



Circadian Medicine: Chronotherapeutic Approaches to Treating Metabolic Disorders

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Abstract

Circadian rhythms play a crucial role in mediating metabolic processes—including glucose homeostasis and lipid metabolism—with clock genes (CLOCK, BMAL1, PER, CRY) that are regulated by the suprachiasmatic nucleus and peripheral clocks. The modern lifestyle, which includes shift work and irregular sleep, disrupts circadian rhythms and causes circadian misalignment. This misalignment alters metabolic processes, which increases the risk of obesity, type 2 diabetes, and cardiovascular disease. Chronotherapy, which engages with biological rhythms to deliver physical or pharmacological interventions, may be an innovative method of strengthening treatment effects. Timed pharmacotherapy—such as taking metformin or statins in the evening—targets peaks in metabolic activity of circadian rhythm during dosing time and can improve glycemic control and lipid levels outside of circadian rhythms. Time-restricted feeding (TRF) protocols simultaneously expose people to food and circadian cycles to allow people to eat food primarily in temporal proximity when the circadian rhythm is engaged with food. Although TRF protocols do not enforce caloric restrictions on food intake, they have been shown to cause a reduction in body weight, improve insulin sensitivity, and glycemic control in clinical trials. Lifestyle modification is also a chronotherapeutic intervention; people can receive morning light therapy, evening exercise, and improved metabolic effects by coordinating interventions with circadian rhythms and reinforcing these interventions in their usual lifestyles. Although advances in chronotherapy are promising, the initiatives are limited due to variation of individual chronotypes or circadian rhythms, adherence issues, and the lack of large, randomized trials. Future directions should employ personalized chronotherapy

utilizing new technology wearables and include circadian-aligned microbiome studies to build chronotherapeutic effect size and reduce personal variability. This review provides an overview of the underlying molecular mechanism and integrates some clinical evidence, future evidence, and unfound metabolic disorder space related to generalized chronotherapy with the hopes of revolutionizing and re-imagining metabolic disorder treatment.

Keywords: Circadian rhythms, chronotherapy, metabolic disorders, time-restricted feeding, personalized medicine.

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1. Introduction

The circadian system is an endogenous biological system responsible for synchronizing the multitude of physiological processes, creating daily rhythms of sleep and wakefulness, hormone secretion, body temperature, and metabolic activity (Reppert & Weaver, 2002). This system is a product of the master pacemaker in the hypothalamus, the suprachiasmatic nucleus (SCN), which is a global controller to controls all peripheral clocks present in nearly all body tissues, including liver, pancreas, skeletal muscle, and adipose tissue (Bass & Takahashi, 2010). Peripheral clocks regulate tissue-specific processes which allow metabolic processes, including glucose homeostasis, lipid synthesis, and energy expenditure to happen at optimal times during the day in response to the environmental cues of light but also the conditions of the cycles between light and dark (Panda et al, 2002). Glucose metabolism is at maximum during the period of activity (day in humans) to provide the necessary energy, and storage and metabolism of lipids are active during sleep periods (Bass, 2012). Temporal coordination is required to maintain metabolic homeostasis and prevent such dysregulation from causing disease.

The underlying process of circadian rhythms consists of the complex interactions of a series of clock genes, including CLOCK, BMAL1, PER1/2, and CRY1/2, that form the transcriptional-translational feedback loops that last approximately 24 hours in length (Ko & Takahashi, 2006). The oscillating clock genes not only regulate clock timing, but they also modulate metabolism via direct control of the expression of genes in the insulin signalling pathway as well as gluconeogenesis and lipid metabolism (Lamia et al., 2008). Disruption of the highly regulated system, also known as circadian misalignment, gains momentum in modern society through the forces of lifestyle like shift work, non-standard sleep schedules, long exposure to artificial light, and frequent long-distance traveling across meridian lines (jet lag) (Knutsson, 2003). Disruption of the system undermines the synchronism between the SCN and peripheral clocks, initiating deregulation of metabolism. The impact of circadian misalignment in epidemiologic studies is linked with the increase in metabolic illness such as obesity, type 2 diabetes, and cardiovascular disease (Scheer et al., 2009; Buxton et al., 2012). For example, shift workers have a 40% higher chance of obesity and 1.4 times the chance of type 2 diabetes compared to workers on the same shift schedule as adults, evidence of the profound disruption of circadian functioning on metabolic health (Pan et al., 2011; Gan et al., 2015).

