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The role of circadian rhythm disruptions in the diabetes pathogenesis

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Diabetes mellitus has become a major global health concern with increasing prevalence worldwide. Recent studies have highlighted the critical role of the circadian rhythm, the body's internal biological clock, in the pathogenesis of diabetes. The circadian system regulates glucose metabolism, insulin secretion, and energy homeostasis. Modern lifestyle factors such as sleep disturbances shift work and irregular eating patterns disrupt circadian rhythms promoting insulin resistance and glucose intolerance. At the molecular level, mutations or altered expression of clock genes contribute to diabetes development. Clinical and experimental evidence suggests that maintaining the circadian integrity can reduce the diabetes risk and the chronotherapy time-based treatment approaches may enhance the therapeutic efficacy. The future advances including genetic profiling, AI-assisted monitoring and microbiota modulation hold promise for improved diabetes management. This review comprehensively examines the relationship between diabetes and circadian disruption emphasizing the importance of circadian biology in preventing and treating the metabolic diseases.

Keywords: diabetes, melatonin, sleep, circadian rhythm

Diabetes mellitus

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia resulting from impaired insulin secretion or insulin resistance. According to reports from the World Health Organization (WHO), more than 500 million individuals worldwide suffer from diabetes and this number is expected to be doubled within the next 20 years (WHO 2023). Diabetes affects not only glucose metabolism, but also multiple organ systems through complications such as cardiovascular diseases, renal failure, neuropathy, and retinopathy (Cho et al. 2018).

In recent years, it has been recognized that the development of diabetes is influenced by not only the genetic predisposition and lifestyle factors, but also by biological rhythms (Bass and Takahashi 2010). The circadian rhythm refers to physiological and behavioral processes that recur in approximately 24-h cycles in the organisms. This rhythm regulates the sleep-wake cycle, body temperature, hormone secretion, and metabolic activities (Takahashi 2017).

In diurnal animals like humans, physiological processes such as body temperature, hormone secretion, and activity levels peak during the light-time phase. In contrast, nocturnal animals exhibit these rhythmic peaks during the dark-time phase reflecting their opposite temporal organization of circadian rhythms. Many metabolic processes, such as pancreatic β-cell glucose sensitivity, hepatic gluconeogenesis capacity, and insulin sensitivity in skeletal muscle, are governed by the circadian clock (Cedernaes et al. 2019). Consequently, disruption of the circadian rhythm, for example due to shift work, chronic sleep disturbances or irregular eating patterns may lead to severe impairments in glucose metabolism and thus

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to the predisposition of diabetes development (Reutrakul and Van Cauter 2014; Panda 2016).

The aim of this review is to examine the physiological basis of the circadian rhythm and to show how its disruption may contribute to the diabetes pathogenesis in light of current scientific evidence. Additionally, experimental and clinical studies exploring this relationship will be presented by shedding light on the future research directions and therapeutic strategies.

Fundamentals of the circadian rhythm

The term "circadian rhythm" is derived from the latin "circa diem," meaning "about a day," and refers to biological processes recurring in approximately 24-h cycles in organisms. This rhythm is an evolutionarily conserved system present from bacteria to mammals (Takahashi 2017). In the human body, the circadian rhythm regulates numerous vital processes including the sleep-wake cycle, feeding behavior, hormone secretion, and body temperature (Bass and Lazar 2016).

At the cellular level, the circadian rhythm is driven by molecular clock mechanisms. The central clock resides in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN synchronizes with environmental time cues by receiving light signals from intrinsically photosensitive retinal ganglion cells containing melanopsin in the retina (Moore and Eichler 1972; Hatori et al. 2008). The SCN also coordinates peripheral clocks located in organs such as the liver, muscle, and pancreas, thus controlling the organism's overall temporal system (Dibner et al. 2010).

