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Circadian Rhythm Disruption and Metabolic Syndrome: Exploring the Molecular and Clinical Links Between Biological Clocks and Cardiometabolic Health

Rajeev Agrawal[1], Manila Jain[2]

[1]Research Scholar, Malwanchal University, Indore (M.P)
[2]Professor, Malwanchal University, Indore (M.P)

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Corresponding author: Rajeev Agrawal
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Abstract:

Metabolic syndrome is a major global public health concern characterized by a cluster of interconnected metabolic abnormalities, including central obesity, hyperglycemia, hypertension, dyslipidemia, and insulin resistance. Recent scientific evidence suggests that disruptions in circadian rhythms the body's intrinsic biological clock system play a critical role in the development and progression of metabolic disorders. Circadian rhythms regulate numerous physiological processes, including glucose metabolism, lipid homeostasis, hormonal secretion, cardiovascular function, immune responses, and energy balance. Modern lifestyle factors such as sleep deprivation, shift work, artificial light exposure, irregular eating patterns, and reduced physical activity contribute to circadian misalignment, thereby increasing the risk of obesity, type 2 diabetes mellitus, cardiovascular disease, and other metabolic complications.

This paper reviews the molecular mechanisms linking circadian clock genes, metabolic regulation, and cardiometabolic health. It examines evidence from clinical and experimental studies demonstrating how disturbances in circadian rhythms affect adipose tissue function, glucose tolerance, lipid metabolism, hepatic activity, cardiovascular regulation, and inflammatory pathways. Furthermore, the study discusses the emerging concept of "Circadian Syndrome," which expands the traditional understanding of metabolic syndrome by incorporating circadian disruption as a fundamental etiological factor. The findings highlight the importance of maintaining circadian health through appropriate sleep patterns, lifestyle modifications, and chronobiological interventions to prevent and manage metabolic diseases in modern societies.

Keywords: Circadian Rhythm, Metabolic Syndrome, Circadian Syndrome, Obesity, Type 2 Diabetes Mellitus, Cardiovascular Disease, Sleep Deprivation, Clock Genes, Glucose Metabolism, Chronobiology

Introduction

Hyperlipidemia, central obesity (intra-abdominal), hyperglycemia, and hypertension are the metabolic disorders that make up metabolic syndrome (MS). Approximately 25–40% of people aged 25–64 have multiple sclerosis (MS), making it a significant public-health concern globally (San Antonio Heart Study). Additional hallmarks of multiple sclerosis include increased circulating triglyceride levels, decreased HDL-cholesterol levels, hypertension, and impaired fasting glycaemia. Inflammatory and/or thrombotic markers, like C-reactive protein (CRP), Tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and

plasminogen activator inhibitor type 1 (PAI-1), can either rise or fall in blood levels, which is another sign of multiple sclerosis.

Obesity and multiple sclerosis are on the rise across the globe, afflicting both developed and developing nations. The root causes of this pandemic are excessive food consumption and lack of physical exercise. The increasing prevalence of artificial light and nocturnal labour, as well as the general trend towards deliberate decrease of sleep, are being implicated in the aetiology of multiple sclerosis, according to clinical epidemiological studies. These common circadian behavioural and sleep disorders exhibit symptoms such as an increased hunger, poor glucose and lipid metabolism, and extensive changes in the hormonal signals associated with fullness. Recent research by Sheer et al. demonstrated that artificially misaligning human volunteers with their circadian cycles and behavioural patterns led to unfavourable cardiometabolic outcomes, simulating the effects of jet lag and shift work in a controlled clinical setting. Research in humans has provided experimental geneticists with the foundational molecular mechanism governing these 24-hour circadian rhythms of physiology. They demonstrated that the clock runs on a conserved transcription translation feedback loop that cycles every 24 hours. Interestingly, the circadian system in mice is impacted in both directions by obesity and a high-fat diet. This points to the interconnected nature of metabolism, circadian rhythms, sleep, and several molecular and behavioural pathways. So, changes in energy balance caused by obesity may trigger a "vicious cycle" of disruptions to the circadian rhythm, which in turn worsens the initial metabolic imbalance.

