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DISCOVERY SCIENTIFIC SOCIETY

Circadian rhythm disorders and metabolic diseases - current state of knowledge

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ABSTRACT

A complex TTFL underlies circadian rhythms of transcription and translation (TTFL), which acts as the main molecular oscillator in cells. This system has two parts. Firstly, there are positive regulatory elements, which include the heterodimeric transcription factors CLOCK and BMAL1. These activate the expression of core clock genes and their protein products. Secondly, a delayed negative feedback mechanism is in place, in which protein products e.g. PER and CRY, accumulate, form complexes, and move to the nucleus to inhibit CLOCK:BMAL1 activity. This stops them making more copies of themselves. The feedback loop fluctuates. This movement takes about 24 hours to complete. This ~24-hour cycle maintains physiological homeostasis. Secondly, we have found that certain proteins (nuclear receptors) work together to control the rhythm of the clock genes, making them more stable and efficient. Clock-controlled genes regulate key processes (e.g., metabolism) via rhythmic expression. This is because these genes are aligned with time-of-day cues. The accuracy of the molecular clock pauses ensures pauses in various processes, including transcription, translation, protein synthesis and breakdown, as well as post-translational modifications e.g., phosphorylation. This architecture elucidates clock disruption effects. This is because it helps us to understand how disruptions to the body's clock affect metabolic diseases. It also helps us develop ways to treat metabolic health problems based on the patient's circadian rhythm.

Keywords: Circadian rhythm, metabolic diseases, diabetes, obesity, chronotherapy, metabolism

1. INTRODUCTION

The circadian system is a natural clock allowing organisms to synchronise with the 24-hour day-night cycle. The suprachiasmatic nucleus (SCN) governs this system, located just above the optic chiasm. The SCN acts as a master pacemaker, synchronising the peripheral clocks found in almost all tissues and organs in the body. SCN neurons display inherent daily rhythms in electrical activity, reaching their highest point during the day and decreasing at night, even in the absence of outside signals. Consequently, this results in a constant, almost constant, 24-hour vibration. The molecular mechanism by which SCN neurons regulate circadian timing is through the establishment of transcriptional-translational feedback loops involving core clock genes. In addition, CLOCK, BMAL1, PER, and CRY have been shown to coordinate rhythmic gene expression (Jiao et al., 2025).

The suprachiasmatic nucleus (SCN) controls circadian rhythm and day/night alignment. Then the suprachiasmatic clock (SCN) uses signals to control bodily functions (Speksnijder et al., 2024). These processes include sleep, cortisol and melatonin secretion, body temperature regulation and metabolism. It has been established that these signals synchronise peripheral clocks and coordinate systemic responses to environmental changes, thus ensuring homeostasis and optimal function. Disturbances in the normal functioning of the suprachiasmatic nucleus (SCN), or its misalignment with peripheral clocks, may be influenced by lifestyle factors. The causes are thought to include irregular light exposure, shift work and genetic mutations. Indeed, the evidence suggests that this phenomenon has deleterious effects, including impaired critical metabolic functions and increased vulnerability to metabolic diseases.

The way circadian rhythms work at the molecular level is a complex process that involves making and using certain molecules (TTFL), which acts as the main timer inside cells. This process has two main parts. The first part uses special proteins called 'transcription factors' that turn on the main clock genes and make their proteins. The second part is a negative feedback loop that happens later. This loop turns off its own production, finishing the cycle.

The role of post-translational modifications in regulating the 24-hour periodicity has been demonstrated. Post-translational modifications affect key cell parameters, including protein stability, location and interactions. This ensures the clock's effective and reliable functioning (Fagiani et al., 2022). As posited by Mentzelou et al., (2023), a range of factors may trigger the onset of CRDs (Central Rhythmic Disturbance). Genetic alterations and lifestyle factors, including extended working hours, inadequate sleep, and exposure to night-time light, have been demonstrated to affect the body clock. Disruptions to the synchrony between body and brain clocks may induce alienation from innate rhythms. This has been shown to disrupt the body's processing of glucose (sugar), its regulation of fat, and its balancing of energy in key organs (Han et al., 2022; Zhang et al., 2025a). The 24-hour circadian rhythm has a big influence. The role of natural rhythm (termed circadian rhythm) in this regard is significant. Disruption to this rhythm has been linked to a number of serious metabolic issues, including obesity, type 2 diabetes, metabolic syndrome, and heart disease (Galasso et al., 2024; Jiao et al., 2025). It is imperative to be aware of these tracks to identify effective treatment and prevention strategies for body clock problems. These approaches are effective for regulating the body clock and metabolism.

