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ახალგაზრდა მკვლევარები

Vol. 4 Issue 2, 2026

https://doi.org/10.52340/jr.2026.04.02.16



FROM CIRCADIAN MISALIGNMENT TO METABOLIC DISEASE: THE ROLE OF HYPOTHALAMIC-PITUITARY-ADRENAL AXIS HYPERREACTIVITY IN PERIPHERAL INSULIN RESISTANCE AND HEPATIC STEATOSIS - A NARRATIVE REVIEW

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Abstract

Background: Circadian rhythms are essential for maintaining metabolic homeostasis by regulating a number of metabolic processes, including energy balance, glucose metabolism, and endocrine function. Shift work, non-rational work habits, and exposure to artificial light can disrupt activity of the hypothalamic-pituitary-adrenal (HPA) axis, which may result in metabolic dysfunction. This review examines the connection between circadian disruption, HPA axis dysfunction, peripheral insulin resistance and metabolic dysfunction-associated steatotic liver disease (MASLD).

Methods: The English language, open access literature from October 2018 to August 2026 was reviewed. PubMed, Google Scholar, Scopus and the National Center for Biotechnology Information (NCBI) were used to search for the individual keywords and Boolean combinations of circadian rhythms, HPA axis, insulin resistance, type 2 diabetes, and hepatic steatosis. Relevance of articles was selected based on their title and abstract. Data were integrated based on the biological processes and physiological pathways.

Results: Preclinical and clinical data indicate that circadian misalignment causes a miscoordination between central and peripheral clocks, affects the regulation of the HPA axis, and influences cortisol. Chronic glucocorticoid elevation can lead to insulin signalling abnormalities, such as IRS-1/PI3K pathway dysfunction and decreased GLUT4 glucose uptake. At the same time, insulin resistance may be worsened by an impaired response of glucocorticoids and activation of inflammatory pathways. Disrupted clock expression in the liver impacts lipid metabolism by regulating fatty acid oxidation (PPARα) and lipogenesis (SREBP-1c) along with altered cortisol signalling. These alterations could allow for an increase in free fatty acid availability, accumulation of fat in the liver and progression of MASLD.

Conclusion: Circadian disruption and HPA axis dysfunction are some of the interconnected mechanisms that can be involved in insulin resistance and MASLD. But there were a number of methodological differences among studies and the confounding effects of sleep deprivation, stress, and circadian misalignment make it difficult to interpret the results as causal. More mechanistic and longitudinal investigations are required to fully elucidate these connections and determine the effectiveness of intervention using circadian rhythm for prevention of metabolic disease.

Keywords: Circadian disruption, HPA axis, Insulin resistance, MASLD, Hepatic steatosis, Metabolic disorders.

Introduction

Metabolism is a vital part of life; it is a series of reactions that provide cells with the necessary energy needed to carry out everyday function (1). Metabolic disorders are a group of disorders characterized by impaired body metabolism leading to various complications with increased morbidity and mortality (2). In recent years, there has been an increasing prevalence of metabolic disorders (3). Type 2 Diabetes and Metabolic Dysfunction-Associated Steatosis Liver Disease (MASLD) are two common metabolic disorders with a prevalent global burden (4) contributing to a wide range of significant complications, ranging from cellular damage to chronic, life-threatening organ failure (5,2). These disorders share identical upstream mechanisms, such as insulin resistance, chronic low-grade inflammation, and adipose tissue dysfunction. Targeting upstream mechanisms can halt multiple disorders simultaneously, whereas targeting downstream mechanisms treats each organ as an individual entity (4). To understand the shared upstream mechanisms, it is crucial to examine the key regulator of human physiology: the circadian rhythm.

The circadian rhythm is an intrinsic, 24-hour system organized hierarchically to regulate physiological processes. The central pacemaker, located in the suprachiasmatic nucleus (SCN) coordinates functions such as glucose metabolism, endocrine regulation, and mitochondrial energy metabolism through peripheral clocks in individual organs and the hypothalamic-pituitary-adrenal (HPA) axis (6–8). At the molecular level, these clocks are governed by core clock genes operating via transcription-translation feedback loops. For instance, the core clock gene BMAL1 (brain and muscle ARNT-like protein 1) modulates insulin secretion by pancreatic beta cells (9), illustrating the direct influence of circadian mechanisms on metabolic homeostasis. Circadian clocks adapt to social and environmental cues, known as zeitgebers, to maintain physiological equilibrium (8).