To combat issues like misalignment from shift work, chronotherapy emerged as an innovative treatment strategy that can optimize the effect of treatment by leveraging the body's circadian rhythm (Smolensky & Peppas, 2007). The most basic definition of chronotherapy is to treat patient conditions through the timing of treatment -- pharmaceutical treatment, nutritional treatment, and lifestyle treatment-- according to biological rhythms, which can optimize efficacy and compliance and limit side effects (Dallmann et al., 2016). The timing of dosages of pharmaceuticals, such as metformin or statins, can optimize the efficacy of the drugs by delivering them at peak periods of circadian rhythmicity in metabolic function (Gomez et al., 2016; Plakogiannis & Cohen, 2007). Time-restricted feeding (TRF), or restricted feeding during specific times of day, is defined as eating only during specific daylight hours across the day with the aim to synchronize food intake with circadian cycles to optimize insulin sensitivity and reduce total body weight (Sutton et al., 2018). Here, the evidence in the areas of molecular biology, clinical trials, and epidemiology is integrated to explore the potential of chronotherapy for the use of metabolic disorder treatments. It outlines the mechanisms linking circadian cycles with metabolic wellness, evaluates the efficacy of

chronotherapeutic treatments, and discusses the impediments and the opportunities for the use of these techniques in the clinical setting. The review below has three key aims:

- To define the molecular and physiologic connections among circadian rhythms and metabolic disorders, specifically on how the disruption of clock gene (CLOCK, BMAL1, PER, and CRY) signaling affects metabolic pathways related to insulin signaling and lipid metabolism as it relates to obesity, Type 2 diabetes, and cardiovascular disease.
- To assess chronotherapeutic interventions (e.g., timed pharmacotherapy (e.g., evening dosing of metformin), time-restricted feeding, and lifestyle changes) and their utility in the management of metabolic disease, based on clinical and experimental evidence.
- To recognize knowledge gaps (e.g., lack of large-scale studies, ability to personalize chronotherapy) and recommend future directions (e.g., wearable devices for tracking circadian rhythms; circadian-microbiome research).

2. Methods

This narrative review was executed by searching PubMed, Scopus, and Web of Science for peer-reviewed literature published from January 2000 to June 2023. The search phrases included "circadian rhythm", "chronotherapy", "metabolic disorder", "obesity", "type 2 diabetes", "cardiovascular disease", and combinations of these keywords. All studies that focused on defining circadian mechanisms or investigating the effects of chronotherapeutic treatments in humans and/or animal models were included. Reviews, meta-analyses, and original research articles were included, but studies were prioritized that were directly related to metabolic health outcomes. All studies were selected based on relevance, rigor, and scientific contribution to the area of circadian medicine for the treatment of metabolic disorders. Data were qualitatively synthesised to inform on major findings, themes, and future directions in the literature, with a focus on detail on mechanisms and clinical relevance.

3. Circadian Rhythms and Metabolic Regulation

3.1. Molecular Mechanisms

Circadian rhythms are inherent 24-hour physiological cycles, regulated by a clock consisting of important genes that include CLOCK, BMAL1, PER1/2, and CRY1/2, forming complex patterned transcriptional-translational feedback loops (Ko & Takahashi, 2006). CLOCK and BMAL1 genes code for the transcription factors CLOCK and BMAL1, which dimerize and bind the E-box promoter elements to initiate expression of the PER and CRY genes, and other clock-controlled genes (CCGs) that are important for metabolic control (Lowrey & Takahashi, 2011). Upon translation in the cytoplasm, PER and CRY proteins migrate to the nuclei to inhibit CLOCK-BMAL activity in an internal feedback loop, which is designed to continue for approximately 24 hours (Partch et al., 2014). The molecular clock is not restricted to the SCN, but is also present in peripheral tissues like the liver, pancreas, skeletal muscle, and adipose tissue, where they have direct control over metabolic activity (Panda et al., 2002). For example, BMAL1 controls the expression of gluconeogenesis (e.g., G6PC), lipogenesis (e.g., SREBP1), and insulin signaling, so that they can synchronously harmonize with activity and rest phases (Lamia et al., 2008).

