Circadian rhythm disorder induced type 2 diabetes mellitus: pathogenesis and therapeutics

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Abstract. Incidence rate of Type 2 diabetes mellitus (T2DM) is increasing rapidly nowadays. T2DM is related to poor sleep hygiene and shift work, and both circadian rhythm and chronotype may have a significant impact on the risk of T2DM. Many recent studies have shown that the morbidity and treatment of T2DM are significantly related to the pattern and the circadian rhythm (CR). However, there is still a lack of comprehensive knowledge of association between it and T2DM, and there are a lot of gaps in the application and efficacy evaluation of circadian rhythm therapy for T2DM. This review improves the understanding of the pathogenesis of T2DM and further clarifies the influence and significance of CR on glucose metabolism, provides prevention and treatment options for T2DM. And promotes the application and progress of circadian rhythm therapy in the treatment of T2DM based on the effect of CR to T2DM.

Keywords: Circadian rhythm, diabetes, glucose metabolism, circadian rhythm therapy, therapy.

1. Introduction

Circadian rhythms are internal depictions of the solar day which enable adaptations to predictable temporal changes in the environment. The rhythm is regulated by molecular clockworks in the brain, that undergo the light/dark cycle every single day and reset to approximately 24h. The peripheral clocks throughout the body get temporal information from the master clock in the hypothalamus via neuronal, hormonal/humoral, and temperature pathways. Thus, these internal timekeepers regulate and coordinate the optimal timing of physiological processes. Circadian rhythms, for example, regulate the sleep-wake cycle, secretion of hormones, and metabolism [1].

However, the extensive application of artificial light at night during the past century has muddled the distinction between day and night. Shift work, high-pressure work patterns, increased pressure, inappropriate sleep environment, and other adverse effects have disrupted circadian rhythm in modern people. An inverted circadian schedule can disrupt the body's circadian rhythm, causing disruptions in sleep-wake cycles and eating patterns, which can have a host of serious health consequences. Extensive research confirms that long-term circadian rhythm disruption (CRD) contributes to many chronic diseases and even plays an important role in diabetes.

90-95% of diabetes is Type 2 diabetes mellitus (T2DM). Initially high insulin levels and insulin resistance are the pathophysiological features of T2DM. The capability of the β cells to secrete insulin progressively declines. The complexity of T2DM is ultimately an outcome of the mixed factors of beta cell malfunction and insulin resistance. T2DM has a variety of causes. Although the exact etiology is not known, autoimmune beta cell destruction did not occur, and the patient had no other known diabetic etiology. Most but not all people with T2DM are overweight or obese, being overweight or obese, especially with excess belly fat, can lead to some degree of insulin resistance [2].

There are many T2DM patients in the world, and diabetes is also a major health problem in the world. In addition, as fast-paced, stressful, irregular modern lifestyles become more common, type 2 diabetes rates are also increasing. Recent years, there has been increasing both laboratory and clinical evidence that circadian rhythms disruptions (CRD) and sleep problems increase the risk of T2DM. Poor sleep hygiene, such as insomnia, are linked to T2DM. Poor quality of sleeping was linked to high risk of T2DM and obesity, and has also been linked to impaired quality of life [3]. Both sleep duration and chronotype may have a significant impact on T2DM risk; one has later chronotype has

a higher risk of T2DM than the earlier. This effect is largely driven by a range of unhealthy behaviors [4].

At present, the mechanism of circadian rhythm disruption promoting the pathogenesis of T2DM is not perfect. Non-pharmacological treatments that can improve sleep hygiene in people with T2DM include structured sleep education program, behavioral therapy, exercise [5]. But the application of circadian rhythm therapy in the treatment of T2DM is few. There are therapeutic gaps, and the efficacy of circadian rhythm therapy also needs to be evaluated. This review discusses the relationship between CR disruption and DM based on recent literatures. In addition, this review summarizes the current proven circadian rhythm therapy drugs for T2DM by tabulation and graphing using meta-analysis and comparation.

2. The relationship between T2DM with CR

2.1. Circadian Rhythm Disruption (CRD) Increase the Risk of T2DM

T2DM can cause a variety of metabolic and homeostasis disorders, especially sugar metabolism disruption which adversely affects the integrity and supply of blood vessels and may affect organ functions. Approximately 537 million individuals worldwide are diagnosed with diabetes, the majority of whom have T2DM; by 2045, it is anticipated that the figure will increase to 783 million; globally, the percentage of those missing an official diagnosis of diabetes is around 45% [6]. In addition, a large number of individuals have diabetic states like impaired fasting glucose and mild glucose intolerance. Recent researchers have found that circadian rhythms disorder can increase the risk of a variety of metabolic diseases, particularly T2DM.