The HPA axis is a neuroendocrine network that plays a crucial role in regulating the circadian rhythm by adapting to stress while maintaining the body's homeostasis (7). Central to this function is the regulated release of cortisol, the primary glucocorticoid controlled by the HPA axis, which follows a diurnal rhythm, peaking throughout the regular sleep-wake cycle and progressively declining, reaching its lowest concentration in the late evening or early night. Under normal conditions, cortisol works in conjunction with peripheral clocks to regulate hepatic gluconeogenesis and lipid utilisation

(10). However, chronic circadian disruption of the HPA axis decreases the organism's capacity to cope with stress leading to impaired neuroendocrine regulation (7).

In modern everyday life, lifestyle habits such as shift work, chronic sleep disruption, and artificial light exposure induce circadian misalignment. The circadian misalignment affects key metabolic pathways, including insulin secretion, hepatic glucose production, and overall energy, increasing susceptibility to obesity, insulin resistance, and cardiometabolic disorders (6). Furthermore, chronic circadian disruption can lead to a wide range of complications, including neurological, psychological, metabolic, and cardiovascular complications, and also increases the risk of mortality of the organism (11). Similar endocrine and metabolic disturbances are also observed in extreme operational conditions, such as human spaceflight. Based on recent studies regarding space exposome factors such as altered gravity, space radiation, and hostile and confined environments lead to profound cardiometabolic shifts, including insulin resistance and altered homeostasis (12). These extreme environments serve as a valuable physiological model for studying how systemic stress and chronodisruption lead to endocrine dysregulation, offering broader insight into metabolic disorders.

Despite these observations, a significant knowledge gap exists regarding the exact interplay between circadian disruption, subsequent HPA axis hyperreactivity, and their cumulative progression toward peripheral insulin resistance and hepatic steatosis (13).

This review aims to highlight how upstream mechanisms, particularly circadian disruption and HPA axis dysfunction, contribute to metabolic disorders like Type 2 Diabetes and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD).

Methodology

This paper is structured as a narrative review, presenting a non-systematic revision of current literature on the topic concerning the effects of circadian disruption on HPA axis and its metabolic consequences, specifically peripheral insulin resistance and hepatic steatosis. To construct this review, each author independently identified, evaluated and reviewed key academic literature published between October 2018 and August 2026.

To maintain the consistency and accessibility, specific inclusion criteria were established during the selection process. Only journal articles published in the English language and available via open-access platforms were considered for inclusion. Articles were screened by title and abstract to make sure they were relevant to the research topic. Individual search keywords as well as Boolean combinations of relevant terms were used for the literature searches. Following search terms included: circadian, hypothalamic-pituitary-adrenal axis, HPA axis, insulin resistance, diabetes, hepatic steatosis, fatty liver disease, metabolic disorder. Literature searches were done across major electronic databases, including PubMed, Google Scholar, Scopus, National Center for Biotechnology Information (NCBI) and more.

In this review, a narrative synthesis approach was adopted. The authors organized the literature by biological mechanisms and physiological pathways rather than chronological order of publication. By using the framework, this review provides an overview of how circadian disruption alters normal HPA

axis regulation. Consequently, these changes lead to systemic metabolic disturbances, focusing primarily on pathophysiological mechanisms of insulin resistance and hepatic steatosis.