The molecular clock exists in all cells and tissues that contain nuclei. Circadian clock genes including CLOCK, BMAL1, PER (period), and CRY (cryptochrome) are expressed in metabolically active tissues such as the pancreas, liver, adipose tissue, and skeletal muscle. This clock system operates through transcription-translation feedback loops. Among the key clock genes are CLOCK and BMAL1. These genes form heterodimers that initiate the transcription of target genes including PER and CRY. The synthesized PER and CRY proteins accumulate in the cytoplasm and then translocate to the nucleus, where they inhibit the transcriptional activity of the CLOCK:BMAL1 complex. This negative feedback loop generates an approximately 24-h cycle (Partch et al. 2014).

This molecular clock mechanism is present both in the SCN and peripheral tissues. However, the proper function of peripheral clocks depends on synchronization by signals from the SCN. Otherwise, circadian desynchronization occurs leading to metabolic irregularities (Kornmann et al. 2007).

Light is the most potent zeitgeber (time-giver) for the circadian clock. Specialized photoreceptor cells in the retina, especially intrinsically photosensitive retinal ganglion cells (ipRGCs) expressing melanopsin, detect light and transmit signals to the SCN (Hattar et al. 2002). Through this mechanism, the organism synchronizes its internal biological clock to the external day-night cycle. In addition, environmental factors such as feeding time, physical activity levels, and social cues act as secondary zeitgebers (non-photic time-givers) influencing the circadian rhythm (Mistlberger 1994; Reinke and Asher 2016).

Although under SCN control many peripheral clocks are also sensitive to independent zeitgeber stimuli. A significant portion of these clocks are located in metabolic organs and regulate the timing of fundamental processes such as glucose homeostasis (Mohawk et al. 2012). Pancreas: insulin secretion exhibits circadian fluctuations, increasing in the morning and decreasing at the night (Marcheva et al. 2010). Liver: metabolic pathways including gluconeogenesis, lipogenesis, and glycogen synthesis are circadian-regulated. Mice deficient in BMAL1 show severe impairments in these processes (Lamia et al. 2008). Skeletal muscle: glucose uptake and energy expenditure vary according to circadian phase. The timing of physical activity particularly affects glucose tolerance (Sato et al. 2017). Proper functioning of this system is critical for metabolic homeostasis. Mutations in clock genes or disruptions in signals from the SCN can cause serious disturbances in glucose metabolism and reduce insulin sensitivity (Paschos and FitzGerald 2017). This may contribute to the development of metabolic diseases, especially type 2 diabetes mellitus (T2DM), over time.

The relationship between metabolism and circadian rhythm

Metabolism encompasses all biochemical processes related to energy production and utilization. The timing of these processes is optimized to align with the organism's daily physiological rhythm. The circadian clock system plays a critical role in regulating metabolic processes such as glucose homeostasis and energy balance (Bass and Takahashi 2010).

Insulin sensitivity is notably higher during morning hours leading to enhanced glucose tolerance, whereas this sensitivity decreases in the evening (Morris et al. 2015). Consumption of an equivalent

amount of carbohydrates in the morning results in a lower glycemic response compared to intake in the evening, which elicits a higher glycemic reaction (Qian et al. 2019). This phenomenon indicates that insulin efficacy varies depending on the time of the day.

Circadian clock genes, including CLOCK, BMAL1, PER, and CRY, are expressed in metabolically active tissues such as the pancreas, liver, adipose tissue, and skeletal muscle (Bass 2012). These genes generate approximately 24-h rhythmic molecular oscillations through transcription-translation feedback loops. Genetic mutations or dysregulation in the expression of these clock genes can lead to disturbances in the glucose metabolism.

For instance, the whole-body knockout of BMAL1 results in impaired glucose tolerance, reduced insulin secretion, and disrupted lipid metabolism contributing to metabolic syndrome (Rudic et al. 2004; Marcheva et al. 2010). Tissue-specific BMAL1 deletion in pancreatic β-cells impairs insulin release and disrupts the rhythmic expression of genes involved in insulin exocytosis (Marcheva et al. 2010).