Adverse Effects of Alterations in Circadian Rhythms: Clinical Evidence

A correlation between Americans sleeping less and an increase in metabolic illnesses has been observed. A substantial amount of data indicates that obtaining less than seven hours of sleep per night raises the chance of developing type 2 diabetes and obesity, even after adjusting for age, BMI, and other potential confounding factors. Children that get less sleep are more likely to be overweight, for example. There may be a disturbance in the natural cycle of sleep/activity, feeding/fasting, energy storage/utilization due to the slow reduction in sleep duration and the regular expansion of nighttime activities.

Inadequate sleep, extra body fat, and the risk of diabetes may be due to a combination of factors, including decreased energy expenditure, increased hunger, and alterations in glucose metabolism. For instance, after a glucose challenge, healthy individuals who had four-hour sleep cycles for six nights in a row showed reduced insulin sensitivity. Another possible mechanism by which sleep deprivation induces hunger is by raising levels of the orexigenic hormone ghrelin (a peptide mostly released by the stomach) and decreasing levels of the hormone leptin (a hormone specific to adipose tissue that promotes fullness) in the bloodstream. Energy expenditure might be affected by both hormones.

Strangely, those who have been diagnosed with night eating syndrome seem to be more likely to be overweight. Metabolic problems are linked to diseases that affect the length and quality of sleep. Sleep apnea syndrome is a prevalent sleep disorder among metabolic disorders; some have hypothesised that it caused clock gene malfunction. Furthermore, research has shown that effective therapies for sleep apnea may enhance glucose metabolism and energy balance. Furthermore, narcoleptic individuals may be more likely to gain weight due to a disruption in the circadian oscillation of leptin. There is still a long way to go before we can unravel the

molecular aetiology of metabolic problems in sleep-deprived conditions.

Evidence for a Molecular Link Between Circadian and Metabolism Systems

A fresh window of opportunity has opened up to study the circadian and metabolic systems' interplay thanks to genetic models of circadian disturbance. Earlier studies discovered that the transcriptional activity of CLOCK/BMAL1 and NPAS2/BMAL1 are regulated by the nicotinamide adenine dinucleotide cofactors, NADP(H) and CLOCK/BMAL1, respectively. Because reduced versions of these cofactors increase DNA binding and oxidised forms decrease binding, the activity of this core clock component is related with the cell's metabolic condition. Two new investigations have established additional connections between the core molecular clock and the biological process of NAD production.

Genomic regulation of the circadian rhythmicity of the nicotinamide phosphoribosyl transferase (NAMPT) gene is regulated directly by CLOCK/BMAL1 in peripheral tissues like the liver and WAT. Because of this regularity, NAD levels in the liver change every day. Nampt and NAD production are downstream targets of CLOCK/BMAL1, as indicated by the lower amounts of Nampt RNA and NAD in the livers of ClockŔ19/Ŕ19 and Bmal1−/− mice, as well as higher levels of Nampt and NAD in the livers of mice lacking CRY1 and CRY2.

Recent research has identified SIRT1 as a new regulator of the circadian clock; SIRT1 is a deacetylase that is dependent on NAD and sensitive to nutrition; NAD also plays a function in cellular redox activities. I should remark that while NAMPT and NAD levels are at their highest, SIRT1 activity is at its peak as well. The recruitment of SIRT1 to clock-related genes follows its physical binding to CLOCK and BMAL1, two positive-limb components of the core clock apparatus. Manipulating SIRT1 genetically or pharmacologically throughout the NAD production route reveals that SIRT1 inhibits CLOCK and BMAL1. According to these findings, CLOCK/BMAL1 operates in a positive feedback loop controlling NAD synthesis and SIRT1 activity, while SIRT1 acts in a negative feedback loop controlling CLOCK/BMAL1 activity.

From Circadian Disruption to Metabolic Disease

A) **What have we learned from the experimental models?**

What role does circadian misalignment play in the metabolic comorbidities of diabetes, obesity, and cardiovascular disease? Multiple lines of evidence suggest that disruptions in circadian rhythm may significantly impact inflammation, fibrinolysis, fluid homeostasis, vascular responsiveness, and glucose regulation. The core clock and other metabolic processes, such as adipogenesis, inflammation, and thrombosis, are impacted by nuclear receptor superfamily members, which include those downstream of REVERBα and the RORs. These members represent a crucial link between the circadian and metabolic pathways. There is evidence that disruptions to the clock network cause metabolic problems, and experimental models have helped show how the clock network affects metabolic gene expression.

