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Effect of Circadian Rhythm on Metabolic Processes and the Regulation of Energy Balance

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Abstract
Background: The circadian timing system or circadian clock plays a crucial role in many biological processes, such as the sleep-wake cycle, hormone secretion, cardiovascular health, glucose homeostasis, and body temperature regulation. Energy balance is also one of the most important cornerstones of metabolic processes, whereas energy imbalance is associated with many diseases (i.e., obesity, diabetes, cardiovascular disease). Circadian clock is the main regulator of metabolism, and this analysis provides an overview of the bidirectional effect of circadian rhythm on metabolic processes and energy balance. ***Summary:*** The circadian timing system or circadian clock plays a crucial role in many biological processes, but the increase in activities that operate 24/7 and the common usage of television, internet, and mobile phones almost 24 h a day leads to a gradual decrease in the adequate sleeping time. According to recent research, long-term circadian disruptions are associated with many pathological conditions such as premature mortality, obesity, impaired glucose tolerance, diabetes, psychiatric disorders, anxiety, depression, and cancer progression, whereas short-term disruptions are associated with impaired wellness, fatigue, and loss of concentration. In this review, the circadian rhythm in metabolic processes and their effect on energy balance were examined. ***Key Messages:*** Circadian rhythm has a bidirectional interaction with almost all metabolic processes. Therefore, understanding the main reason affecting the circadian clock and creating treatment guidelines using circadian rhythm may increase the success of disease treatment. Chronopharmacology, chrononutrition, and chrono-exercise are the novel treatment approaches in metabolic balance.

Introduction

The term circadian is derived from two Latin words, circa (approximate) and dies (day), denoting approximately "one day" [1]. Circadian rhythm is also called the biological/circadian clock [2] and refers to behavioral, physiological, and molecular changes with a cycle length of approximately 24 h [3]. The circadian clock can be divided into 2 parts: the central clock, residing in the suprachiasmatic nucleus (SCN) of the hypothalamus, which receives light cues, and the peripheral clocks residing in various tissues throughout the body. The peripheral clocks play an integral and unique role in each of their respective tissues, driving the circadian expression of specific genes involved in a variety of physiological functions [4].

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The main stimulus for the SCN is light [5]. However, blind individuals have circadian cycles (e.g., sleep-wake cycles) and this cycle lasts longer than 24 h. This finding led to the idea that other stimuli, in addition to light, can act as a stimulus for the human biological clock [6]. A review study found temperature, hormones, nutrients, distribution of nutrients, some nutrients (alone; e.g., glucose, amino acids, ethanol, and retinoic acid), feeding/fasting state, sleep-wake state, physical activity to be effective stimuli for the circadian cycle in various peripheral pathways [5]. Interestingly, it was reported that there were variations in the effects of the circadian rhythm in men versus women [7].

Mainly, the sleep-wake cycle regulates the circadian rhythm. However, in the modern world, the increase in activities that operate 24/7 and the common usage of television, internet, and mobile phones almost 24 h a day leads to a gradual decrease in adequate sleeping time [8]. An epidemiological study reported that the duration of overnight sleep decreased by 18 min during the last 30 years [9]. The deterioration of the sleep-wake cycle, especially in healthy individuals, can be the main cause of many diseases such as premature mortality, obesity, impaired glucose tolerance, diabetes, psychiatric disorders, anxiety, depression, and cancer progression, fatigue, and loss of concentration [10, 11]. Another epidemiological study showed that working at least 3 nights per month for 15 or more years could increase the risk of colorectal cancer in women [12]. In rats, circadian syncope disruption accelerates the development of diabetes by causing function and mass loss in beta cells [13]. In an experimental study, circadian rhythm disorder caused cardiovascular and renal damage in hamsters [14]. In a study conducted with schizophrenic patients, participants had severe circadian sleep-wake disorders although their mood, mental status, and psychotic episodes were stable [15]. In this review, the role of circadian rhythm in metabolic processes and the bidirectional effects of circadian rhythm on energy balance were examined. In accordance with this purpose, studies which were published from 2000 to 2018 were reviewed. In addition, 3 significant articles which were published in 1984, 1993, and 1996 were also added. Basically, Google Academic (bibliographic database), PubMed, Scopus, Web of Science, and Science Direct databases were used to scan scientific articles. Besides, resources in Gazi University Central Library were also scanned. The terms such as "circadian clock or circadian rhythm" or "biological clock" and "hormones or metabolism or energy balance or energy expenditure or thermogenesis, metabolic homeostasis or metabolic regulation or clock genes or dietary composition, meal patterns or meal time or physical activity or exercise or sports" were used as keywords. At the end of this scanning, 4,456 articles were found. After screening titles and abstracts, duplicate articles and articles that were not published in English were excluded. The final count of articles was 82, which consisted of articles that were free and available in the form of full text. In addition, the book chapters were also used to examine the subject.