In the pancreas, the proper functioning of the CLOCK/BMAL1 complex is essential for insulin synthesis and secretion. BMAL1-deficient mice exhibit a marked reduction in insulin secretion (Marcheva et al. 2010). In the liver, overexpression of the PER2 protein leads to increased gluconeogenesis and elevated hepatic glucose production (Zhang et al. 2009). In the muscle and adipose tissues, fluctuations in the expression of circadian clock genes influence insulin-mediated glucose uptake (Bray and Young 2011). Specifically, the muscle-specific deletion of BMAL1 results in significant impairments in glucose homeostasis (Menet et al. 2014).

Nutrient timing is also closely associated with this system. The timing of food intake throughout the day can affect the synchronization of peripheral clocks. Particularly, high caloric intake at night or eating late at night disrupts peripheral clocks' alignment with the central clock located in the SCN. This phenomenon, known as "circadian desynchronization," predisposes to metabolic dysfunction (Potter et al. 2016).

The interventions such as time-restricted feeding are proposed to have beneficial effects in the prevention and treatment of metabolic diseases (Chaix et al. 2014).

Individuals working night shifts experience disturbances in the light-dark cycle and meal timing, adversely impacting the circadian clock. These disruptions increase the risk of obesity, insulin resistance, and T2DM (Reutrakul and Van Cauter 2014). Chronic circadian disruption has been associated with impaired insulin signaling imbalances in leptin and ghrelin levels and elevated pro-inflammatory cytokines (Wefers et al. 2018).

Animal models provide substantial evidence in this regard. Mice harboring CLOCK gene mutations develop features of metabolic syndrome including obesity, hyperglycemia, hyperlipidemia, and insulin resistance (Turek et al. 2005). Human studies corroborate these findings reporting higher HbA1c levels and impaired glucose tolerance among shift workers (Manodpitipong et al. 2017)

Causes of the circadian rhythm disorders

Light, the most potent regulator of the circadian rhythm, reaches the SCN via the retina and synchronizes the biological clock with environmental time. However, exposure to artificial light at night, particularly short-wavelength blue light, in modern life delays the circadian rhythm. This suppresses melatonin secretion, prolongs sleep onset latency, and creates a misalignment between the biological clock and the environmental time (Czeisler and Gooley 2007; Chang et al. 2015).

Working night shifts or irregular shift schedules induces chronic desynchronization between the circadian clock and environmental cues. Shift workers experience reduced sleep duration, suppressed melatonin production, and disrupted synchronization between metabolic clocks and behavioral cycles (e.g., meal timing). This chronic circadian disruption predisposes individuals to impaired glucose metabolism, eventually leading to insulin resistance, obesity, and T2DM (Arble et al. 2010; Wang et al. 2011).

Chronic sleep deprivation, delayed sleep phase tendencies, sleep apnea, and insomnia adversely affect the circadian rhythm. There is a bidirectional relationship between sleep and glucose metabolism: insufficient sleep reduces insulin sensitivity, while impaired glucose regulation negatively impacts sleep quality (Spiegel et al. 1999; Tasali and Van Cauter 2002). For instance, even a shortening of sleep duration till 4–5 h/night can deteriorate glucose tolerance (Buxton et al. 2012).

Meal timing plays a critical role in aligning peripheral circadian clocks (e.g., pancreas and liver) with the central SCN clock. Eating late at night causes peripheral clocks to become misaligned with the SCN leading to disturbances in lipid and glucose metabolism, decreased insulin sensitivity, and abdominal obesity (Garaulet and Gomez-Abellan

2014; Zarrinpar et al. 2016). Studies have shown that consuming the same calories earlier in the day results in better glycemic control compared to late intake (Jakubowicz et al. 2013).

Physical exercise not only increases energy expenditure, but also helps re-entrain peripheral clocks. Regular physical activity supports the regulation of melatonin levels, cortisol secretion, and the healthy functioning of the sleep-wake cycle. Conversely, lack of exercise weakens these systems, contributing to circadian disruption (Miyazaki et al. 2001; Youngstedt et al. 2019).