B) **Clock disruption in adipose tissue**

Not obesity itself, but improper distribution of fat throughout the body and excess adipose tissue are major risk factors for obesity-related diseases. Obesity in the center of the body, as opposed to the periphery, is linked to multiple sclerosis and cardiovascular disease 3. Nevertheless, the exact processes that cause this correlation, if any, are still up

for debate. New evidence from both animal and human studies suggests that adipogenesis and the location of subcutaneous vs visceral depots may be affected by the expression of the circadian clock transcription network inside adipose tissue.

The clock mechanism in adipose tissue regulates the expression of many enzymes that are involved in lipid metabolism. A number of lipogenesisrelated variables were upregulated in 3T3-L1 adipocytes when BMAL1 was expressed by adenovirus, but adipogenesis was hindered in adipose cell lines when BMAL1 was deleted. Adipocyte formation in vitro may be enhanced by heme, the natural ligand of REV-ERBα/β, as has been recognised for quite some time. Activating SIRT1, which regulates the clock network, may improve insulin sensitivity and reduce inflammatory response in adipocytes, albeit the precise effect is yet unclear.

C) Clock disruption and impaired glucose tolerance

In order to give the best therapeutic care for diabetes, it is crucial to understand how the circadian rhythm regulates glucose metabolism. This is because type 2 diabetes is marked by a disruption of the normal cyclic regularity of glucose tolerance. Glucose tolerance and insulin activity vary rhythmically throughout the day, according to strong evidence from human research. One example is the difference in oral glucose tolerance between morning and evening. This is believed to be due to a mix of factors, including decreased insulin synthesis and altered insulin sensitivity in the evening. The "dawn phenomenon," in which glucose levels rise soon before the active phase starts, has also been the subject of substantial research. Glucose metabolism varies throughout the day, and research in rats has shown that this fluctuation is maintained in large part by the SCN.

These findings provide more evidence that circadian clocks are involved in glucose metabolism regulation, although the precise molecular mechanisms by which this is achieved are yet unknown. Recent advances in human genome-wide association studies and experimental animal model systems have begun to shed light on the molecular links between rhythms and glucose metabolism. Research from multiple separate groups suggests that genetic differences in the melatonin receptor may contribute to impaired glucose homeostasis, and that melatonin therapy of pancreatic βcells inhibits glucose-induced insulin release. Glucose homeostasis requires a functioning clock network, as hypoinsulinemic hyperglycemia develops in Clock gene mutant mice and poor glucose tolerance is shown in Bmal1 nullizygous animals. An essential but as-yet-unsolved question in circadian mutant animal research is the molecular basis of reduced glucose tolerance.

D) Impact of circadian systems on cardiovascular function

Circadian variations in endogenous factors, such as activity of the autonomic nervous system, concentrations of blood catecholamines, coagulability, heart rate, regulation of blood pressure, and platelet aggregability, increase the likelihood that myocardial infarction will begin in the mornings. On the flip side, changes to the heart's circadian rhythm are associated with diabetes mellitus and pressure overload-induced hypertrophy. Hypothesised to have a role in myocardial contractile dysfunction are changes in circadian regulation of fuel management by the heart. Some insight into the circadian system's effects on vasculature has come from the discovery of genes that show diurnal control in mouse major arteries.

Blood pressure and thrombo-occlusive response are influenced by clock gene expression in the vasculature. Because

they control how much blood pressure rises first thing in the morning, clock genes may affect when clinical cardiovascular events occur. It is worth noting that mice lacking core clock genes have altered diurnal variation in epinephrine and norepinephrine levels. This could potentially provide light on why these animals do not exhibit circadian variation in their heart rates and blood pressures. Curiously, when contrasted with wild-type mice, the mutant animals exhibited a diminished reaction to immobilization stress.

Time of day-dependent responses to environmental stresses may be regulated by core clock expression in peripheral vasculature. It is possible that Per1 modulates aldosterone production as part of the clock system's effects on blood pressure. Anea et al. demonstrated in Bmal1-knockout and Clock mutant mice that endothelial dysfunction is marked by an impaired ability of the blood vessels to adapt and a vulnerability to thrombosis. Endothelial dysfunction in Bmal1-knockout mice has been associated with aberrant Akt and nitric oxide signalling. The vascular phenotype in Clock mutant mice appears to be caused by behavioural disruption rather than Clock mutation or Bmal1 deficiency alone, as light entrainment brought the deficits in endothelium-dependent arterial relaxation back to normal in these animals.