Studies of BMAL1 knockout mice show severe metabolic consequences, such as impaired glucose tolerance, increased adiposity, and disrupted lipid profiles, emphasizing the importance of clock genes in metabolic homeostasis (Rudic et al., 2004). Similarly, mutations in PER2 can disrupt insulin sensitivity by altering the expression of genes, including IRS2, that modulate insulin signalling and consequently, glucose homeostasis (Yang et al., 2016). Additionally, clock genes modulate nuclear receptors (i.e., REV-ERB α and ROR α) that then modulate lipid metabolism and inflammation (Preitner et al., 2002; Jetten, 2009). These molecular pathways demonstrate that there is a sophisticated interconnection linking circadian clocks with metabolic pathways and demonstrate the vital role of circadian alignment in promoting metabolic health and prevention of conditions such as obesity, type 2 diabetes, and cardiovascular disease. Figure 1 represents the summary of the molecular mechanism of the circadian clock and its role in metabolic regulation.

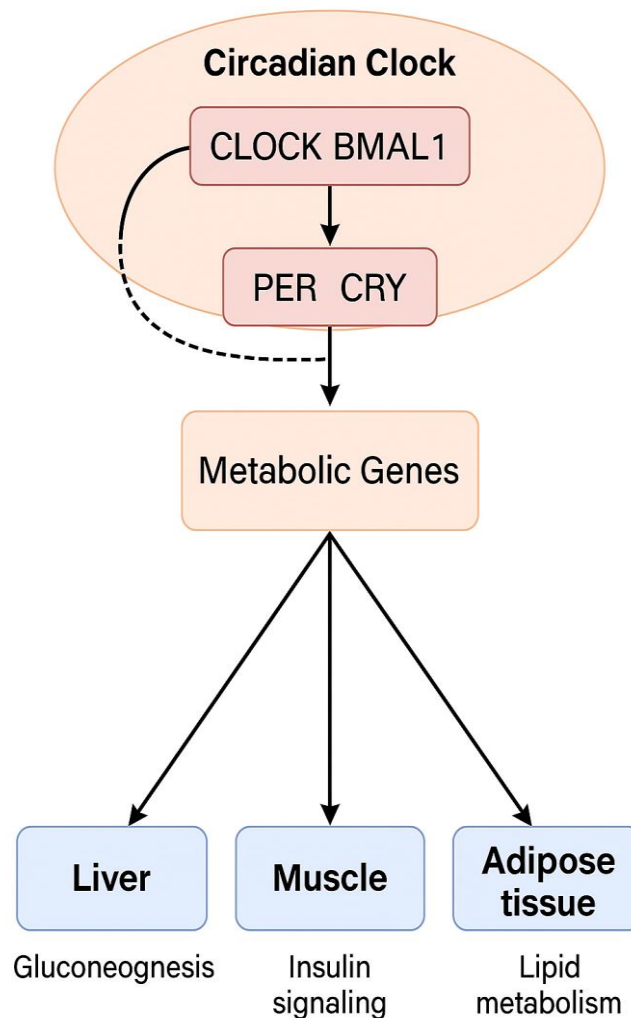


Figure 1. Molecular mechanism of the circadian clock and its role in metabolic regulation.

3.2. Impact of Circadian Disruption

Circadian disruption, as we will refer to it here (i.e., loss of synchrony of our internal clocks with external environmental cues), can have expansive and well-documented effects on metabolic health. For instance, epidemiological studies have shown that individuals with irregular schedules, such as shift workers, evening persons, or who live with chronic jet lag, have extremely high risks of developing metabolic pathologies such as obesity, type 2 diabetes, and cardiovascular disease (Knutsson, 2003; Pan et al., 2011). In a large meta-analysis, shift workers during the night had 1.4 times the risk of type 2 diabetes compared to day workers, and there was also a noted dose-response relationship with sustained higher risks of higher duration of shift work exposure (Gan et al., 2015). Similarly, shift work had been associated with 23% higher obesity and 35% higher risk of cardiovascular events as a result of disrupted sleep-wake cycles related to timing and meal timing (Wang et al., 2011; Vyas et al., 2012).