A sizable section of the world's population is more likely to have disrupted sleep due to environmental factors, and a small number of people are genetically sensitive to sleep disorders and circadian dysrhythmia. A myriad of metabolic consequences is related with CR and sleep disruptions, especially T2DM [7]. CRD leads to many sleep problems, such as insomnia, fragmented sleep, chronotype delay (going to bed later and waking up later), reduced sleep duration, etc. These sleep problems can also directly worsen CRD. The physiological drive to sleep in humans may be suppressed by purposeful sleep deprivation or can be disrupted by the environment or CRD. And short sleep duration leads to a higher risk of T2DM. People who have problems of short duration of sleeping were sensitive to T2DM (RR 1.63 [1.37; 1.94], $p < 0.0001$) compared to people with normal sleep duration [8].

Sleep duration of 4.8 hours on average was found to be short when working nights. In research involving 2860 male workers, among who working in the night had high risk of T2DM than daytime workers [9]. Selecting two T2DM cohorts, the result supports that insomnia have the adverse effect on T2DM [3]. In another study, after two nights of fragmented sleep, the subjects' insulin sensitivity decreased [10]. It has been shown that decreased sleep length and quality increase the possibility of T2DM. High intensity of work, life pressure and poor lifestyle may lead to CRD, and CRD-induced insomnia, sleep fragmentation, short sleep duration and late sleep and late rise may increase the risk of T2DM.

After circadian dysregulation, the decline in insulin sensitivity gets heavier than after sleep deprivation alone, but islet beta cells responded similarly and showed decreased function in both conditions [11]. The effect of CRD to T2DM is more remarkable than the effect of sleep disorders. Chronotypes is related to the phase of CR, controlling the day-to-day sleep/wake cycle. Early chronotypes tend to go to bed and wake up early, while late chronotypes prefer the opposite. By assessing weight, body composition, insulin sensitivity, and measuring fat and carbohydrate metabolism, after dividing the 51 participants into staying up group and early/normal group based on their sleep and wake times, a recent study suggests that those who stayed up late showed decreased insulin sensitivity and decreased ability to use fat for energy, which means the high risk of T2DM [12].

Late chronotypes are more sedentary and less physically active, means late chronotypes may be at higher risk for T2DM because of people with T2DM also prefer an unhealthy lifestyle characterized by being sedentary and insufficiently physically active [4]. CR genes knocked out (K.O.) mice are always diabetic and have lots of metabolic disorders. Cryptochrome (Cry) and BMAL are core loop components of molecular circadian clock, which directly control the CR in every cell in the body. Glucose intolerance, liver gluconeogenesis increases and cortisol level increase in Cry1/Cry2 double K.O. mice. And BMAL K.O. mice also get glucose insensitivity, but the causes may be the decrease of liver gluconeogenesis and the insulin level. In a word, the blood glucose levels in BMAL K.O. mice and cry1/cry2 K.O. mice are higher than normal mice. So, it shows that the absence of circadian clock may cause the diabetic phenotype, but BMAL can improve liver gluconeogenesis and insulin level. So, the facts in the circadian clock components genes K.O. mice show the misalignment of the clocks of pancreas and liver may cause diabetes.

The phenotypes of these experimental animals confirm the important role of CR in glucose metabolism and the role of CRD in T2DM from another perspective. Sleep/wake cycles can determine and influence fasting/feeding cycles, and the loss of synchrony between circadian and fasting/feeding cycles can also affect glucose metabolism regulation.

2.2. Circadian Rhythm Disruption Contribute to the Pathogenesis of T2DM

Recent research has shown that changes in circadian rhythm are related to metabolic dysfunction of T2DM. Circadian rhythm genes bmal1, clock, and per3 in skeleton muscle have altered transcriptional cycles in T2DM patients, which are associated with reduced volume of CR genes and disrupted diurnal oxygen consumption. There is a link between mitochondrial function and circadian rhythm, and it is disrupted in T2DM patients [13]. Although most T2DM patients also show CRD features, the idea that T2DM causes CRD remains controversial, with studies showing that T2DM has no significant causal effect on insomnia and other indicators of CRD [3]. The improvement of CRD is also beneficial for T2DM treatment. Improvements in CRD in experimental animals can also reduce blood glucose and insulin resistance and improve T2DM phenotypes. Some molecules that regulate CR like Lithium, Nobiletin, melatonin and Metformin, can also improve diabetes while stabilizing CR in patients.