Finally, mutations or genetic variants in circadian clock genes can cause rhythm disturbances. Polymorphisms in genes such as CLOCK, BMAL1, PER, and CRY alter the duration of the circadian cycle, influencing whether individuals are morning or evening types. Moreover, these genetic variations have been associated with insulin resistance, fasting glucose levels, and obesity (Woon et al. 2007; Scott et al. 2008).

Pathophysiology of the diabetes

Diabetes mellitus is broadly classified into several main categories: type 1 diabetes (T1DM), T2DM, gestational diabetes mellitus (GDM), and monogenic forms such as maturity-onset diabetes of the young (MODY) and neonatal diabetes. T1DM is characterized by autoimmune destruction of pancreatic beta cells leading to decreased or absent insulin production, typically manifesting during childhood or adolescence (Atkinson 2012). T2DM, on the other hand, arises from a combination of insulin resistance and impaired insulin secretion. It is more prevalent in adults and commonly associated with obesity, sedentary lifestyle, and genetic predisposition (American Diabetes Association 2020). This review focuses on T2DM, as circadian rhythm disruption is predominantly linked to insulin resistance and metabolic dysregulation (Bass and Lazar 2016).

Under normal physiological conditions, insulin secreted by pancreatic beta cells facilitates glucose uptake in muscle, liver, and adipose tissues. However, with insulin resistance, these target tissues respond inadequately to insulin, resulting in decreased glucose uptake in muscle and adipose tissue, increased hepatic gluconeogenesis, compensatory hyperinsulinemia, and eventual beta cell dysfunction (Kahn et al. 2014). These processes culminate in hyperglycemia and the clinical manifestations of diabetes.

Importantly, the pathogenesis of T2DM is multifactorial, involving complex interactions among various metabolic regulators. Adipokines secreted by adipose tissue, such as leptin and adiponectin, play a critical role in modulating insulin sensitivity and systemic inflammation. Myokines released from skeletal muscle influence glucose metabolism and insulin action, while hepatokines secreted by the liver regulate glucose homeostasis and lipid metabolism. Additionally, proinflammatory cytokines including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) contribute to chronic low-grade inflammation, exacerbating insulin resistance and beta cell dysfunction.

Diabetes is not solely related to insulin, but also involves other metabolic hormones such as glucagon, cortisol, leptin, adiponectin, and ghrelin. The secretion of these hormones follows circadian patterns: cortisol peaks in the morning to increase glucose production; leptin rises at night to promote satiety; ghrelin, the hunger hormone, increases during the night (Scheer et al. 2010). Dysregulation of these hormones can impact the insulin sensitivity (Buxton et al. 2012).

Systemic low-grade chronic inflammation plays a significant role in diabetes pathophysiology. Proinflammatory cytokines like IL-6 and TNF-α secreted from adipose tissue disrupt insulin signaling pathways and exacerbate resistance (Hotamisligil 2006). Additionally, oxidative stress associated with hyperglycemia adversely affects beta cell function, promoting disease progression (Robertson 2004).

Poorly controlled diabetes over long-term results in microvascular complications (diabetic nephropathy, retinopathy, neuropathy) and macrovascular complications (coronary artery disease, cerebrovascular events, peripheral artery disease). The development of these complications can be influenced by circadian disruption, as intravascular pressure, endothelial function, and coagulation factors exhibit diurnal variability (Scheer et al. 2010).

Mechanisms linking the circadian disruption and diabetes

Circadian rhythm regulates various metabolic processes such as glucose tolerance, insulin secretion, and hepatic gluconeogenesis. However, circadian rhythmicity in non-diabetic and diabetic subjects might differ significantly. For instance, existing evidence shows that glucose tolerance and insulin sensitivity follow a circadian pattern in healthy individuals, but these patterns can be disrupted or phase-shifted in diabetic patients (la Fleur et al. 2001; Stenvers et al. 2019). In diabetic individuals, some

rhythms may shift in phase, while others may be completely lost or replaced by new pathological oscillations (Bass and Takahashi 2010; Marcheva et al. 2011). This implies that knowledge derived from the circadian rhythmicity in healthy subjects cannot be directly translated to diabetic populations, especially when considering chrono-therapeutic interventions. Therefore, the optimal timing of chronotherapy in diabetic patients should be based on a rhythm specific to the diabetic state, rather than extrapolated from non-diabetic models.