E) **Circadian rhythms and hepatic function**

When it comes to metabolic syndrome, the liver is also an important player. Enzymes that are vital to the liver's function and that affect glucose and lipid homeostasis are regulated by BMAL1 and CLOCK, two genes. New evidence suggests that the liver clock helps maintain steady blood sugar levels while at rest; mice deficient in Bmal1 in this gene showed hypoglycemia during fasting. Direct modulation of phosphoenolpyruvate carboxykinase (Pepck) may be one of the hepatic effects of BMAL1 and CLOCK. To go along with this, hepatocyte circadian gene expression is altered in animals with type 2 diabetes and high-fat diets. Components of the adiponectin signalling pathway also encountered a phase delay due to HFD. A significant risk factor for cardiovascular disease, steatosis, may be exacerbated if changes to the circadian regulation of adiponectin signalling diminish its preventive benefits.

Since the expression of the hepatic clock gene controls the generation of both bile acid and apolipoprotein, its disruption may impact various aspects of hepatic lipid homeostasis. Many proteins involved in lipid metabolism undergo diurnal variation in both rats and humans. Some examples of these proteins are apolipoprotein AIV, hepatic cytochrome P450, cholesterol 7 α-hydroxylase, and HMG CoA reductase. An intriguing fact is that Reverbα, an important regulator of bile acid metabolism, controls the neutral bile acid synthesis route. During the late light phase, the mouse liver displays high levels of Rev-erbα expression, which suppresses the hepatic expression of both E4BP4 and small heterodimer partner (SHP). Reducing levels of SHP and E4BP4 may assist control the cholesterol and bile acid balance during the day by reversing the inhibitory effects of bile acids on the transcription of the cholesterol 7α-hydroxylase (CYP7A1) gene. Every day, Rev-erbα modulates SREBP signalling through circadian rhythms to control the expression of genes associated with cholesterol and lipid balance.

F) **Clock dysfunction in the immune system**

Along with lipogenesis, lipid catabolism, and thrombosis, the circadian system may impact inflammatory pathways, which could contribute to the development of cardiovascular disease. Various types of cells in the immune system, including macrophages, include the circadian transcription factor Rev-erbα, which may

have a mechanistic impact on the inflammatory response. Interestingly, REV-ERBα enhances the TNF-κB induced NF-κB response, whilst RORα inhibits it. One possible aetiology of type 2 diabetes is abnormalities in the clock genes' rhythmic mRNA expression in peripheral leucocytes of diabetic patients.

The Circadian Clock and Metabolic Derangement

In humans, the circadian system regulates nearly every aspect of metabolism and health. Humans and nearly all other forms of life have a suprachiasmatic nucleus (SCN) in the hypothalamus that houses their master "Body Clock," which controls our circadian cycles. In order to keep the metabolism in check, this master clock controls many bodily activities and synchronises the peripheral clocks of almost every cell in the body. This includes the essential tissues like adipose, muscle, liver, and heart.

Environmental cues may impact circadian rhythms. To activate or deactivate genes that regulate the internal clock function of a person, light serves as the primary signal impacting the SCN master circadian clock. Other environmental elements that primarily impact peripheral clocks include dietary intake and temperature fluctuation.

It is important to put this scenario in context with the ongoing global epidemics of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), given the enormous changes that have occurred in Western and even traditional-living societies as a result of modernization and globalisation in the last several decades. Included in this broad category are dietary shifts, variations in light exposure as a result of artificial light pollution, shift work as a result of industrialization, variations in time zones as a result of jet travel, regulated room temperature, and consistent food supply. Some have hypothesised that this causes circadian rhythm abnormalities, which in turn cause the current global epidemics of type 2 diabetes, cardiovascular disease, and obesity.