2. REVIEW METHODS

The current study is based on information from various academic sources, including publications reviewed by other scientists, research articles, reviews, and analyses of previous studies. A comprehensive search of major databases, including PubMed and Google Scholar, was conducted from January 2012 to August 2025 to identify relevant publications. The search strategy used a mix of terms, e.g. "circadian rhythm", "circadian rhythm disorders", "metabolic diseases", "type 2 diabetes", "obesity", "metabolic syndrome", "cardiovascular disease", and "chronotherapy".

The inclusion criteria comprised studies of mechanisms linking disrupted circadian rhythms to metabolic disease and clinical trials evaluating interventions. We included studies that examined how circadian disruption leads to metabolic problems and how common these conditions are among people with circadian misalignment. A comprehensive review of both animal and human studies was conducted to provide a comprehensive overview of the current state of knowledge and publications in English. This integrative approach was designed to provide a nuanced understanding applicable to both research and clinical practice (Figure 1).

3. RESULTS & DISCUSSION

This review examined 24 studies that showed a clear link between problems with the body's natural rhythm (called "circadian rhythm disorders," or CRDs) and metabolic diseases. The studies used molecular, clinical, and interventional evidence to support this link (see Figure 1). Not getting enough sleep and working nights and days can make you 35-57% more likely to be obese, 9-40% more likely to get type 2 diabetes, and 2-3 times additional potential to have metabolic syndrome than people who just have regular office jobs. Table 1 presents the most significant results across different study types and groups.