Circadian rhythm disruption increases the timing misalignment between central (SCN) and peripheral clocks, a condition termed "circadian desynchronization". Shift work (Smolensky and Lamberg 2013), nocturnal eating habits, and irregular sleep-wake cycles trigger this phenomenon (Karatsoreos 2014). As a consequence of the circadian desynchronization, pancreatic beta cells secrete insulin out of phase with feeding cycles, often resulting in reduced insulin secretion during the active/feeding phase (daytime in humans) and inappropriate secretion during the rest/fasting phase (nighttime). Hepatic gluconeogenesis, which normally decreases during the active phase in response to insulin, remains elevated or inappropriately high during the daytime when insulin action should suppress glucose production (Marcheva et al. 2010). Meanwhile, insulin sensitivity in muscle and adipose tissue, which typically peaks during the active phase to promote glucose uptake, is reduced during the daytime impairing glucose clearance. These mistimed rhythms collectively contribute to impaired glucose homeostasis (Rudic et al. 2004).

Furthermore, mutations or dysregulated expression of core clock genes severely impair metabolic homeostasis: BMAL1 deficiency leads to an impaired glucose tolerance and reduced insulin secretion, while CLOCK gene mutations are associated with obesity, hyperglycemia, and hypertriglyceridemia (Turek et al. 2005). Overexpression of PER2 stimulates hepatic gluconeogenesis (Zhang et al. 2010) and polymorphisms in CLOCK and CRY2 genes have been linked to increased diabetes risk in human studies (Bonnefond et al. 2012).

Melatonin, a hormone secreted primarily during the night, is a key regulator of circadian rhythm and also plays an important role in glucose metabolism. The presence of melatonin receptors (MT1 and MT2) in pancreatic islets suggests that melatonin directly influences insulin secretion (Ramkisoensing and Meijer 2015). Carbohydrate intake during late-night hours when melatonin levels are high can suppress insulin release and exacerbate postprandial glycemia (Peschke 2008). In addition, genetic polymorphisms in the MTNR1B gene, which encodes a melatonin receptor, have been associated with impaired glucose tolerance and increased T2DM susceptibility (Lyssenko et al. 2009).

Disruption of circadian rhythms also disturbs hormonal balance by altering cortisol secretion patterns (abnormally high or low morning levels) reducing leptin and increasing ghrelin levels resulting in impaired appetite control, overeating, weight gain, and ultimately insulin resistance (Taheri et al. 2004). Moreover, circadian misalignment negatively affects immune regulation by promoting chronic low-grade inflammation and oxidative stress. Elevated levels of proinflammatory cytokines, such as IL-6 and TNF-α, have been observed in night shift workers (Suarez-Barrientos et al. 2011; Reinhardt et al. 2019), further contributing to the pathogenesis of insulin resistance and T2DM.

Findings from the observational and experimental studies

In recent years, numerous epidemiological and observational studies have investigated the relationship between circadian rhythm disruption and diabetes. Notably, the prevalence of diabetes has been shown to be significantly increased among shift workers (Pan et al. 2011). According to data from the Nurses' Health Study (Harvard 2003–2015), the risk of T2DM was elevated by 40% in individuals engaged in shift work for more than ten years (Pan et al. 2011).

The UK Biobank study has demonstrated that individuals with disrupted sleep patterns had significantly higher HbA1c levels and impaired glucose tolerance (Kita et al. 2012). Data from NHANES have revealed that individuals consuming late-night meals exhibited higher fasting glucose levels and increased incidence of diabetes (Nettleton et al. 2008; Scheer et al. 2009; McHill et al. 2017).