Metabolic Syndrome Components and Circadian Disruption

Noncommunicable diseases (NCDs) include obesity, type 2 diabetes, cardiovascular disease (CVD), cancer, and mental disorders—all components of the Metabolic Syndrome are a major contributor to the high health and socioeconomic costs that most countries face. The result might be a "perfect storm" that would put many countries' health care finances in jeopardy. Non-alcoholic fatty liver disease (NAFLD), cognitive deficits, depression, sleep problems, and other comorbidities are frequently associated with this cluster of cardiometabolic risks. Irregular sleep-wake cycles have been associated with the metabolic syndrome, a group of health problems that includes obesity, diabetes type 2, heart disease, and high blood pressure. Obesity and type 2 diabetes are more common in those who work shifts or have problems sleeping because their circadian clock is disrupted.

There are ongoing debate and dispute over the shared underlying aetiology of this clustering of cardio-metabolic risk factors and their related comorbidities. Although the exact cause is still up for debate, theories have pointed to insulin resistance, a central proinflammatory state produced by fat, and heredity as possible culprits. Our proposal of the Circadian Syndrome, which combines elements of the Metabolic Syndrome with others, builds on earlier speculations that disturbances of the circadian cycle may play a role.

The Metabolic Syndrome: The Controversy on its Relevance and Definition

The name Metabolic Syndrome is still most commonly used to describe this cluster of metabolically-related CVD risk factors, despite significant attempts to discredit the syndrome as a clinical entity.

Despite several efforts to cast doubt on the syndrome as a clinical entity, the term Metabolic Syndrome is still most often used to represent this cluster of CVD risk factors related to metabolism. Although certain risk factors for cardiovascular disease do tend to cluster, the results show that the Metabolic Syndrome is still not well-defined, its pathophysiology is unknown, and its value as a risk marker for CVD is highly controversial. There is insufficient evidence to diagnose it as a syndrome, according to our research.

A number of organisations and individuals have proposed diagnostic criteria and components for the Metabolic Syndrome in the decades leading up to this point, and they have occasionally been at odds with one another. There was a great deal of misunderstanding caused by this, which had a negative impact on efforts to reach a general agreement on the cause of the condition, its essential features for diagnosis, and the anticipated long-term consequences.

The 2009 statement "Harmonising the Metabolic Syndrome" aimed to clarify matters pertaining to the agreed-upon essential components and their diagnostic criteria. It was jointly issued by a consortium including the International Diabetes Federation (IDF) Task Force on Epidemiology and Prevention, the National Heart, Lung, and Blood Institute, the American Heart Association, the World Heart Federation, the International Atherosclerosis Society, and the International Association for the Study of Obesity.

Components of the Proposed Circadian Syndrome.

Increasing evidence links these cardio-metabolic risk factors with comorbidities linked to circadian rhythm disorders, suggesting that all or almost all of the cluster's components may share a common aetiology. Circadian rhythm abnormalities may be of paramount importance, according to these findings. This frequently seen cluster of health problems and risk factors can be caused by disruptions in the circadian rhythm. Cardiovascular disease (CVD) risk factors include dyslipidaemia, type 2 diabetes, ageing, hypertension, sleep apnea, NAFLD, depression, and other mental health issues.

For these and other reasons, including growing evidence of a link to the body's natural circadian rhythm, we propose changing the name of the present "harmonised" Metabolic Syndrome to the "Circadian Syndrome" and including the aforementioned co-morbidities.

I don't see why this proposition is being put up. Our contention that disruptions to the circadian rhythm could underlie the grouping of what, at first glance, seem to be distinct biological occurrences is supported by the review that follows. New insights into epigenetic regulation may pave the way for a more thorough understanding of the pathophysiological mechanisms underpinning the present-day Metabolic Syndrome.

Circadian Disruption and Associations With Risk Factors

Cardiovascular-related components

Heart rate and blood pressure, which are physiologically regulated by the cardiovascular system, and cardiac diseases such as arrhythmias are all known to exhibit circadian oscillations. Myocardial infarction and sudden cardiac death also fluctuate during the day. Research in both animals and humans has shown that circadian clocks play a significant role in the aetiology and pathophysiology of cardiovascular disease, in addition to their utility in disease prevention and therapy. Circadian rhythm genes may have an effect on heart pathophysiology and physiology, according to some research. This is because the circadian clock directly affects cardiac function, and the metabolic

syndrome is closely associated to obesity, diabetes, and cardiovascular disease. Both the central and peripheral clocks have an effect on behaviour and the neurohumoral environment; the former directly via the circadian clock of the cardiomyocytes and the latter indirectly through other mechanisms.