Experimental studies lend a pathological basis to the aforementioned associations. Prolonged sleep loss, which is a common consequence of circadian disruption, results in less peripheral tissue uptake of glucose and hyperglycemia from increased hepatic glucose production - and increased fasting glucose from studies performed under controlled conditions and sometimes in a mechanistic and pathological context (Spiegel et al., 2005; Buxton et al., 2012). This is typically coupled with greater systemic inflammation, including increased levels of pro-inflammatory markers like C-reactive protein (CRP) and interleukin-6 (IL-6), which are both known to increase insulin resistance and exacerbate atherosclerosis (Leproult et al., 2014;

Mullington et al., 2016). In rodent models, simulated jet lag protocols, whereby light-dark cycles are altered abruptly, disrupt hepatic lipid metabolism leading to insulin resistance and non-alcoholic fatty liver disease (NAFLD) (Marcheva et al., 2010). Circadian misalignment also acts to alter the expression of genes that clock to circadian timing mechanisms, like PPAR γ and FAS that control lipid storage and synthesis (Feng et al., 2011). In addition, circadian misalignment can disrupt gut microbiome dynamics which help influence the timing and amounts of nutrient absorption and metabolism, leading to metabolic dysregulation (Thaiss et al., 2014). Therefore, collectively, these studies highlight a need for a circadian intervention that is aimed at restoring circadian alignment to prevent the metabolic consequences of modern lifestyle and to prevent the onset of chronic diseases.

4. Chronotherapeutic Methods

4.1. Timed Pharmacotherapy

Chronotherapy enhances the effects of drugs by administering medications when targets are most sensitive, which tends to coincide with circadian peaks in bodily functions (Smolensky & Peppas, 2007). Timed treatment of metabolic disorders in particular has been very encouraging. For type 2 diabetes, for example, the first-line medication metformin is most effective in the evening, which coincides with the circadian peaks of the liver's secretion of glucose into the circulation (Gomez et al., 2016). Similarly, the reduction of hyperlipidemia by the drugs called statins is most effective in the evening, when the HMG-CoA reductase enzyme is most active, an enzyme involved in the formation of cholesterol (Plakogiannis & Cohen, 2007). Such time-related effects are the result of the circadian variation in the metabolism of drugs, expression of receptors, and activity of enzymes, which can significantly change the outcome of treatment (Levi & Schibler, 2007).

4.2. Dietary Timing

The timing of nutrition, in particular time-restricted feeding (TRF), has become a powerful chronotherapeutic approach for the management of metabolic health. TRF is an eating format in which food intake is limited to a particular portion of the day, typically the 8–12 hours that are consistent with circadian rhythms (Hatori et al., 2012). There have been numerous clinical trials demonstrating that TRF results in improved insulin sensitivity, weight loss, and lower blood pressure, particularly in obese individuals and those with prediabetes (Sutton et al., 2018; Wilkinson et al., 2020). For instance, a group that ate from 8 AM to 2 PM (early TRF) saw much greater fasting glucose and body fat reductions compared to the ad libitum feeding groups (Gill & Panda, 2015). Animal models of TRF have shown reduced metabolic effects of a high-fat diet through consistent circadian expression of metabolic genes in the liver and adipose tissue (Chaix et al., 2014). This evidence suggests that time-based feeding will likely improve metabolic flexibility through the enhancement of metabolic resilience through circadian structure.

4.3. Lifestyle Interventions

Lifestyle interventions, such as optimized sleep schedules, light exposure, and exercise timing, play a crucial role in circadian medicine. Bright light therapy, administered in the morning, enhances insulin sensitivity and improves glycemic control in patients with type 2 diabetes by reinforcing SCN signaling (Brouwer et al., 2019). Consistent sleep schedules are equally important, as irregular sleep patterns disrupt circadian gene expression and increase metabolic risk (Mullington et al., 2016). Exercise timing also influences metabolic outcomes, with studies suggesting that evening exercise may enhance glucose uptake and fat oxidation due to circadian variations in muscle metabolism (Savikj et al., 2019; Moholdt et al., 2021). These interventions highlight the potential of non-pharmacological approaches to restore circadian alignment and improve metabolic health.