Discussion

Circadian System and Metabolic Homeostasis

The mammalian circadian rhythm is a 24-hour endogenous cycle that is organized hierarchically to synchronize everyday physiological functions with the external solar cycle. At its core is the central pacemaker, located within the SCN in the hypothalamus. It receives signals from the retina, which then synchronizes peripheral clocks in metabolically active tissues, such as the brain, lungs, liver, and pancreas, through neural and hormonal signals (14). Other cues, such as feeding, temperature, and glucocorticoids, can also modulate these peripheral clocks independently (15,6). At the molecular level, these clocks are driven by transcription-translation feedback loops (TTFLs). The positive arm consists of the core transcriptional activators CLOCK (circadian locomotor output cycles kaput) and BMAL1(brain and muscle ARNT-like protein 1), which heterodimerize and bind to E-box sequences to activate transcription of the target clock genes PER (period) and CRY (cryptochrome). The negative arm consists of PER and CRY proteins that form a repressive complex with CK1 (casein kinase 1) and repress the CLOCK-BMAL1 complex, thereby maintaining a 24-hour oscillation (16).

Beyond maintaining the molecular feedback loops, the circadian system also controls the rhythmic secretion of key endocrine hormones, which oscillate throughout the 24-hour cycle, such as melatonin, insulin, cortisol, and growth hormone. Melatonin, also known as the hormone of darkness, is secreted by the pineal gland and regulated by the light-dark cycle. It peaks during the night and declines when exposed to light to facilitate wakefulness (17). Whereas cortisol peaks right before waking up, and the lowest levels are present during the initial phase of sleep (18). Growth hormone is regulated by the SCN and sleep stages, exhibiting a pulsatile surge during the early phase slow wave sleep (19,20). Finally, insulin is secreted by the pancreas in response to elevated glucose after a meal. It is regulated both by the SCN following a diurnal pattern and by peripheral clocks influenced by feeding patterns to maintain the glucose levels (21).

The liver, skeletal muscle, adipose tissue, and pancreas maintain glucose and lipid homeostasis through continuous physiological crosstalk. In response to elevated blood glucose, pancreatic beta cells secrete insulin, which promotes glucose storage and utilization in peripheral tissues to match the whole body's metabolic demands. Specific tissue transporters mediate this action, GLUT2 in the liver and GLUT4 in the skeletal muscle and adipose tissue. Simultaneously, the liver regulates glucose production and lipid metabolism, while circulating triglycerides are hydrolyzed within the adipose and muscular tissue capillaries by lipoprotein lipase. This interorgan coordination is further maintained by substrate cycles such as the Cori and Cahill cycles (22).

To achieve metabolic homeostasis, it is important to synchronize feeding behaviour, sleep-wake cycles, and endocrine signalling. The circadian clock has evolved to process nutrients most efficiently during the optimal times when an organism is awake and active (14). This temporal coordination ensures that

core metabolic processes, such as glucose and lipid homeostasis and energy expenditure, are tightly regulated by internal feedback mechanisms to match environmental demands (6). When this alignment is stable, there is better anticipation of the circadian rhythm. However, disruptions such as those individuals exposed to prolonged alterations in the light-dark cycle, like shift workers, severely challenge these tightly regulated mechanisms, leading to circadian misalignment and increased predisposition to metabolic disorders (23).

Circadian Misalignment as a Driver of Endocrine Dysfunction

Due to the modern lifestyle and demanding social schedules, circadian disruption has increased across various populations. The primary causes can be broadly categorized into external factors and internal factors. External factors typically involved misalignment between light exposure, social or occupational stress, behavioral patterns such as eating and sleeping habits and the circadian clock located in SCN or other body tissues (11). While internal factors include misalignment between SCN and the peripheral clocks throughout the body {Updating}. Whether the underlying causes are external or internal, the fundamental mechanism of circadian disruption is due to desynchronization between the central pacemaker (SCN) and peripheral metabolic clocks. While SCN controls circadian rhythm mainly based on 24-hour solar cycle, receiving light signals via the retinal pathways, the peripheral clocks in metabolic organs such as liver, pancreas, and skeletal muscle are heavily influenced by food intake, nutrient availability and physical activity (24,8). Which means behaviors such as nocturnal eating could lead to severe internal desynchronisation, as peripheral metabolic organs adjust to food intake while the SCN remains aligned with the external light-dark-cycle (25).