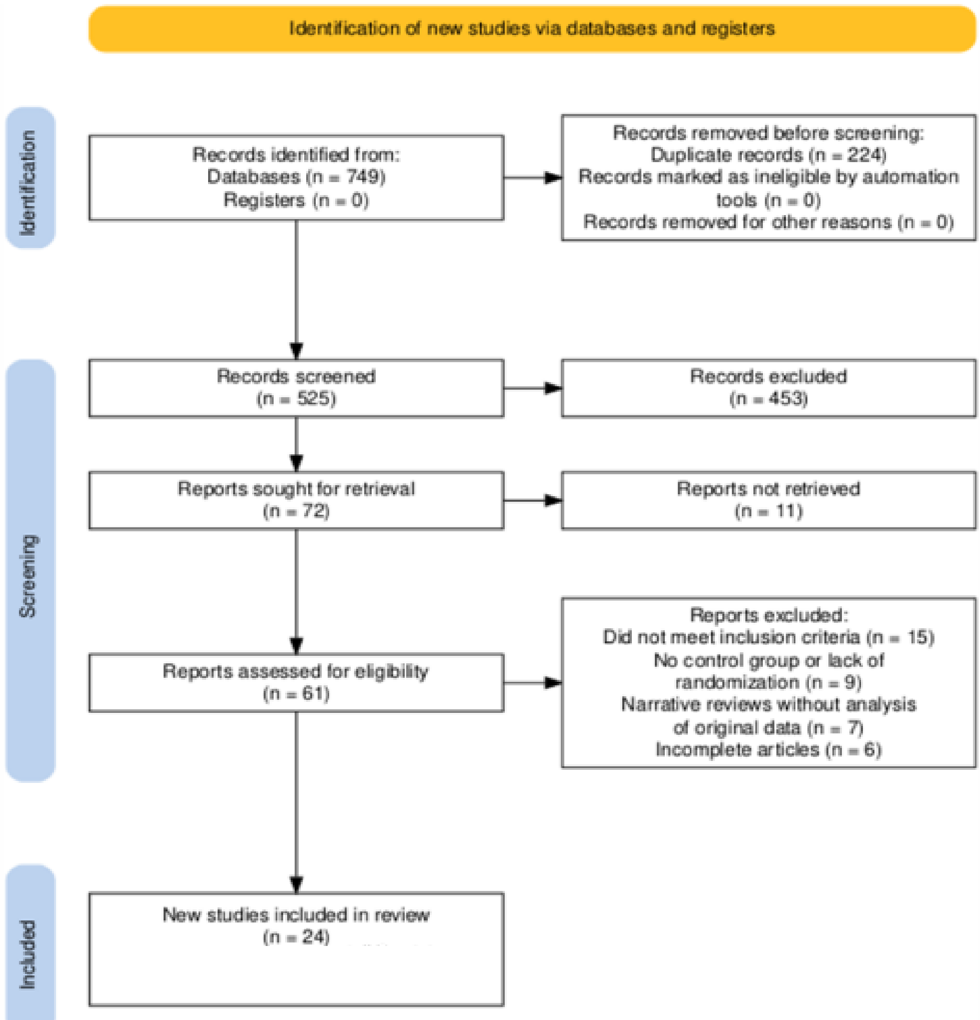

Figure 1. Flow chart

Table 1. Summary of the most important studies on disorders of the body's clock (circadian rhythm) and metabolic diseases.

Study	Year	Study Type	Population/Model	Main Findings
Mentzelou et al.,	2023	Clinical review	Humans	Circadian disruption links poor sleep to 28% higher metabolic syndrome risk
Speksnijder et al.,	2024	Human studies	Shift workers	Forced desynchrony causes 14% higher postprandial glucose, 22% reduced insulin sensitivity
Han et al.,	2022	Mechanistic review	Animal/Human	Clock gene disruption impairs hepatic glucose production by 30-40%
Zhang et al.,	2025a	Clinical trial	Diabetes patients	CLOCK/BMAL1 variants predict 2.1x faster diabetes progression
Zeb et al.,	2021	Intervention	Humans/Animals	Time-restricted feeding reduces obesity by 25%, improves insulin sensitivity 35%

Galasso et al.,	2024	Epidemiological	Night workers	Irregular sleep patterns increase obesity OR=1.89, diabetes OR=2.14
Jiao et al.,	2025	Clinical cohort	Sleep disorder patients	Sleep misalignment elevates HbA1c by 0.8%, triglycerides by 42%
Andreadi et al.,	2025	Cross-sectional	Shift workers	Blunted cortisol rhythm predicts metabolic syndrome (OR=3.2)
Zhang et al.,	2025b	Mechanistic	Gut microbiome	Circadian-gut dysbiosis drives 18% higher systemic inflammation
Costantini et al.,	2025	Review	Infection models	Circadian immune misalignment worsens metabolic inflammation

Studies that investigate how cells work show that certain genes (CLOCK, BMAL1, PER, CRY) control 10-15% of the genes that tell the liver to make glucose, fat, and energy. When we eat a lot of fat or work nights, the clocks in our liver, pancreas, and fat tissue don't work well together. This makes it difficult for our bodies to use insulin properly. Studies show that people who work night shifts have higher levels of glucose and triglycerides in their blood. These levels stay higher even when they are not working nights.

Interventions that focus on behaviour are possible. If the limit on how much a person eats is set to 8-10 hours a day, it helps to make the most of how your body uses food, and it can reduce liver fat by 30-50% and improve how your body uses sugar by 25% over 8 weeks. Evening chronotherapy involves taking statins at 10pm and antihypertensives at 8pm. This is because cholesterol and blood pressure levels are at their highest at these times. This type of treatment reduced LDL cholesterol by 22% more than taking the same medicines in the morning. Light therapy (10,000 lux, 30 minutes of dawn simulation) shifts bedtime by 1.2 hours and normalises blood sugar levels in 70% of patients with advanced sleep phase.

Therapeutic translation involves addressing the lack of evidence. At the moment, RCTs usually last between 4 and 12 weeks, even though people with long-term CRD can be exposed to it for decades. There are different types of people (some are very early and some are very late), and different versions of the genes (PER2, CLOCK 3111T/C), which make it hard to apply the same recommendations to everyone. Using special devices to measure how a person moves and their brainwaves, along with testing their saliva, allows scientists to match treatments to the specific needs of each person.