Circadian Synchronization in Metabolic Homeostasis

Many studies explain the relationship between human physiology, certain diseases, and circadian rhythm [12–15]. Metabolic homeostasis is an essential component that regulates energy metabolism, especially in adipose tissue. The adipose tissue is a central metabolic organ that regulates the whole-body energy homeostasis. The white adipose tissue functions as a key energy reservoir for other organs, whereas the brown adipose tissue accumulates lipids for cold-induced adaptive thermogenesis. Adipose tissues secrete various hormones, cytokines, and metabolites (termed as adipokines) that control systemic energy balance by regulating appetitive signals from the central nervous system as well as the metabolic activity in peripheral tissues [16]. For example, leptin has specific receptors on the hypothalamus and is released from the main adipocytes. This hormone plays a regulatory role in energy metabolism by increasing the activation of the sympathetic nervous system and increasing thermogenesis by increasing thyroid hormones. In thermogenesis, UCP (uncoupling) protein inhibits ATP synthesis in mitochondria, allowing energy to be consumed as heat. Leptin increases the level of thyroid hormones and activation of the sympathetic central nervous system, resulting in more UCP formation and thus greater energy use [17]. The release of leptin hormone occurs in a circadian cycle and serum leptin levels peak at night [18]. Thus, disruption of circadian balance can affect leptin secretion, thermogenesis, and energy homeostasis, indirectly.

On the contrary, some hormones released from the hypothalamus show more activity at night. The most striking example of this is the "growth hormone." The levels of growth hormone peak between 2:00 and 4:00 a.m. If the crosstalk between circadian rhythm and growth hormone is disrupted via sleep disorders, growth hormone cannot be released at normal levels. Therefore, it is necessary to pay particular attention to the sleep patterns of children [19].

Cortisol is a steroidal hormone secreted from the adrenal glands. It regulates many metabolic processes such as glycogenolysis, lipolysis, and proteolysis [20]. The amount and frequency of cortisol secretion is regulated via the circadian rhythm. The cortisol concentration in circulation reaches a peak level just before waking in the morning. The cortisol gradually declines throughout the day. It reaches its lowest level during sleep after midnight [21]. Cortisol is a major hormone that regulates the metabolic events in the body. It increases the use of cortisol, glucose, free fatty acids, and amino acids from endogenous fuel stores. Therefore, high levels of cortisol function as a catabolic hormone that reduces lean body and muscle mass, and increases energy consumption [22]. In addition, glucose tolerance and insulin secretion vary throughout the day. In the natural course of metabolism, both insulin sensitivity and insulin secretion decrease at night (especially between 3:00 and 5:00 a.m.) in comparison to morning hours. This metabolic process, the dawn phenomenon, highlights the impact of circadian control on glucose metabolism [23]. In the natural physiological processes of the body, hormones working as antagonists of insulin (especially growth hormone) exhibit hyperinsulinemic activity because of the decrease in insulin secretion between 3:00 and 5:00 a.m., so that blood sugar levels return to normal. This is counteracted with additional physiologic insulin secretion in non-diabetic or non-insulin-dependent individuals. Conversely, when insulin release is disturbed, the effect of growth hormone released during the night, especially in diabetic patients, may not be mitigated. This results in a pathologic circadian rhythm, which can lead to morning hyperglycemia independent of eating patterns [24].