To investigate whether restricting food intake during daytime hours can influence this internal desynchronization and prevent the onset of glucose intolerance (26), conducted a controlled human laboratory trial. In this study, night-worker participants were divided into two eating schedules. The group that restricted their food consumption strictly to daytime hours despite staying awake and working during night showed preserved central-peripheral clock synchronization. Furthermore, their endogenous rhythm of glucose and insulin remained aligned with core body temperature, resulting in stable postprandial glucose level with no impairment in glucose intolerance and no drop in β-cell responsiveness. In contrast, the group that consumed meals during nighttime work hours developed severe central-peripheral clock desynchronization, along with significant decline in glucose intolerance.

The physiological consequences of circadian disruption manifest directly through marked impairments in glucose regulation, insulin sensitivity, and lipid metabolism (27) When individuals engage in irregular behaviors that conflict with their normal circadian cycle (nighttime eating, shift work, late light exposure, irregular sleep), central-peripheral clock misalignment occurs. At the cellular level, this misalignment blunts the first-phase of insulin secretion from pancreatic β-cells and reduces the translocation of GLUT4 in skeletal muscle tissue (28). Together, these cellular disruptions reduce overall insulin sensitivity, impaired glucose tolerance and lead to elevated postprandial blood glucose concentrations. Additionally, circadian misalignment contributes to lipid dysregulation, characterized

by increased levels of plasma triglycerides. It also suppresses leptin production, a hormone responsible for signaling satiety, which subsequently increases appetite and promotes overeating. Consequently, chronic metabolic misalignment significantly contributes to the development of obesity, type 2 diabetes and cardiovascular diseases (27).

These metabolic impairments affect directly in increasing risk of diseases across multiple populations that are experiencing frequent circadian disruption. A clinical Cohort review analyzing data from multi hospitals across several countries demonstrated that shift workers in healthcare have significantly higher overall risks of developing metabolic and cardiovascular conditions compared to day workers. Specifically, shift workers exhibited a 9% higher risk of developing type 2 diabetes, a 17% increase in overall cardiovascular morbidity and a 20% increase in cardiovascular mortality (29). Additionally, another Cohort study that evaluated the same 1,211 male workers in four years from three South Korean manufacturing companies revealed that night shift workers had a significantly higher risk of developing metabolic syndrome compared to their day-shift coworkers (30). Collectively, these findings highlight the critical role of circadian alignment in maintaining long-term metabolic health and reducing chronic disease susceptibility.

HPA Axis Hyperreactivity in Circadian Disruption

The hypothalamic-pituitary-adrenal (HPA) axis is a major neuroendocrine feedback loop for homeostasis and stress responses. It includes cascades and feedback systems involving Corticotropin-Releasing Hormone (CRH) and Arginine Vasopressin (AVP) released from hypothalamic parvocellular neurons that stimulate the anterior pituitary to release adrenocorticotropic hormone (ACTH) (31,32). ACTH stimulates the adrenal cortex to produce glucocorticoids (cortisol in humans, corticosterone in rodents). Glucocorticoids negatively feedback to the pituitary and higher areas of the brain, regulated by mineralocorticoid receptors (MRs) for basal homeostasis and glucocorticoid receptors during stress to regulate further hormonal production, (31). The suprachiasmatic nucleus (SCN) is the central pacemaker that synchronizes the hypothalamic-pituitary-adrenal (HPA) axis with a 24-hour circadian rhythm, (31,32). In diurnal organisms such as humans, the levels of cortisol are lowest during early sleep and start to increase during late sleep, reaching the peak in the morning to prepare the body for daily activities, (31). The cortisol awakening response (CAR) is a 50-100% rise in cortisol in the first 30 to 45 min after waking, preparing the central nervous system for daily stressors mediated by SCN-adrenal projections. Furthermore, every 20 to 120 minutes ultradian pulses driven by pituitary-adrenal feedback are superimposed on the circadian rhythm. There are two ways of managing stress reactions in organisms, which are predictive homeostasis that helps to optimize the allocation of resources in anticipation of environmental alterations and reactive homeostasis (allostasis) that responds to stress. During acute stress, the central stress system is activated instantly, causing cortisol synthesis in under thirty minutes, (31,32). The hormone makes the individual feel more alert and increases the allocation of energy to important matters at the expense of unnecessary actions (31).