3. The Mechanism of CRD Effect on T2DM

3.1. The Mechanism of CR

The suprachiasmatic nucleus (SCN) houses the primary circadian master pacemaker and clock. All the body's major organs and tissues, including the liver, the lungs, and the muscles, have cell autonomous CR. Their timing coordination and rhythm-related actions require SCN. Due to a greater degree of intercellular coupling among neurons, the SCN is more robust and resilient to internal phase disturbances. Therefore, signals of SCN clock or body systemic signals, such as temperature and metabolic state, have an impact on peripheral cell clocks. Numerous cellular activities are impacted by the coordinated modulation of clock-controlled genes (CCGs) by circadian oscillators of the particular tissue where they reside.

3.2. How Normal CR Controls the Glucose Metabolism

The circadian system coordinates metabolism in a cycle about 24 hours each day. This rhythm organizes metabolism by temporarily isolating opposing metabolic processes and predicting repeated cycles of eating and fasting to increase the metabolic efficiency.

Most of the enzyme of glucose metabolism pathways, especially for the rate limiting step enzymes like PFK, glycogen synthase, etc., and glucose transporters like GLUT 2, GLUT 4, are circadian, whose genes are CCGs. Confirmation from multiple preclinical studies shows that Bmal, Clock D19, per 1/2, Rev-erbα and Cry 1 genes is necessary for the healthy metabolic rhythm. In addition, mice with mutations in any one of these genes may show diabetic phenotypes. In healthy individuals, the

degree of glucose tolerance and insulin sensitivity, both indicators of glucose intake and handling, are also time dependent. In the morning, tolerance of glucose and sensitivity of insulin are both at higher level, which means the peak volume and lasting time of blood glucose level change are lowest after breakfast and highest after dinner which controlling the meals are identical.

Oral glucose tolerance has a circadian rhythm. Fasting blood sugar is almost higher in the morning [14]. The most remarkable thing about this is that people having normal glucose tolerance had metabolic characteristics like those of pre-diabetics in the evening. The CR of beta cell reactivity, production of insulin, and insulin clearance can be linked in part to these periodic shifts in glucose tolerance.

Insulin plays an integral role in blood sugar regulation. Metabolic process regulation and anabolism promotion are the main physiological functions of insulin. In tissue cells, insulin promotes glucose uptake and utilization. It also stimulates glycogen production, inhibits gluconeogenesis, and lowers blood sugar levels. The receptor tyrosine kinase (RTK) pathway is the mechanism that triggers insulin to begin acting biologically at the cellular level by attaching to specific receptors on the target cell membrane.

The normal insulin secretion pattern is split into two parts: basal insulin, which is released to help maintain the normal fasting blood sugar level, and prandial insulin, which is released to slow the rise of postprandial blood sugar and maintain the normal postprandial blood sugar level. The primary role of the early phase of insulin secretion during meals is to restrict the endogenous glucose in the liver, which regulates the magnitude and length of the postprandial glucose spike.

Insulin secretion responses vary throughout the day, with beta cell reactivity higher in the morning [15]. However, it appears that the peak of the physical response to meals in terms of insulin secretion and production rates falls later in the day. The highest insulin production rates take place in the morning and the afternoon, while the lowest levels occur at night when people are sleeping. Additionally, insulin clearance varies throughout the day, and insulin is metabolized more rapidly by hepatocytes at night [15].

CR molecular components BMAL and CLOCK form heterodimer. Then, the BMAL-CLCOK dimer activator binds to cell-specific enhancer in the upstream of the insulin gene and promotes the recruit of transcriptional machinery to accelerate and increase the transcription of insulin gene in beta cell nucleus. It is worth mentioning that nucleosome H3K27Ac and H3K4Me2 modifications are found upstream of insulin gene in pancreatic beta cells.