Melatonin is an important hormone in circadian synchronization. This hormone is involved in many biological and physiological regulations in the body. It is an effective hormone for human biorhythm (circadian rhythm). The main role of this hormone is to maintain the biological clock and to adjust the body rhythm [25]. Synthesis and release of melatonin is stimulated in the dark, at night, while it is suppressed by light during the day [1]. Especially between 11:00 p.m. and 5:00 a.m., melatonin secretion peaks and its blood concentration increases 3–10 fold [25]. However, exposure to light at night causes the plasma melatonin levels to fall [1].

Lipid metabolism is also affected by circadian oscillations. Studies show that many proteins related to lipid metabolism (e.g., ApoB, ApoA1, and ApoA4), intestinal microsomal triglyceride transport protein, and intestinal fatty acid binding protein show changes throughout the day [26–28]. In addition, mice studies show that cholesterol and lipid absorption in the dark phase are higher than in the light phase [28]. Some lipid metabolism products exhibit a circadian rhythm as well. For example, circulating non-esterified fatty acids in humans are higher at night due to an increased lipolytic activity [29]. In addition, myocardial infarction episodes and asthma are associated with the circadian cycle of metabolism. These attacks peak at night or early in the morning [30, 31]. In the early hours of the morning, the cardiovascular system improves in response to the activation of sympathetic nerve activity, and in the evening hours, blood pressure and heart rate peak. Cardiac attacks, particularly early in the morning or in the evening, can be caused by this diurnal rhythm of the cardiovascular system. The diurnal rhythm of hormones and some metabolic processes are shown in Figure 1.

Metabolic Regulation of Circadian Rhythms

In mammals, circadian rhythms are controlled mainly by SCN, which are called the master clock. Suprachiasmatic nuclei consist of multiple, single-celled circadian oscillators located at the anterior hypothalamus region of the brain and produce coordinated circadian signals when synchronized [32]. SCN is activated via a nerve bundle called the "retinohypothalamic tract." In this way, SCN regulates the biological clock in living beings and contributes to physiological processes by stimulating other brain regions [2].

Suprachiasmatic nuclei synapse directly with ventral and dorsal subventricular regions, cell bodies located in ventral and dorsal subventricular areas, and the dorsomedial hypothalamus. Even though these regions interact with one another, neurons located in the dorsal supraventricular region are more effective in regulating thermogenesis, whereas the ventral supraventricular region mainly plays a role in the regulation of sleep-wake and activity cycles. In addition, the paraventricular hypothalamus is responsible for corticosteroid release, whereas the lateral hypothalamus is responsible for nutrition and alertness [33].

Although SCN functions as the basic biological clock of metabolism, studies carried out in the 2000s have shown that autonomic circadian oscillators present in peripheral organs and tissues, such as the liver, intestine, heart, and retina, contribute to metabolic processes via cellular clock genes in these organs/tissues [32, 34, 35]. Suprachiasmatic nuclei have an important role in the reg-