When the internal physiological clock mismatches with an external schedule because of elements such as shift work and poor sleeping habits, it is referred to as circadian misalignment. The eating schedule

and autonomic tone stimulate peripheral clocks in the liver and stomach organs while light-dark changes affect the signaling mechanism of SCN causing "phase misalignment" (31). "Circadian misalignment chronically results in improper activation of HPA axis and inhibits the brain from regulating CRH/ACTH secretion due to exposure to glucocorticoids hence causing glucocorticoid resistance. When there is chronic stress or circadian misalignment, there are abnormal cortisol levels especially the reduced morning rise in cortisol levels related to Cortisol Awakening Response (CAR), (31,32). There will be high evening cortisol levels contrary to the normal fall during late afternoons caused by disturbed circadian rhythms. The high evening cortisol levels stimulate Corticotropin-Releasing Hormone (CRH), inhibiting slow-wave sleep and leading to insomnia (32). The lack of fall in cortisol at night causes fragmented sleep and increased pro-inflammatory cytokines causing excessive daytime sleepiness and inflammation. Accordingly, the lack of the normal cortisol rhythm is associated with insulin resistance, metabolic syndrome, and cardiovascular load (31). The main stress reaction system consists of the HPA axis and Sympathetic Nervous System (SNS) that work in parallel (31,32). The LC/NE system gets stimulated by CRH-producing cells of the PVN of the hypothalamus, forming the positive feedback loop, thus enhancing alertness through excitation via excitatory input to the PVN. The SNS is directly innervated by the adrenal cortex and controls ACTH hormone production, where sympathetic input alters the responsiveness of adrenal functions during the day (31). Catecholamines like epinephrine and norepinephrine initiate fast "fight or flight" response, while glucocorticoids facilitate the process via increasing adrenergic receptors activity and fueling metabolism. Overexcitability of SNS may be caused by shift work or night time awakening leading to continuous release of glucocorticoids from the adrenal gland and increase in the evening cortisol levels, aggravating hypertension (32).

Persisting activation of innate immune mechanisms causes chronic mild systemic inflammation termed "metaflammation". This state is characterized by increased levels of pro-inflammatory cytokines such as IL-6 and TNF-alpha in the absence of any symptoms of infections (31). There is evidence of a reciprocal connection between sleep deprivation and the neuroendocrine disturbance associated with the HPA axis and the sympathetic nervous system (33). Long periods of waking up trigger these systems as stressors and change the sensitivity of the receptors. Chronic elevation of cortisol can lead to the down-regulation of glucocorticoid receptors in immune cells which causes the insensitivity to cortisol's anti-inflammatory effects, (31,32). Moreover, sleep deprivation enhances the activation of NF-kB transcription factors in immune cells and leads to increased pro-inflammatory markers causing a disturbance of NREM sleep architecture and further circadian strain (32). The results of the meta-analysis carried out by Dressle et al. (2022) show that patients with chronic insomnia have abnormal diurnal cortisol rhythm including high evening cortisol levels and non-classical cortisol awakening response. This indicates poor regulation of the circadian rhythm of the HPA axis, resulting in hyper-arousal as a consequence of persistent disruption of sleep. The study also observes that circadian misalignment can be seen in shift work, long distance flights and space travel. Chronic desynchronization of peripheral clocks and central pacemakers is experienced by pilots and cabin crew during long-term flights due to crossing time zones (34). Clinically, it has been observed that there is an abnormal pattern of cortisol secretion and inflammation associated with cognitive exhaustion.

During the spaceflights in the environment of ISS, where the light cycle of 24 hours is absent along with alterations in gravity, neuroendocrine stress occurs with disruption in cortisol rhythms and high inflammatory cytokines (34). The sleep pattern is adversely impacted due to cortisol disruption and immune malfunction along with psychological impairment (32).