In the evening, as insulin sensitivity declines by 34%, it appears that the rhythm of peripheral insulin sensitivity also plays a role in the diurnal fluctuation of blood sugar management. Circadian factors and intracellular pathways that mediate glucose absorption and utilization may be major reason for change of insulin sensitivity in peripheral cells [16]. And the circadian rhythm of free fatty acids reflecting glucose homeostasis. Cortisol, controlled by master clock, may also be responsible for changes in the circadian rhythm of plasma glucose and insulin, and cortisol can inhibit the later production acutely and induce insulin resistance for a longer period.

Glucose and insulin have endogenous circadian rhythms, with the highest levels around habitual arousal. To counter the drop in blood sugar levels caused by sleeping on an empty stomach and provide energy for the sleeping body. Although the increase in glucose levels at night correlates in number and timing with the level of cortisol, insulin secretion rates at night parallels glucose only in healthy subjects, not diabetic adults [17]. Glucagon promotes gluconeogenesis and glycogenolysis to increase blood glucose. CRY, one of the major components of CR core loop, has a higher level in the daytime and inhibits the signal pathway of glucagon to repress gluconeogenesis genes, like G-6-Pase, expression. The inhibition of gluconeogenesis by CRY is relieved because of CRY level gets decreased by the negative feedback mechanism of CR at night and sleep time. Secretion of insulin, leptin, cortisol, and glucagon etc., insulin sensitivity, gluconeogenesis, and key intermediary pathways of glucose metabolism, are rhythmic and under direct control of the circadian clock.

3.3. How CRD Affect T2DM

The increased risk of T2DM caused by CRD is mainly caused by the misalignment of the secretion rhythms of glucose metabolism-related hormones and the rhythms of peripheral cells sensitivity to these hormones, the misalignment of work, eating, sleep and other behaviors with the metabolic rhythm, and the metabolic disruptions caused by the changes of CR amplitude, phase, period, and other factors. The main mechanism of CRD to T2DM is shown in Fig. 1

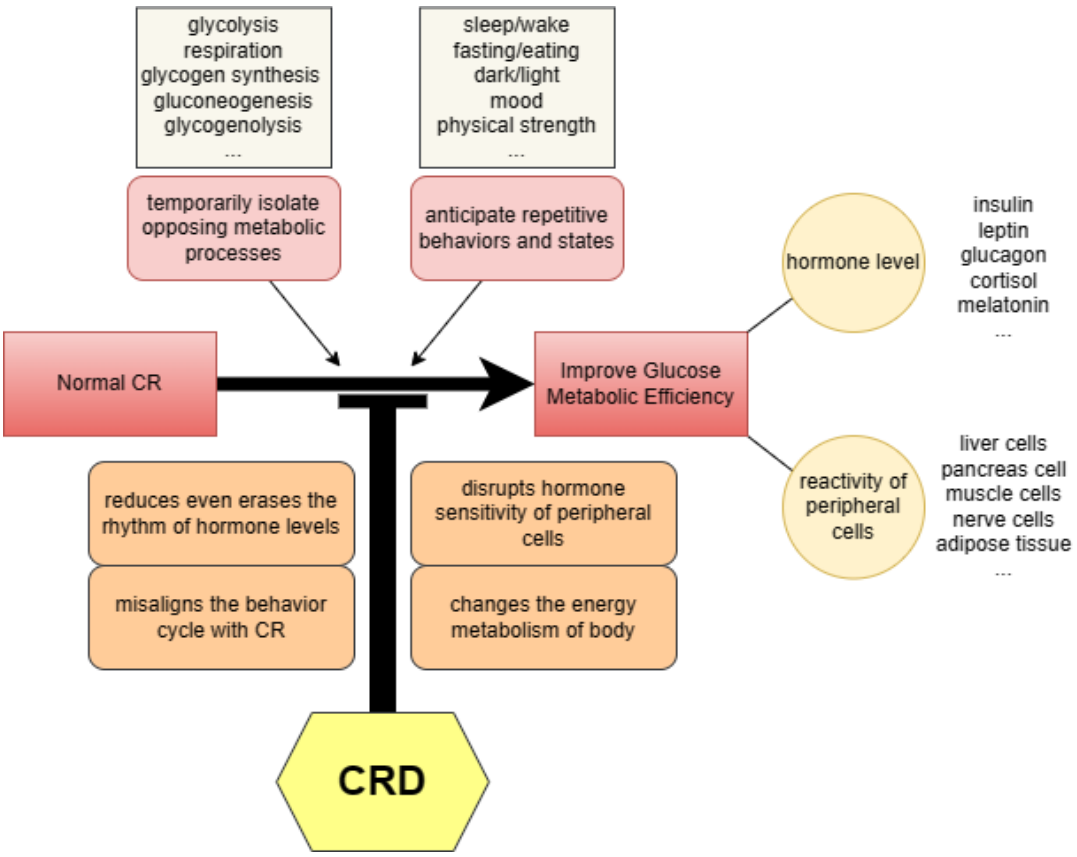


Figure 1. Mechanism of regulation of glucose metabolism by CR and the disruption of glucose metabolism which leads to T2DM by CRD.