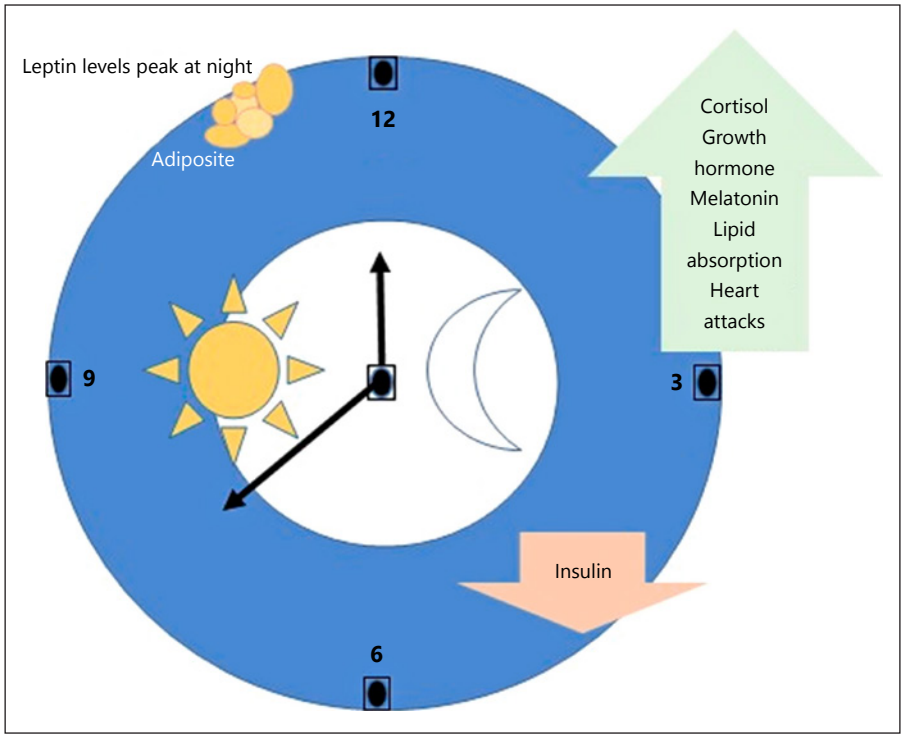

Fig. 1. The diurnal rhythm of hormones and some metabolic processes. The release of leptin hormone occurs in a circadian cycle, and serum leptin levels peak at night. The levels of growth hormone peak between 02:00 and 04:00 a.m. The cortisol concentration in circulation reaches a peak level just before waking in the morning. İnsulin secretion decrease at night (especially between 03:00 and 05:00 a.m.). Synthesis and release of melatonin is stimulated in the dark at night, while it is suppressed by light during the day. Lipid absorption in the dark phase is higher than in the light phase. Myocardial infarction peak at night or early in the morning.

Table 1. Genes of the circadian rhythm and their roles [2]

Gene	Role in circadian rhythm
Per 1	PER/CRY interaction, CLOCK/BMAL1 inhibitor
Per 2	PER/CRY interaction, CLOCK/BMAL1 inhibitor
Per 3	PER/CRY interaction
Cry 1	Interaction with PERs, CLOCK/BMAL1 inhibitor
Cry 2	Interaction with PERs, CLOCK/BMAL1 inhibitor
Tim	Dimerization with PER
CLOCK	Transcription factor
BMAL1	Transcription factor

ulation of glucose metabolism. Insulin sensitivity and glucose uptake are impaired in rats with lesions in their SCN [36]. Deterioration in the circadian clock can lead to impaired insulin secretion and hypoinsulinemia [29]. Circadian rhythm-related CLOCK and BMAL1 proteins are involved in the production and release of insulin by binding to the circadian rhythm-regulating distal regions of pancreatic β-cells [37]. Both Type 1 and 2 diabetes have insulin insufficiency or absence due to β-cell damage. Therefore, the role of circadian rhythm in the etiology of diabetes should not be overlooked in terms of β-cell damage [38]. Clock genes and tasks regulating circadian rhythms in mammals are summarized in Table 1 [2].

In mammals, circadian clock homeostasis is enabled by feedback (negative) and feed-forward (positive) mechanisms influencing transcription, translation, and post-translational events [5, 29]. The transcriptional feedback pattern is mediated through the Cry1, Cry2, Per1, and Per2 proteins. The CLOCK and BMAL1 proteins bind to the E-promoter region on the Per and Cry genes and induce their expression. At a later stage, Per and Cry heterodimerize and translocate from the cytoplasm to the nucleus to inhibit CLOCK/BMAL1-induced gene expression [37, 39]. This negative feedback mechanism is important for the circadian system to work effectively.

Circadian Rhythm and Energy Homeostasis

Energy metabolism is regulated by many hormones, enzymes, and transport systems, and circadian rhythm effectively modulates their expression, secretion, and/or activation [40]. The metabolic pathways that provide energy homeostasis are coordinated by metabolites that propose changes and proactively prepare the molecular environment as well as acute signaling systems that respond instantaneously to changes in circadian clocks [41].

Hormone receptors, interactions between genes, and intracellular oxidation/reduction reactions drive the regulation of energy metabolism at the cellular level. These pathways have important interactions with the biological metabolism clock. The circadian clock can affect the function of hormone receptors (peroxisome proliferator activated receptor [PPAR]α, PPARγ, and REV-ERBα) and some genes at the cellular level (sirtruin) [41, 42].

