control. Physicians can begin assessment by inquiring about current symptoms and sleep-related history, including difficulty falling asleep, frequent nocturnal awakenings, vivid dreams, and daytime sleepiness. A thorough review of the patient's medical background, particularly OSA-related complications, is essential. Encouraging patients to record their sleep duration, onset and wake times, frequency of nighttime awakenings, and daytime sleepiness may assist physicians in better understanding their sleep patterns and challenges. Effective treatment options include weight loss and exercise, positive airway pressure therapy, devices supporting chin advancement during sleep, and surgical interventions to modify soft pharyngeal tissue or facial bones, thereby enlarging the upper airway [103]. Patients with asymptomatic or mild OSA that does not affect driving safety may benefit from lifestyle interventions, including weight management and increased physical activity. For patients with excessive daytime sleepiness and refractory hypertension, interventions such as positive airway pressure are recommended [103].

A meta-analysis revealed that lifestyle interventions markedly reduced the incidence of metabolic disorders in individuals with OSA (RR = 0.60; 95% CI: 0.48–0.74; $p < 0.01$), as well as fasting blood glucose (MD = –0.63; 95% CI: –0.75 to –0.50; $p < 0.00001$), blood pressure, and waist circumference [104]. Additionally, a randomized controlled trial revealed that continuous positive airway pressure (CPAP) therapy reduced the incidence of metabolic syndrome in OSA patients (RR = 0.82 [95% CI: 0.75–0.90]; $p < 0.01$), as well as reductions in fasting blood glucose (MD = –0.07; 95% CI: –0.10 to –0.03; $p = 0.001$), blood pressure, triglycerides, and waist circumference [104]. Therefore, effective diagnosis and management of comorbid OSA, particularly via lifestyle modification and CPAP therapy, are crucial for mitigating associated metabolic dysfunction, reducing metabolic syndrome (MetS) incidence, and improving glucose regulation.

Physical Activity

Physical activity is an accessible, low-cost, and effective strategy for managing diabetes. Research confirms that regular exercise can reset the brain's circadian pacemaker, promote better sleep, and influence peripheral muscle clocks [67]. Through metabolomics profiling, Sato *et al*. [105] demonstrated that diurnal metabolic responses to physical activity were more robust in the morning compared to the evening. Morning exercise enhanced glycolysis and fatty acid oxidation, facilitating the catabolism of branched-chain amino acids (BCAAs) such as leucine, isoleucine, and valine. Leucine and isoleucine suppress pyruvate dehydrogenase complex activity, inducing mitochondrial dysfunction and toxic intermediate accumulation, ultimately impairing pancreatic β-cell function [105]. The BCAA-induced metabolic shift following morning exercise may help maintain the function of pancreatic β-cells via this mechanism. Therefore, regular physical activity and its beneficial metabolic effects on blood glucose homeostasis are intrinsically linked to circadian biology, with optimized exercise timing potentially supporting T2DM prevention and management.

Exercise also improves sleep quality and counteracts metabolic impairments induced by sleep deprivation, including mitochondrial dysfunction, insulin resistance, and glucose intolerance [106,107]. Numerous studies have demonstrated that high-intensity interval training (HIIT) effectively mitigates the negative metabolic effects of sleep deprivation. The primary mechanism involves HIIT's ability to significantly mitigate sleep restriction-induced impairments in mitochondrial respiratory function and skeletal muscle protein synthesis, thereby restoring metabolic homeostasis, including reducing the abnormal elevation in

glucose and insulin area under the curve (AUC), and correcting disruptions in non-esterified fatty acid (NEFA) levels [108–111]. Light and moderate-intensity exercise appears insufficient to mitigate the metabolic damage associated with sleep restriction. For example, light-intensity walking, though it interrupts prolonged sedentary behavior, does not impact glucose metabolism during sleep restriction, and moderate-intensity exercise fails to prevent increases in peak glucose response induced by sleep loss [112]. Collectively, these findings underscore the critical importance of exercise intensity in determining metabolic resilience against sleep restriction, highlighting HIIT as an efficacious intervention for mitigating the deleterious effects induced by sleep deprivation.

Dietary Therapy

In addition to modifying dietary structure and the distribution of macronutrients, caloric restriction (CR), intermittent fasting (IF), and intermittent energy restriction (IER) regimens hold significant potential for improving glucose metabolism. These interventions collectively induce organism-wide changes in hormonal profiles, metabolic compounds, and growth regulators, including insulin, glucose, and insulin-like growth factor 1 (IGF-1) [113].

As a dietary intervention, CR reduces overall caloric intake while exerting beneficial effects ranging from cellular mechanisms to systemic functions. It interacts in complex ways with the circadian rhythm. In multiple tissues, CR upregulates the expression of clock genes *Per1* and *Per2*. Furthermore, caloric restriction enhances hepatic *Cry2* and *Bmal1* average daily expression and modulates circadian rhythm gene expression across multiple regulatory levels in hepatic tissue. CR reprograms multiple circadian clock gene expressions in the SCN, consequently restoring circadian rhythmicity. The SCN regulates food intake by generating feeding signals synchronized with local peripheral clocks in other tissues or organs, influencing glucose and lipid metabolism while delaying T2DM progression [114].

The temporal pattern of food consumption critically affects diabetes onset. Dietary intake serves as a zeitgeber, entraining circadian rhythms by modulating hypothalamic neural activity [115].

Time-restricted eating (TRE), a daily intermittent fasting approach, limits food consumption to a defined timeframe but allows non-caloric beverages, including water, unsweetened tea, and coffee, during fasting periods. Study indicates that neuronal activity is synchronized with circadian rhythms in the hypothalamus during simulated TRE patterns, whereas delayed food intake disrupts neuronal alignment, thereby impairing circadian rhythms. Maintaining a TRE pattern can help preserve the health of the hypothalamic circadian rhythm and prevent metabolic disorders [116]. An RCT [117] demonstrated improved insulin sensitivity in 60 patients with T2DM after 12 weeks of following a 10-hour TRE regimen (8:00–18:00 eating window and 18:00–8:00 fasting). These findings suggest that controlled energy intake, early meal timing, and nighttime fasting are protective strategies against T2DM.

Conclusion

The circadian system functions as an endogenous regulatory network that coordinates numerous physiological processes. Disruptions caused by shift work, social jetlag, irregular meal timing, altered light exposure, or sleep deprivation are strongly associated with the development of T2DM. This connection arises from the adverse effects of circadian misalignment on insulin secretion and action, lipid metabolism, and energy balance, thereby increasing the risk of obesity and insulin resistance. Moreover, circadian disruption can aggravate pancreatic dysfunction through mechanisms such as inflammation and oxidative stress. Therefore, interventions that promote circadian alignment, such as light exposure management, lifestyle rhythm regulation (including consistent sleep-wake cycles), regular physical activity, and dietary optimization, are essential for reducing T2DM risk and supporting metabolic health.

Availability of Data and Materials

Not applicable.

Author Contributions

MZ, WL, MTF and WPT contributed to the study design and manuscript writing. MZ and MTF conducted the literature search. All authors were involved in the critical revision of the manuscript. All authors have read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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