Experimental studies have provided more direct evidence of the effects of circadian disruption on glucose metabolism. For instance, a five-day delay in sleep timing by 5 h resulted in a 20% reduction in insulin sensitivity and an increase in fasting glucose levels (Leproult et al. 2014). Elevated melatonin levels at night have been shown to increase postprandial glucose following carbohydrate ingestion (McMullan et al. 2013). Eating misaligned with the circadian phase (e.g., consuming breakfast at 2:00 a.m.) disrupts insulin response and decreases glucose tolerance (Hatori et al. 2012).

Animal studies in mice and rats have elucidated the metabolic consequences of disrupted circadian genes. CLOCK mutant mice developed obesity, hyperinsulinemia, hyperglycemia, and hepatic steatosis under normal feeding conditions (Turek et al. 2005). BMAL1-deficient mice exhibited severely impaired insulin secretion resembling a T2DM phenotype (Marcheva et al. 2010). Shift work models in rodents demonstrated hepatic steatosis and impaired glucose tolerance (Paschos et al. 2012).

Variants of the MTNR1B gene (melatonin receptor gene) have been strongly associated with elevated fasting glucose and increased T2DM risk (Lyssenko et al. 2009). Certain polymorphisms in the CRY2 gene have been linked to impairments in glucose metabolism (Bonnefond et al. 2012). PER3 gene variants have been reported to influence sleep duration and glucose levels (Patke et al. 2020).

In vitro studies have shown that insulin secretion follows a circadian pattern, whereas disruption of this rhythm by environmental factors induces beta cell stress and increased apoptosis (Lee et al. 2013). Disruption of clock gene expression in peripheral tissues negatively affects the regulation of glucose transporters (such as GLUT4), thereby reducing glucose uptake (Barnea et al. 2009).

Circadian rhythm-based therapeutic and preventive approaches

Therapeutic strategies grounded in the circadian biology aim to synchronize drug administration timing, nutrition, and activity patterns with biological rhythms, a concept known as "chronotherapy" (Smolensky et al. 2016). Timing insulin and oral antidiabetic agents according to circadian rhythms can enhance treatment efficacy; for example, evening administration of metformin may more effectively suppress nocturnal gluconeogenesis (Cederroth et al. 2019). Administration of GLP-1 analogues in the morning may lead to an improved appetite suppression and glycemic control (Vilsboll et al. 2012).

Melatonin not only regulates sleep, but also exerts beneficial effects on glucose metabolism. Melatonin supplementation in night shift workers has been reported to improve glucose metabolism and reduce HbA1c levels (Garaulet and Gomez-Abellan 2014). Melatonin receptor agonists (e.g., ramelteon) resynchronize circadian rhythms and enhance sleep quality in diabetic patients (Tsunoda et al. 2016). However, melatonin supplementation may increase hyperglycemia risk in individuals carrying MTNR1B polymorphisms highlighting the importance of personalized therapy (Lyssenko et al. 2009).

Time-restricted feeding (TRF), which limits caloric intake to a defined daily window (e.g., 8–10 h), particularly when initiated early in the day and concluded with an early dinner, aligns with circadian rhythms and improves insulin sensitivity (Gill and Panda 2015). TRF has been associated with reductions in fasting glucose, HbA1c, insulin levels, weight loss, and inflammatory markers (Sutton et al. 2018).

To improve sleep quality and synchronize biological rhythms, the following measures are recommended: maintaining consistent sleep schedules every day minimizing exposure to screen light at night by using blue light filters (Chang et al. 2015) and employing morning light therapy to advance the biological clock, especially beneficial for shift workers (Burgess et al. 2003).

The metabolic effects of physical activity vary by the day time. Morning exercise has been shown to more effectively reduce blood glucose levels (Karstoft et al. 2017). There are also other findings indicating that afternoon exercise is more effective in T2DM (Savikj et al. 2019; Keller et al. 2025). Evening exercise may be beneficial for glycogen depletion, but intense late-night workouts can disrupt sleep patterns (Stutz et al. 2019).