Nuclear hormone receptors (PPARα, PPARγ, REV-ERBα, RORα, HNF4α, TRα, and NURR1) and ligands present in metabolic tissues function as sensors that combine circadian and metabolic pathways [41]. For example, PPARs are a link between the circadian clock and energy metabolism. PPARγ localizes in adipose tissue and activates transcriptional factors that increase lipogenesis and lipid storage. PPARα from nuclear hormone receptors triggers ketogenesis and hepatic fatty acid oxidation in response to starvation. PPARδ is the most prevalent nuclear cell receptor in the body and is able to correlate daily changes in body temperature with the circadian clock [43].

The rhythmic expression and activation of metabolic pathways are mainly associated with the coordination of clock genes (BMAL1, Per2, Per1, Per3, Cry1, and Cry2) in liver and adipose tissues. There is a link between BMAL1 protein, lipogenic pathways, and cellular clock mechanisms. REV-ERBα (a transcriptional repressor of BMAL1) and RORα (a positive regulator of BMAL1) are nuclear hormone receptors regulating lipogenesis. Moreover, both are modulated by CLOCK: BMAL1. PPARα plays a role in lipid and lipoprotein metabolism. PPARα directly binds to the promoter region of the BMAL1 protein, which regulates the PPARα expression via the CLOCK: BMAL1 heterodimer [44].

Another factor that affects the circadian rhythm function is the sirtuin (SIRT) genes. SIRT family genes are NAD+ dependent class III deacetylase enzymes that affect many cellular functions including human metabolism, aging, cancer, and cell senescence. There are 7 variations of the SIRT family (SIRT 1–7). The regulation of gene expression is the most important mechanism influenced by the SIRT family. SIRT1, SIRT6, and SIRT7 predominantly localize in the cell nucleus, SIRT2 in the cytoplasm, and SIRT3, SIRT4, and SIRT5 in the mitochondria. SIRT1 plays a significant role in the regulation of metabolic processes such as insulin sensitivity, lipid metabolism, and gluconeogenesis, as well as human lifespan [45]. SIRT1 modulates CLOCK: BMAL1 activity and contributes to the circadian cycle. SIRT 3–5 genes regulate intracellular pathways such as fatty acid oxidation, ketogenesis, urea cycle, and oxidative phosphorylation [33].

Intracellular oxidation-reduction (redox) status is an important factor that regulates the clock genes in peripheral tissues. CLOCK proteins can bind effectively only in the presence of reduced NADH and NADPH, BMAL1, and E-box sequences. On the contrary, nicotinamide adenine dinucleotide oxidase forms (NAD+ and NADP+) inhibit the binding of the CLOCK: BMAL1 complex to DNA [32]. Thus, the NAD/NADH redox status of the cell can lead to circadian phase changes by influencing the transcriptional activity of the BMAL1: CLOCK genes [46].

Intracellular NAD+ levels as well as elevated AMP (adenosine monophosphate) levels are indicators of low energy. When intracellular ATP levels are reduced, AMPK (AMP-activating protein kinase) functions as a food sensor and activates intracellular energy supply pathways. Thus, the AMP/ATP ratio may also be a link between circadian rhythm and energy metabolism [47].

Effect of Circadian Rhythm on Energy Balance

The energy produced and stored in metabolism is used to maintain metabolic activities such as basal metabolic rate, physical activity, and thermal effect of foods [48].

Francis G Benedict first described the circadian changes in energy metabolism in 1915 [49]. Furthermore, Haugen et al. [50] found that the resting metabolic rate was 6% higher at noon than in the morning hours. One of the most important factors affecting the basal metabolic rate is the sleep pattern. Sleep and circadian rhythm are the main components of energy metabolism regulation [48, 51]. There are 2 phases of sleep: rapid eye movement (REM) and non-REM [52]. The sympathetic nervous system activity and dreams increase during the REM period. Body temperature, heart rate, respiratory rate, and blood pressure increase during REM. Irregularities in the REM period increase due to the activity of the sympathetic nervous system [53]. Because of the increases in body temperature and energy expenditure in the brain (brain energy consumption during this period is approximately 25%), the metabolic rate during sleep reaches its highest point in the REM phase [54]. Therefore, deterioration of the sleep cycle due to late sleeping, jet lag, shift work, and so on can lead to a decrease in the basal metabolic rate by altering the timing of the REM phase of sleep.