Hypertension

Systolic and diastolic blood pressures fluctuate throughout the day in healthy individuals, following the circadian rhythms of hormones including aldosterone, cortisol, and sympathetic nervous system activity. When you're asleep, your blood pressure drops; when you're awake, it rises. Nocturnal hypertension, often called "non-dipping," is when blood pressure does not drop during the night. It is associated with a substantially higher risk of cardiovascular morbidity and death compared to office-based hypertension. Hypotension that does not decrease in blood pressure has been associated with insulin resistance, obesity, metabolic syndrome, and type 2 diabetes. There is some evidence that sleep apnea is a common factor in metabolic syndrome, obesity, and non-dipping hypertension. In addition, the release of catecholamines and aldosterone is decreased, and nocturnal hypertension is lessened, by improving oxygenation by constant positive air pressure throughout the night. A potential strategy to lessen the likelihood of cardiovascular disease (CVD) is to tailor hypertension medication to each patient's unique biological rhythms. Observed shifts in the day-night blood pressure pattern are also strong indicators of cardiovascular events and injury to target organs.

Lipids

In both the onset and management of metabolic diseases and cardiovascular disease, lipids—components of the Metabolic Syndrome play a significant role. Consequently, there is growing evidence that the circadian clock is crucial for maintaining healthy lipid levels in animals and humans, which impacts not just nutrition and other bodily processes but also cardiovascular disease (CVD). You may find critiques of this topic in more depth elsewhere.

Obesity

Important tissues, such as adipose tissue, have their own clocks in addition to the central hypothalamus clock. Central (abdominal) obesity in particular is strongly associated with metabolic syndrome, which in turn raises the risk of type 2 diabetes, insulin resistance, cardiovascular disease, and other issues. The article outlined how circadian rhythms, namely the adipocyte circadian clock, play a part in the onset of obesity. Obstructive sleep apnea is a serious co-occurring condition that is strongly linked to obesity, as previously stated.

Blood Glucose Levels, Glucose Tolerance and Circadian Effect

The fact that glucose tolerance varies throughout the day has been recognised for quite some time. Oral glucose tolerance, plasma insulin levels, and non-esterified fatty acid levels were investigated in our 1974 study with regard to the impact of time of day. Glucose tolerance is impaired in the evening as a result of the body's circadian cycle, which manifests as elevated blood glucose levels in the afternoon. Maintaining a steady blood glucose level requires a delicate balancing act between the absorption of glucose by muscles and adipose tissue and its input from meals or the liver. Second, the SCN affects the sensitivity of organs including the pancreas, liver, and muscle to insulin and glucose; and third, it affects the rhythms of feeding, which alter the cycles of glucose and insulin. These two mechanisms work together to control concentration. This cycle relies on a well-oiled central clock and has nothing to do with the availability of food. It is advised that the oral glucose tolerance test and

fasting glucose be given first thing in the morning for diabetes testing due to the necessity of maintaining glucose homeostasis. Failure to do so may lead to an incorrect diagnosis.

Conclusion

The growing body of evidence indicates that circadian rhythm disruption is a significant contributor to the development of metabolic syndrome and related cardiometabolic disorders. The circadian clock regulates essential physiological processes including glucose metabolism, lipid regulation, blood pressure control, hormonal balance, immune function, and energy homeostasis. Disturbances caused by sleep deprivation, shift work, irregular eating habits, and exposure to artificial light can impair these regulatory mechanisms and promote obesity, insulin resistance, hypertension, dyslipidemia, and cardiovascular disease. Molecular studies have revealed complex interactions between circadian clock genes and metabolic pathways, demonstrating that metabolic health and circadian regulation are closely interconnected. The emerging concept of Circadian Syndrome provides a broader framework for understanding the clustering of metabolic and behavioral disorders associated with circadian misalignment. Therefore, strategies aimed at restoring healthy circadian rhythms including adequate sleep, regular meal timing, physical activity, and chronotherapeutic interventions may offer effective approaches for preventing and managing metabolic diseases. Future research should focus on developing personalized circadian-based interventions that can improve metabolic outcomes and reduce the global burden of non-communicable diseases.

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