Considering individual differences such as genetic clock gene polymorphisms, chronotype (morningness/eveningness), lifestyle, and work schedules, personalized circadian-based treatment protocols are being developed to enhance the diabetes management efficacy and patient adherence (Patke et al. 2020).

The future perspectives and research directions

The clinical application of circadian biology, termed "chronomedicine," is anticipated to play a central role in the prevention and treatment of metabolic diseases including diabetes (Smolensky et al. 2016). Adjusting pharmacokinetics and pharmacodynamics according to diurnal variations may improve the therapeutic outcomes (Hermida et al. 2013). Personalized treatments based on the circadian genetic profiling could be developed via genetic screening (Rudic et al. 2004).

Emerging innovations include screening tests targeting clock gene polymorphisms such as MTNR1B, CLOCK, BMAL1, PER, and CRY, which could predict diabetes risk and guide lifestyle interventions tailored to individual circadian profiles (Bonnefond et al. 2012).

AI-driven mobile applications and wearable devices (e.g., smartwatches, glucose monitors) can

monitor the sleep-wake cycles, physical activity, meal timing, and glucose levels, thereby encouraging behaviors aligned with circadian rhythms. These technologies have shown efficacy in diabetes control (Rodriguez-Leon et al. 2021).

The gut microbiome displays circadian oscillations in composition and function, which influence the glucose metabolism and the insulin sensitivity. Recent studies reveal that gut microbiota functions in synchrony with circadian rhythms (Thaiss et al. 2016). Disruption of microbial rhythms contributes to dysbiosis, inflammation, and increased risk of T2DM. Future interventions may include probiotic or prebiotic supplementation to support circadian-microbiota alignment (Leone et al. 2015).

Circadian gene expression is regulated not only by DNA sequence, but also epigenetically via histone modifications and DNA methylation, which modulate CLOCK/ARNTL complex activity (Azzi et al. 2014). Pharmacological targeting of these epigenetic mechanisms may enable precise regulation of clock genes in the future.

Current literature has limitations: most studies are short-term, long-term outcomes are underexplored, and factors such as sex differences, aging, and genetic diversity are rarely considered. Moreover, controlled randomized trials in shift work populations remain insufficient (Suwazono et al. 2009; Pan et al. 2011). Addressing these gaps will clarify the efficacy of circadian-based approaches in diabetes treatment.

Conclusions and recommendations

Disruption of the circadian rhythms plays a critical and decisive role in the pathophysiology of diabetes. Both fundamental research and clinical findings demonstrate that biological clocks interact closely with insulin sensitivity, pancreatic function, hormone secretion, and metabolic processes. Lifestyle factors such as shift work, irregular sleep habits, and late-night eating significantly contribute to circadian rhythm disruption by increasing the diabetes risk.

Accordingly, adopting lifestyle modifications aligned with circadian biology is paramount in diabetes prevention and treatment. Regular sleep schedules, time-restricted feeding protocols, and appropriately timed exercise support metabolic homeostasis and may prevent disease progression. Chronotherapy-adjusting medication timing according to the circadian rhythms can enhance the treatment efficacy. Potential benefits of circadian rhythm regulators such as melatonin and its receptor agonists should be considered within personalized treatment frameworks.

In the future, integrating circadian rhythm genetic profiling into clinical practice will facilitate development of individualized, more effective, and targeted therapeutic protocols. Increasing long-term large-scale clinical trials will further elucidate the circadian rhythm-diabetes relationship and optimize the treatment strategies.

Summary. A comprehensive understanding of circadian rhythm impacts on the diabetes onset and management opens new horizons in disease prevention and therapy. Incorporating biological timing into the clinical practice will not only improve therapeutic outcomes, but also significantly enhance the patients' life quality.

Conflicts of interest: *The authors declare no conflicts of interest.*

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