3.3.1. Different subtypes of T2DM and the main features of it

The subtypes of T2DM are shown in Table 1. Major clusters in European populations have been recognized as MOD and MARD, and major clusters in Asian populations have been found as SIDD [18]. Although there are different subtypes of T2DM, insulin resistance is a major reason. The glucose amplitude was about twice as high in people with diabetes as it was in control subjects with a BMI match [17].

Table 1. Subtypes of T2DM

T2DM subtypes	Severe insulin-deficient diabetes (SIDD)	Severe insulin-resistant diabetes (SIRD)	Mild obesity-related diabetes (MOD)	Mild age-related diabetes (MARD)
Pathological features	1. GAD antibody is negative but has other features of type I diabetes. 2. Hypoinsulin. 3. High HbA1c (hemoglobin A1c). 4. Early insulin requirement. 5. High rates of retinopathy and kidney disease	1. Obesity. 2. Insulin resistance 3. Later onset. 4. Increased risk of complications of organs.	1. Obesity. 2. Mild insulin resistance. 3. Earlier onset.	1. Later onset. 2. Lower risk of complications

3.3.2. Hormone effects

After CRD, levels of many metabolic hormones are changed. Compared with healthy individuals, the whole-day cortisol, leptin, and epinephrine level are significantly decreased, the blood glucose and blood insulin level are increased, especially after meal, which means insulin resistance -- even though insulin is produced in large quantities, blood glucose level remains high and the rate of glucose absorption and utilization remains extremely low, and the peaks of cortisol and epinephrine get delayed and misaligned in CRD individuals. In addition, even healthy men may develop T2DM symptoms such as insulin resistance, leptin decrease and free fatty acid increase after a week of 5-h sleep restriction, not mention CRD individuals.

In adults with diabetes, the temporal rhythm of insulin secretion rates is not pronounced. And CRD may cause insufficient bata cell compensation and misalign the CR cycle and fasting/eating cycle, which can increase the degree of insulin insensitivity and decrease glucose tolerance [19]. A recent study suggests that participants who went to bed early and weak up early were more sensitive to insulin than those who stayed up late. However, people who stay up late are insulin resistant, and requiring more insulin to lower blood sugar levels [12].

Cortisol is a glucocorticoid secreted by the fasciculata of the adrenal cortex, and is normally secreted in a circadian rhythm. Its main effect is to increase gluconeogenesis and is also an important factor affecting protein and fat metabolism. And cortisol can inhibit insulin secretion acutely and induce insulin resistance for a longer period. In mice models, Cry1-/-/Cry2-/- mice have an increased cortisol and diabetic phenotypes which is caused by absent of CR genes. That means CRD may lead to the misalignment of cortisol level with sleep/weak cycle, and the wrong cortisol level may cause mice get diabetic. In human studies, the rhythms of glucose or insulin may be attributed in part to the change of cortisol rhythms in people with T2DM compared with healthy adults [17].

Leptin can regulate hunger and energy expenditure. After meals, leptin water rises rapidly to make people feel full. People with CRD have slower increases and lower levels of leptin after meals and throughout the day, leading to binge eating because it is difficult to achieve satiety and lower energy expenditure and store fat. Increased fat tissue can also lead to problems such as insulin insensitivity. These abnormalities in leptin levels, including secretion rate, peak, whole-day level and phase, lead to a substantial increase in the risk of T2DM in CRD populations.