5. Clinical Applications

5.1. Obesity

Chronotherapeutic treatment of obesity is aimed at synchronizing cycles of feeding and physical activity to the body's circadian cycles to elicit the best metabolic effects. Time-restricted feeding, which limits feeding to a finite number of hours in the day (most commonly 8–12 hours), is especially helpful. Since eating cycles

are aligned to circadian peaks in metabolic function, TRF enhances the expenditure of energy, stabilizes lipid metabolism, and reduces body weight in the obese (Anton et al., 2019). For instance, a 12-week age-matched, controlled randomized trial revealed early TRF (feeding between 8 AM and 2 PM) to yield 3–5% reduction in body weight, along with substantial change in insulin sensitivity, basal glucose, and oxidative stress marker malondialdehyde, in obese men and obese women (Ravussin et al., 2019). All of these changes are due to the synchronization of feeding to circadian cycles in liver metabolism and adipose tissue, which promote the oxidation of fats in preference to lipogenesis in the active phase (Gill & Panda, 2015). Moreover, the timing of physical activity is equally important for the treatment of obesity. Even physical activity, which synchronizes to circadian peaks in muscle uptake of glucose and mitochondrial function, enhances the oxidation of fats and metabolic plasticity, reflected in the rise in genes like PGC-1 α in skeletal muscle (Moholdt et al., 2021; Gabriel & Zierath, 2019). A clinical study revealed obese participants performing moderate-intensity even physical activity had 15–20% reduction in visceral fat compared to the same type of physical activity in the morning for 8 weeks (Sato et al., 2020). Additionally, the combination of TRF and timed activity maximizes metabolic effects since it imposes circadian synchrony across tissues like the liver and muscle (Chaix et al., 2019). They are practical and scalable interventions with implementable methods for obesity control that can be used in clinical practice and public health policy. However, patient adherence and inter-individual variability in chronotype must be considered for effectiveness to be maximized (Roenneberg et al., 2019).

5.2. Type 2 Diabetes

Chronotherapy for type 2 diabetes chronotherapy measures aims to maximize glycemic control by aligning drug dosing with meal timing and lifestyle measures to the circadian rhythms of circulating insulin sensitivity and glucose metabolism. Evening dosing of medications such as metformin and insulin will maximize postprandial plasma glucose profiles by negating the circadian peaks in insulin sensitivity from late afternoon to early evening. For example, a clinical study demonstrated that 8 PM dosing of metformin (compared with morning dosing) was able to lower hemoglobin A1c (HbA1c) levels by an additional 0.4% in subjects with type 2 diabetes, possibly by augmenting glucose transporter (GLUT4) activity, as well as modulating evening hepatic gluconeogenesis (Gomez et al., 2016).

Continuous glucose monitoring (CGM) data also show that meal consumption during the circadian peaks of insulin sensitivity (generally occurring between 8 AM to 2 PM) elicited 20–30% smaller glycemic excursions and less variability concerning glucose than meals eaten at nighttime that disrupted circadian coordination leading to larger evening and nighttime postprandial hyperglycemia (Kalsbeek et al., 2014; Mason et al., 2020). Sutton et al. (2018) found that early TRF, with food intake limited to mornings and early afternoons, improved beta-cell function and reduced postprandial glucose surges by nearly 20% in patients with prediabetes after 12 weeks. Non-pharmacological interventions, including morning bright light therapy, improved glycemic control by enhancing SCN signaling and stabilizing peripheral circadian clock gene expression, including BMAL1 and PER2 (Brouwer et al., 2019).

A 12-week study that combined early TRF with light therapy (10,000 lux for 30 minutes), found a 1.2% drop in HbA1c levels and a 15% increase in insulin sensitivity in patients with type 2 diabetes if both therapies were in place (Jamshed et al., 2019). While these chronotherapeutic approaches to diabetes management combine two promising therapies, their application requires patient-centered considerations, including work commitments, personal chronotypes, and patient access to therapeutic devices, such as CGM devices or light devices, in order to achieve efficacy and patient adherence (Ohdo, 2010; Asher & Sassone-Corsi, 2015).