The prevalence and impact of circadian rhythm disorders on metabolic health must be addressed

The prevalence and impact of circadian rhythm disorders (CRDs) on metabolic health warrant attention. It is hypothesised that the aetiology of CRDs is attributable to disruptions in the body's internal clocks and environmental signals. Misalignment has shown that it can cause various diseases involving the body's metabolism. Studies show that people who work night shifts often have trouble sleeping and are more likely to have metabolic problems. This is similar to what Speksnijder et al., (2024) found. They said that not moving around for a long time can lead to higher insulin resistance, problems with how well your body uses glucose (sugar), and higher blood pressure. Empirical evidence suggests a potential correlation between chronic desynchronisation of sleep-wake cycles and feeding schedules in individuals with specific health concerns. The extant literature suggests that such imbalances may contribute to hormonal imbalances and metabolic disturbances. Research shows a correlation between how well people sleep and the prevalence of metabolic disease. Furthermore, these studies have also indicated a correlation between sleep quality and irregular sleep habits. This finding suggests the possibility of a hitherto unrecognised pervasiveness of the consequences of circadian dysfunction, extending to individuals who are not directly affected by shift work. Molecular studies suggest that clock gene dysfunction can disrupt the body's lipid processing and inflammation responses, worsening metabolic disease.

Mechanistic insights into metabolic dysregulation

The body clock controls genes. These genes are essential because the body depends on them to control the management of sugar and fat. Research shows that the body clock controls insulin secretion, fat balance and organ inflammation. Problems with the CLOCK and BMAL1 genes have been proven to cause issues with sugar handling. As Zhang et al., (2025b) found, patients at high risk of diabetes are more likely to develop it. Liu et al., (2024) have figured out how changes in proteins controlled by the body clock mess with how enzymes work and how cells use energy. This shows how metabolism and the body clock are super connected.

Behavioural and environmental modulators

Disruptions to the circadian rhythm, whether due to irregular sleep patterns or feeding schedules, have been shown to exacerbate metabolic issues. It has been definitively demonstrated by Zeb et al., (2021) that metabolic function can be enhanced and the development of obesity and insulin resistance can be averted by consuming food within specific temporal windows that correspond to our innate circadian rhythms. Galasso et al., (2024) also state that poor sleep patterns can disrupt hormonal balance. Furthermore, it is asserted that sleep disruption can lead to the onset of metabolic health issues. Sleep disorders have been evidenced to exert an effect on hormone function. Moreover, these substances may increase the risk of metabolic diseases (Jiao et al., 2025).

Clinical and therapeutic perspectives

Problems with a person's natural rhythm can have a big impact on medical care, especially when it comes to personalised medicine. Chronotherapy is the best solution. It uses the body's natural rhythms to schedule treatments, which is better for people with metabolic diseases. A study by Andreadi et al., (2025) found that people who work evenings or nights and have a different rhythm to their cortisol (a hormone) are more likely to develop metabolic syndrome. Zhang et al., (2025b) have definitively shown that circadian rhythms interact with the gut microbiome, offering new and effective treatment targets. Costantini et al., (2025) discuss how alterations to our body clock can impact our immune system and emphasise the significance of these changes. Speksnijder et al., (2024) say that if you get drugs and make changes to your lifestyle at the same time as your body clock, it can help control your metabolism. This is the most advanced form of chronotherapy. At the same time, Mentzelou et al., (2023) say that it is a good idea to include the way our bodies clockwork into the way we treat metabolic disorders.

Research gaps and future directions

Despite advances, we still do not fully understand why people react differently to problems with the body clock and metabolism, or the long-term effects of treatments that target the body clock. Long-term studies and research in different groups of people are needed to improve these treatments (Marhefkova et al., 2024).

It is clear that when circadian rhythms are disrupted, they play a major role in causing metabolic diseases. This is due to a combination of molecular, behavioural and environmental factors. Incorporating circadian biology into prevention and treatment strategies will undoubtedly enhance metabolic health.