3.3.3. Liver glucose production

The nuclear receptor REV-ERB in neurons in SCN controls insulin-mediated circadian rhythms that inhibit liver to product glucose in mice, however it would not affect eating or exercise behavior during the regular light-dark cycles. In T2DM, elevated blood sugar levels after waking are the dawn phenomenon. Dawn phenomenon refers to the fact that the blood sugar control of diabetic patients is satisfactory and stable during most of the night or day, but high blood sugar occurs at dawn, especially after breakfast. Compared with T2DM patients without prolonged dawn phenomenon, T2DM patients with prolonged dawn phenomenon showed different temporal patterns of REV-ERB gene expression, which means CRD may lead to prolonged dawn phenomenon and the misalign of liver insulin sensitivity and insulin level rhythm [20]. CRD may lead to the disturbance of the REV-ERB expression rhythm, thus disrupting the liver's insulin sensitivity, and thus disrupting the liver's glycogenesis processes, such as glycogenolysis and gluconeogenesis.

BMAL can improve liver gluconeogenesis and insulin level. But BMAL K.O. mice also get glucose insensitivity, but the causes may be the decrease of liver gluconeogenesis and the insulin level. So, the facts in the circadian clock components genes K.O. mice show the misalignment of the clocks of pancreas and liver may cause diabetes.

3.3.4. Metabolic level

Recent research suggested that people who went to bed early and rose early burned more fat for energy during rest and exercise, but for people who stay up late, their bodies prefer sugar as a source of energy rather than fat [12]. So, the preference for different energy-supplying nutrients also changes with different chronotypes and CRs. CRD causes the body to metabolize fat more slowly and

consume more carbohydrates, leading to a prolonged rise in blood sugar levels. The buildup and accumulation of adipose tissue is known to increase insulin resistance levels. Those who stay up late or CRD have greater fluctuations in blood sugar levels while their fat consumption decreases, so they are at higher risk of T2DM than those who sleep normally.

4. Circadian Rhythm Therapy on Prevention and Treatment of T2DM

In recent years, more and more studies have proved that improving circadian rhythm is helpful to the treatment of diabetes. Moreover, according to the above description of the relationship between CRD and diabetes, it can also be inferred that adjusting circadian rhythm to synchronize metabolic rhythm and behavioral rhythm can improve diabetes.

4.1. Pharmacological Circadian Rhythm Therapy of T2DM

4.1.1. Metformin

Metformin can be used as an AMPK agonist to interfere with the level of clock or metabolic genes [21]. it leads to a higher level of clock-regulating genes and activation of AMPK which can increase expression of core loop clock component Bmal-1 protein. It adjusts the wrong circadian rhythm and Kir4.1 channel in db/db mice, a classical and appropriate T2DM model, and prevents diabetic retinopathy [22].

4.1.2. Melatonin

The SCN exerts strict control over the synthesis of the hormone melatonin in pineal gland. Melatonin level rises at night and falls throughout the day. It regulates the insulin resistance and improves glucose balance. And numerous researches demonstrated that melatonin helps T2DM patients maintain healthy blood sugar levels and sleep quality [23].

4.1.3. Lithium

A review suggests that Lithium has insulin-like effects to regulate metabolism of cells. Lithium can stabilize CR at the same time of improving the mental problems, or Lithium exerts its psycho-improving effect by improving CR. Lithium is shown a potent inhibitor of GSK3b, and disturb the phosphorylation of REV-ERBα, which can stabilize REV-ERBα [24]. Clinically relevant concentration and above of Lithium can inhibit GSK3B, then protecting REV-ERBα from phosphorylation by GSK3B, and remove the inhibition of REV-ERBα on bmal1 expression, thus, achieving the role of regulating CR. The control of stability of REV-ERBα protein is the key to the regulation of CR and is also the biological target of Lithium. Regarding the effect of lithium on CR and T2DM, Lithium can delay CR phase by inhibiting histone deacetylation and regulating expression of CR genes (bmal1, etc.) and glucose metabolism genes (insulin gene, Pfkfb-1-3, etc.), while normal CR may have a positive effect on improving T2DM. Valproic Acid (VPA), a drug that increases the amplitude of CR but does not change the CR cycle, can make patients with dipolar disorder more prone to T2DM [25].

4.1.4. Others

Some small compounds that target clock elements with metabolic regulatory functions also have beneficial metabolic effects. In primary mouse hepatocytes, the leading REV-ERB agonist, GSK4112, suppresses gluconeogenesis. RORs were also reported to possibly control metabolic processes in a similar way. In obese diabetic mice, SR1555 can decreased food intake and body weight and increased insulin sensitivity. ROR-selective partial inverse agonist SR3335 reduced blood sugar levels and inhibited gluconeogenesis. KL001, a CRY stabilizer and another substance with core clock function, inhibited glucagon-induced gluconeogenesis. Moreover, it has been demonstrated that several CRY stabilizers improve brown adipose tissue differentiation and raise energy expenditure [26].