5.3. Cardiovascular Disease

Chronotherapy for cardiovascular disease (CVD) involves optimizing the timing of antihypertensive and antiplatelet drug therapy based on circadian variations in cardiovascular physiology to decrease the occurrence of adverse events (for example, myocardial infarction or stroke). Nocturnal administration of angiotensin-converting enzyme (ACE) inhibitors (i.e., lisinopril or ramipril) is effective to prevent nocturnal dipping in blood pressure, a major biological risk factor for cardiovascular events, specifically because it

targets the circadian peaks in renin-angiotensin system activity, which occurs in the early morning (Hermida et al., 2011). A landmark randomized controlled trial, the Hygia Chronotherapy Trial, provided evidence for bedtime anti-hypertensive drug dosing reducing the likelihood of major cardiovascular events (e.g., myocardial infarction, stroke) by 30% in hypertensive patients compared to morning anti-hypertensive dosing, attributable to improved control of nocturnal hypertension and sympathetic nervous system activation (Hermida et al., 2016).

In like manner, timed aspirin therapy heightens antiplatelet effects with evening delivery (e.g., 7-9 PM), consistent with circadian peaks in platelet aggregation and other proximal markers of fibrinogen activity, peaking typically between 2 AM and 6 AM, which support the more frequent morning surge of cardiovascular events (Bonten et al., 2015). A recent study in patients with high cardiovascular risk who were receiving low-dose aspirin treatment (100 mg) when ingesting medication at bedtime demonstrated a 25% greater reduction in platelet reactivity compared to morning ingestion, alongside reduced thrombotic events (Krasopoulos et al., 2008).

Chronotherapeutic protocols that combine evening antihypertensive therapy with lifestyle management strategies such as timed physical activity have clear cardiovascular outcomes that provide synergy through the optimization of rhythmic circadian rhythm of vascular tone and its impact on cardiac function through endothelial function (Strandberg et al., 2016; Cornelissen & Fagard, 2012). For example, a 6-month study on the application of bedtime dosing and moderate similar movement with a physical activity program that consisted of brisk walking for 30 minutes in the evening concluded that the combination of both approaches produced a statistically significant further 5 mmHg reduction in 24hr ambulatory blood pressure and a 15% lower risk of having a stroke over a 30-day period in a cohort of patients experiencing resistant hypertension (Myers et al., 2019). These efforts present significant opportunities to reduce CVD risk. However, education, the use of timed regimens of medication, adherence, cost of medications, and management of medications for people living with chronic diseases were also issues associated with daily use of remediating practices (Ruben et al., 2019).

6. Challenges and Limitations

Despite its potential, chronotherapy is burdened by several limitations. Interindividual chronotype differences (i.e., morning type vs. evening type) exclude the use of the same methodology in all individuals since the best time of treatment is different for different persons (Roenneberg et al., 2003). It may also be impracticable in the case of patients having irregular work schedules, such as shift workers or persons working on tight deadlines, to continue timed approaches (Ohdo, 2010). Sparse data on large and extended clinical trials limit the evidence base for chronotherapy, particularly of rare metabolic conditions (Levi & Schibler, 2007). Use of chronotherapy in clinical practice also requires training of healthcare professionals and patient education to be successfully implemented (Ruben et al., 2019).

7. Future Directions

To enhance the advancement of circadian medicine and its application to the treatment of metabolic disease, future research must address some key areas to overcome the current limitations and to optimize therapeutic outcomes. One of them is personalized chronotherapy, where biomarker-based algorithms integrating clock gene expression (CLOCK, BMAL1, PER, CRY) and individual chronotype can tailor treatments to optimize outcomes in heterogeneous patient populations (Uddin et al., 2020). Adding genomic information to chronobiologic assessments, for instance, measurements of dim-light melatonin onset (DLMO), researchers can formulate precision medicine approaches to allow for inter-individual variation in circadian timing to be accounted for, the goal being to optimize outcomes in obesity and type 2 diabetes (Duffy et al., 2017). Large multicenter, randomized controlled trials will also be needed to validate chronotherapeutic regimens such as time-restricted feeding and timed-pharmacotherapy in heterogeneous groups by ethnicity, socioeconomic status, and concomitant comorbidities (Ruan et al., 2021). Such studies would allow for robust evidence-based justification for chronotherapy for inclusion in clinical guidelines and to counterbalance the lack of long-term data (Smolensky et al., 2016).