In addition to the basal/resting metabolic rate, physical activity is an important component of total energy ex-

penditure [55]. However, studies emphasize the different metabolic effects of exercise type, duration, and length. For example, a review study highlights that maximal performance in short-term anaerobic exercises occurs late in the afternoon, usually at noon [56], which also corresponds to the peak body temperature [56, 57]. Body temperature is regarded as the "basic variable" of circadian rhythm and is used as a circadian rhythm marker [58]. There is a 0.9 °C difference in body temperature between morning and evening hours [59]. Body temperature affects muscle activity [60]. This difference between the morning and evening hours can affect exercise performance and, indirectly, the basal metabolic rate.

Meal time affects the physical performance. Exercise before or after a meal has different effects on fatty acid oxidation and appetite metabolism [61–63]. However, it is still unclear when (pre-meal/post-meal exercise) is the most effective time to lose weight. An approach to reduce body weight and facilitate fat loss is to perform postprandial aerobic exercise after an overnight fast [64]. Exercise during fasting causes the use of glycogen deposits to increase fat oxidation, and lowers plasma insulin by increasing plasma epinephrine and norepinephrine levels causing lipolysis. On the contrary, some studies focused on the beneficial effects of postprandial exercise on body weight control compared to exercise during fasting because of its positive effects on appetite and resting metabolism [65]. A study found that a 36-min of moderate exercise on a treadmill significantly increased the resting metabolic rate 40 min after eating a Mediterranean-style breakfast in the first 24 h [66]. In many studies, the total energy intake, dietary patterns, physical characteristics, and duration and severity of exercise are not similar, thereby leading to different interpretations of results.

Another component of total energy expenditure is the thermal effect of nutrients. The thermal effect of foods is influenced by the macronutrient composition of the diet. Lipids have the lowest (0–3%) and proteins have the highest (20–30%) thermogenic effect [67]. In addition, meal timing is an important factor affecting the thermal effect of foods. Diet-induced thermogenesis is higher in the morning hours compared to evening and night hours [68]. Similarly, in a study by Morris et al. [69], the thermal effect from food during the morning was 44% higher than in the evening. The reduction in the thermal effect of foods from morning to evening may primarily be due to the effect of the endocrine circadian system on gastrointestinal physiology. Intestinal motility in the morning hours is more effective than in the evening hours. Two studies on healthy adults revealed that the rate of gastric emptying in the morning (8.00 a.m.) was higher than in the evening (8.00–11.00 p.m.) [70]. In addition, circadian rhythm disturbances, such as shift work and jet lag, cause gastrointestinal system disorders such as abdominal pain, bloating, diarrhea, or constipation. These observations reveal a functional correlation between daily rhythms and gastrointestinal physiology. Hoogerwerf et al. [71] showed that PER2 and BMAL1 protein expressions were associated with the circadian rhythm in the myenteric plexus region, which has an important role in the coordination of colon epithelial cells and colon motility.

Effect of Dietary Intake and Physical Activity on Circadian Rhythms

Here, the impact of the circadian rhythm on energy expenditure components and its role in energy balance has been emphasized. However, some studies have shown that some environmental factors (i.e., food, meal composition, feeding time, and exercises) could be effective on peripheral clocks that exist in several parts of the body such as the liver, the pancreas or the heart [72–75]. The peripheral clocks play an integral and unique role in each of their respective tissues, driving the circadian expression of specific genes involved in a variety of physiological functions. The existence of all these clocks working together and synchronized by the central clock, with many hormones and physiological or environmental variables changing during the day, make this bidirectional interaction on circadian system rather complicated [4].

Food is one of the external synchronizers of our peripheral clocks. The primary role of the circadian clock is to entrain the organism to the environmental cues; this allows the organisms to predict food availability. Limiting food access to a particular time of the day has profound effects on the behavior and physiology of the organisms [72]. Damiola et al. [76] showed that temporal feeding restriction under light-dark or dark-dark conditions could change the phase of circadian gene expression in peripheral cell types by up to 12 h, while leaving the phase of cyclic gene expression in the SCN unaffected.