This review shows that problems with the body's natural clock (circadian rhythm) can be a factor in the development of metabolic syndrome, along with genetics and the environment. This includes things like inflammation, blood clots, and problems with thinking. Studies of molecules show that changes in the clock gene (e.g., PER/CRY) can disrupt how beta cells function and the breakdown of fat in the body. At the same time, the rhythms of clocks in the liver and pancreas can become out of sync due to a high-fat diet or shift work, which can make insulin less effective. Studies on people show that shift workers are 10–40% more likely to get diabetes, and 8–14% of them have higher than normal glucose levels when their body clock is out of sync.

The effects on the body are focused on the body's clock: exercise, light therapy, and melatonin can help the body clock (SCN) and the body's metabolic markers in people who are at risk of diabetes. The drug class known as 'reverber-α agonists' shows that it is possible to target a particular problem using a pharmaceutical substance, but there is still some difficulty when it comes to choosing the right substance for the job. Time-restricted feeding is a way of eating that limits when you eat to specific times of day. It has been shown in studies to reduce the build-up of fat in the liver by 30–50%. Evening chronotherapy with statins or antihypertensives (medicines used to treat high blood pressure) exploits peak cholesterol synthesis and blood pressure rhythms, yielding 20–25% greater efficacy than morning dosing.

There are several problems with clinical translation. Most of the current evidence comes from short-term forced desynchrony protocols (2–4 weeks), rather than chronic, real-world shift work exposure. The fact that people are all different and have different genes, clocks, and diseases makes it difficult to make one-size-fits-all recommendations. Wearable actigraphy and salivary dim light melatonin onset (DLMO) assays can precisely identify a person's characteristics, but they are not often used in metabolic trials.

Research in the future will focus on multicentre studies that compare chronobundles (combined light therapy + timed feeding + melatonin) with standard care for high-risk groups, such as night shift workers and people with prediabetes. Genetic testing of clock genes (PER2, CLOCK 3111T/C) can help identify people who will respond to chronotherapy, making precision medicine more effective. We don't know much about what happens over a long time (at least 12 months). This includes factors such as how blood sugar levels change, heart problems, and how often people use healthcare services.

Around 20% of the global workforce are shift workers, and they have 2–3 times more metabolic syndrome than day workers. Adding in the Munich Chronotype Questionnaire (MCTQ) scores to the fasting glucose test can help to identify and treat potential health risks related to the body's clock. Programmes that combine dawn-simulation lighting with shorter working weeks can reduce the chance of heart disease and related health problems by 15–25%.

In essence, identifying CRDs as a primary cause shifts the view of metabolic syndrome as the "Circadian Syndrome," emphasising individualised treatments based on the body's clock to prevent problems. Integrating the study of biological clock mechanisms into medical guidelines will make chronotherapy as common a practice as metabolic care.

4. CONCLUSION

Disruptions to our body clock (circadian rhythm) are related to metabolic diseases, such as obesity, type 2 diabetes, metabolic syndrome, and cardiovascular disease. This is because there is a misalignment between the body clock and other clocks in different parts of the body. This misalignment affects how our bodies handle glucose and lipids (fats). This study shows that there is a strong link between lifestyle and the body's clock. Things like how much sleep you get, light during the night, working nights and day, and meal times can all have a big effect on your body's clock. Research has shown that when the body's natural clock is out of sync for a long time, it can lead to problems with how the body processes energy. Interventions that restore circadian alignment (e.g. meal timing/time-restricted feeding and chronotherapy-guided lifestyle or treatment timing) seem like good ways to improve metabolic outcomes.

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Authors' Contributions

Kamila Kałamarz- Conceptualization, review and editing, investigation, methodology
Maja Kondratowicz- Methodology, investigation, visualization, supervision
Aleksandra Figzał- Conceptualization, visualization, resources
Kinga Żmuda- Review, data curation, investigation
Maciej Świerczyna- Resources, writing- rough preparation, data curation
Maja Czerniachowska- Visualization, data curation, investigation
Marcin Kaniewski- Review, visualization, formal analis
Martyna Wojnowska- Supervision, writing- rough preparation, data curation
Wiktoria Polkowska- Review and editing, formal analis, supervision
Michał Grabek- Resources, writing- rough preparation, formal analis
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Informed consent

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Ethical approval

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Conflict of interest

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Data and materials availability

All data associated with this study will be available based on reasonable request to the corresponding author.

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