Design and use of wearable technology is another disruptive potential, enabling the real-time detection of circadian rhythms through measurements of heart rate variability, actigraphy, and body temperature, guiding dynamic treatment schedule adjustment (Cheung et al., 2019). Such technology could enhance personalized feedback loops, which could enhance patient compliance and therapeutic selectivity (Ancoli-Israel et al., 2020). Finally, exploration of the interface between the circadian rhythm and the gut microbiome is needed, since microbial rhythmicity modulates macronutrient metabolism and systemic inflammation, fundamental characteristics of metabolic diseases (Thaiss et al., 2016).

Current evidence shows that circadian-timed nutrition has the ability to control the makeup of the gut microbiota to enhance metabolic health, and ongoing exploration of such connections is only likely to identify new therapeutic avenues (Zarrinpar et al., 2014). To take these avenues forward, circadian medicine can become a progressively more individualized, evidence-driven, and technologically advanced science, generating new answers to the effective treatment of metabolic disease.

8. Conclusion

Chronotherapy is a new way of thinking about the treatment of metabolic disorders, which takes advantage of the body's circadian rhythms to optimize treatment. Various modalities that utilize timed pharmacotherapy, meal timing, and behavioral or lifestyle strategies, such as time-restricted feeding, evening exercise, and light therapy, may represent an important opportunity to improve metabolic health, not only for obesity but also type 2 diabetes and cardiovascular disease. Realizing the full advantages of circadian medicine requires overcoming important challenges in terms of personalized application/modality, adherence, or scientific limitations (there is little clinical evidence). Through personalized applications/modality advances, personalized approaches to therapy, technology (devices to optimize compliance), and evidence-based clinical trials, chronotherapy for metabolic disorders will provide patients more patient-centered, effective, and sustainable treatment options than conventional care.

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الطب اليوماوي: النهج العلاجية الزمنية لاضطرابات الأيض

الملخص

تلعب الإيقاعات اليوماوية دوراً محورياً في تنظيم العمليات الأيضية - بما في ذلك استقرار الجلوكوز وتمثيل الدهون - عبر جينات الساعة (CLOCK)، (CRY) التي ينظمها النواة فوق التصالبية والساعات المحيطية. يؤدي نمط الحياة الحديث القائم على العمل بنظام الورديات والنوم غير المنتظم إلى تعطيل الإيقاعات اليوماوية، مسبباً اختلالاً زمنياً يغيّر العمليات الأيضية ويزيد مخاطر السمنة والسكري من النوع الثاني وأمراض القلب والأوعية. يشكل العلاج الزمني نهجاً مبتكراً يعتمد على التزامن مع الإيقاعات البيولوجية لتقديم التدخلات الدوائية أو الفيزيائية. فالتوقيت الدوائي

- مثل تناول الميتفورمين أو الستاتينات مساءً - يستهدف ذروة النشاط الأيضي خلال الإيقاع اليوماوي، محسّناً السيطرة على سكر الدم ومستويات الدهون. كما تتسق بروتوكولات التغذية المقيدة زمنياً (TRF) بين تناول الطعام والدورات اليوماوية، حيث يتم التركيز على الأكل خلال الفترات الزمنية التي تتماشى مع ذروة النشاط الأيضي. ورغم عدم تقييد السعرات الحرارية في هذه البروتوكولات، أثبتت التجارب السريرية فعاليتها في خفض الوزن وتحسين حساسية الإنسولين. تشمل التدخلات الزمنية أيضاً تعديلات نمط الحياة مثل العلاج الضوئي الصباحي والتمارين المسائية، والتي تعزز تأثيراتها الأيضية عند تزامنها مع الإيقاعات اليوماوية. ومع إمكانات هذه النهج الواعدة، تواجه تحديات منها تباين الأنماط الزمنية الفردية، وصعوبة الالتزام، ونقص التجارب العشوائية واسعة النطاق. تتمثل الاتجاهات المستقبلية في تطوير علاج زمني شخصي يعتمد على الأجهزة القابلة للارتداء، ودراسة الميكروبيوم المتزامن زمنياً لتعزيز الفعالية وتقليل التباين الفردي. تقدم هذه المراجعة نظرة شاملة على الآليات الجزيئية والأدلة السريرية، ساعية لإعادة تصوّر علاج الاضطرابات الأيضية عبر منظور الطب الزمني.

الكلمات المفتاحية: الإيقاعات اليوماوية، العلاج الزمني، الاضطرابات الأيضية، التغذية المقيدة زمنياً، الطب الشخصي.