Feeding time has a significant effect on the repertoire, phase, and amplitude of rhythmic gene expression. In a study, it was shown that both temporal pattern of food intake and the circadian clock had an effect on hepatic gene transcription in wild-type mice [73].

The diet composition is another important factor that affects the circadian clock. Kohsaka et al. [74] showed that a high-fat diet in mice led to changes in the period of the

locomotor activity rhythm and alterations in the expression and cycling of canonical circadian clock genes, nuclear receptors that regulate clock transcription factors, and clock-controlled genes involved in fuel utilization in the hypothalamus, liver, and adipose tissue.

One of the notable non-photic cues for regulating the peripheral clock is exercise. It is suggested that physical activity or exercise causes several physiological changes, such as body temperature and hormonal status changes, which are known to affect the peripheral clocks via sympathetic nervous activation and glucocorticoid release [75]. The elevation in body temperature may act as an input to the circadian pacemaker of mammals [77]. In addition, exercise promotes the production and release of melatonin. The beneficial effect of 4 weeks of melatonin treatment to modulate the circadian components of the sleep-wake cycle commonly results in improved sleep quality [78].

On the contrary, molecular circadian clock in peripheral tissues can respond to the time of exercise, suggesting that physical activity provides important timing information for the synchronization of circadian clocks throughout the body. While the exact duration and intensity of exercise required to alter circadian rhythmicity has not been determined, one study in mice found that low-intensity endurance exercise sustained over the course of 2 h per day for 4 weeks was adequate enough to entrain the circadian clock and alter circadian rhythmicity [79].

Generally, when the peripheral clocks are desynchronized from the central clock, it results in chronodisruption [80]. This physiological alteration is related to different illnesses such as cancer, cardiovascular diseases, depression, obesity, and metabolic syndrome [72]. For example, in the treatment of obesity, the basic diet treatment approach is restricted energy intake [81]. Generally, factors that directly affect biological rhythms, such as meal times and sleeping times, are not routinely examined when diets are planned. The circadian clock has an important role in energy homeostasis and metabolic processes. Therefore, the evaluation of factors (shift work, irregular sleep, insomnia, etc.,) that may lead to circadian rhythm disturbances in individuals who have metabolic diseases such as obesity, and the planning of exercise and meal times according to normal biological rhythms (e.g., the choice of protein-containing foods in the morning to increase thermogenesis) can enhance treatment effectiveness.

In recent years, circadian rhythm-depending treatments, nutritional interventions, and exercise approaches have been developed to sustain metabolic health, and these approaches are called "chronopharmacology," "chrononutrition," and "chronoexercise," respectively. Chronopharmacology studies the right timing for the administration of drug doses to increase the efficacy, absorption, and/or efficacy of the drug [65]. For example, the HMG-COA enzyme, a cholesterol-rate limiting enzyme, shows a circadian rhythm in humans. This enzyme peaks at night, so it is recommended to take cholesterol-lowering drugs such as statins at night to maximize their effectiveness [19]. Chrononutrition is an approach to determine the optimal nutrient uptake to maintain health and regulate circadian rhythm [82]. For example, caffeine, nobiletin (a flavonoid present in citrus fruits), and resveratrol in foods may cause circadian rhythm changes at molecular or behavioral levels [83]. Chronoexercise primarily investigates the effect of the length of exercise on the maintenance of health and athletic performance, rapid changes in the internal clock system, or re-regulation of the circadian clock [84].

As a result, circadian rhythm has a bidirectional interaction with almost all metabolic processes and is a primary factor affecting the sleep-wake cycle. Therefore, questioning and utilizing sleep pattern, quality information, and creating treatment guidelines using circadian rhythm may increase the success of disease treatment. For this reason, novel approaches, perspectives, and treatment strategies in metabolic balance could be developed.

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Statement of Ethics

This article does not contain any studies with human participants or animals carried out by any of the authors.

Disclosure Statement

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Author Contributions

Y.S. conducted the literature review and N.A.T. organized and drafted of the manuscript. All authors have read and approved the final manuscript.

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