4.2. Non-pharmacological Therapy Improve T2DM Due to CR Effects

4.2.1. Light therapy

To synchronize the light/dark cycle with circadian cycle, light therapy is helpful. Bright light can stimulate SCN and contribute to circadian synchrony when we get up, which is proved to be useful for regulating the CR and improve the life pattern and quality of people with CRD. In the morning, using high-intensity light can increase the function of CR and the metabolic rhythm by increase their amplitude and accuracy, that decrease the weight, increase the glucose tolerance during treatment of sand rats [27]. Bright light therapy is commonly applicated in the treatments of mental disorders, like depression, and many sleep disorders, like insomnia, is proved to be promising for therapy of T2DM in those patients with depression, and significantly improve the condition of insulin resistance. So, light therapy may observably regulate CR, and make a further effect of improve glucose metabolism that relives and assist in the treatment of T2DM.

4.2.2. Eating behavior improvement

Eating is an important factor affecting metabolic rhythm. The metabolic rhythm of the digestive system, especially the liver and most skeletal muscle cells, will be changed by nutrient intake, blood sugar rise and insulin secretion. The main effect of eating behavior improvement is making the patients who have chronically irregular diet and high energy intake. There are three proven regimens to T2DM treatment, which called chrono-nutrition patterns: calorie restriction, reducing the average energy intake each day; intermittent fasting, by reducing eating time to 6-8 hours per day or following "5:2 intermittent fasting" which requires 2 days for eating only one medium meal and 5 days of normal diet a week; time-restricted feeding, restricting the patient eating food in a certain period every day [23]. Intermittent fasting and time-restricted feeding can ameliorate metabolic disorders by improving the state of the gut flora and thereby restoring a healthier circadian clock. A study demonstrates the protective effect of TRF on T2DM by improving circadian and metabolic rhythms, showing that fed a high-fat diet only in certain 8 hours every day, get a more robust CR and metabolic rhythm and decreasing degree of glucose intolerance, leptin resistance, liver pathology, adiposity, inflammation, and motor coordination, than the mice given ad libitum high fat diet with equivalent calories [28].

4.2.3. Sleep improvement

Sleep improvement is one of the most efficient and effective ways to synchronize the CR with the natural light/dark cycle. Sleep problems can be effectively treated with cognitive behavioral therapy, which helps patients with T2DM have better sleep and a higher quality of life while reducing their glycemic levels [29]. Sleep hygiene and cognitive behavioral therapy interventions may even mediate cardiometabolic risk more significantly than exercise [30].

4.2.4. Exercise

It may be helpful to personalize exercise according to the time of day. A robust CR may be beneficial to prevent and treat T2DM. In addition, exercise activates AMPK, regulates CRY levels to improve circadian rhythms, and simultaneously improves metabolic pathways and insulin sensitivity to improve body function.

4.2.5. Others

Other suggestions for optimizing circadian rhythms in shift work include avoiding extremely lengthy work hours, extending the time between shifts, reducing shifts, and minimizing the number of consecutive night shifts [31]. Certain dietary and lifestyle changes may also help to prevent T2DM and enhance CR.

5. Conclusion

A healthy circadian rhythm regulates and promotes glucose metabolism. On the contrary, the disruption of circadian rhythm may cause many adverse effects on metabolism, such as disrupting or weakening the glucose metabolism rhythm, leading to misalignment of behavior and metabolic rhythm, interfering with the normal expression of clock-controlled genes, reducing insulin sensitivity, causing massive changes in many hormone levels, increasing adipose tissue, etc., thus raise the risk of T2DM and causing diabetes symptoms. The deeper mechanism and significance of circadian rhythm for treatment and prevention of diabetes remain to be explored and explained. This review lists several pharmacological and non-pharmacological circadian rhythm therapies for T2DM prevention and treatment that have been shown to have some effect. However, the correlation between the CR improvement effect of these therapies and the treatment effect of T2DM remains to be explored and verified. More molecular modulators of CR with potential for the treatment of T2DM need to be developed and applied. For further studies, clinical research on the efficacy of circadian rhythm therapy in T2DM is very significant, and its clinical application needs to continue to expand.

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