Table 1. Effects of Circadian Disruption on HPA Axis Function and Its Associated Metabolic and Clinical Consequences

Biological Pathway / Target	Primary Dysregulation under Circadian Disruption	Clinical & Metabolic Outcomes	Citations
Diurnal Cortisol Curve and CAR	Flattening of the curve of the 24-hour circadian rhythm, blunted cortisol awakening response, and increased night-time cortisol	Fragmented sleep, loss of slow wave sleep, hyperarousal during night-time and chronic insomnia	(31,34)
Sympathetic Nervous System (SNS)	Positive feedback loop through CRH stimulation in conjunction with LC/NE system resulting in sympatho-excitation	Continuous imbalance between sympatho-vagal activities, high blood pressure and exacerbation of hypertension	(32,34)
Immune and Environmental Stress	Dysregulation of Glucocorticoid Receptors (GR), activation of NF-kB, clock desynchronization in space flight/flight crew	Systemic metaflammation (elevated IL-6, TNF-alpha, CRP) and severe cognitive exhaustion	(34,33)

Mechanisms Linking Cortisol Dysregulation to Peripheral Insulin Resistance

The process of insulin-induced glucose removal from peripheral tissues is mainly regulated by skeletal muscles, which have been shown to be negatively affected by high cortisol levels (35). Cortisol is known to block the autophosphorylation of insulin receptors and impairs the subsequent phosphorylation of essential downstream mediators such as Insulin Receptor Substrate-1 (IRS-1) and Phosphoinositide 3-kinase (PI3K). The impairment of this pathway results in decreased efficacy of insulin action on the removal of glucose, causing hyperglycaemia as a result of blocked mechanisms of glucose transporters shuttling to the sarcolemma (35,32). Normally, under non-stressed conditions, insulin stimulates GLUT4 translocation through the phosphorylation of IRS-1 and PI3K/Akt pathway. However, glucocorticoids and stress hormones impair the serine phosphorylation of IRS-1, reducing its tyrosine phosphorylation. Long-term glucocorticoid exposure leads to decreased transcription of GLUT4 genes and, subsequently, GLUT4 proteins. Two enzymes that participate in fat breakdown in adipose tissues are Hormone Sensitive Lipase (HSL) and Adipose Triglyceride Lipase (ATGL), which become activated through the presence of high levels of cortisol in the body along with catecholamines

(sympathetic nervous system activity) (35,36). The rapid rate of triglyceride breakdown results in the release of large amounts of free fatty acids in the bloodstream. Toxic lipids (diacylglycerols and ceramides) are formed because of ectopic deposition of high levels of plasma free fatty acids in the liver and muscles, interfering with the normal signalling of insulin receptors (35).

Transcriptional activation: Two important enzymes of gluconeogenesis in the liver, Phosphoenolpyruvate Carboxykinase (PEPCK) and Glucose-6-Phosphatase (G6Pase), were elevated due to cortisol. The ability of insulin to inhibit the endogenous formation of glucose in the body is inhibited by the synergistic actions of glucocorticoids, glucagon, and sympathetic catecholamines, which increase the breakdown of liver glycogen. The result is an uninhibited secretion of glucose from the liver due to increased supply of gluconeogenic precursors (amino acids, glycerol, FFAs) and signaling changes in the liver directly increasing fasting plasma glucose (35,31). Hyperinsulinemia and progressive pancreatic beta-cell dysfunction occur in three phases: the first phase is characterized by compensatory hyperinsulinemia when the beta-cells of the pancreas increase insulin production to overcome insulin resistance and excessive glucose production due to glucocorticoids. In the second phase, long-term glucotoxicity and lipotoxicity occur due to high blood glucose and FFA concentrations, resulting in oxidative stress and endoplasmic reticulum stress in the beta-cells. Finally, the third phase is characterized by metabolic dysfunction as beta-cell apoptosis (35,32). Excessive activation of the HPA axis and sleep disorders increase the production of TNF-alpha, IL-6, IL-1beta, and CRP, resulting in low-grade inflammation in the body (33,34,36). Although cortisol is anti-inflammatory in acute conditions, chronic increase leads to decreased sensitivity of glucocorticoid receptors on immune cells (33). Such disruption promotes activation of inflammatory kinases such as JNK and IKKbeta, worsening the vicious cycle between metabolic insulin resistance and chronic immune activation (35,36). An excessive generation of Reactive Oxygen Species (ROS) by mitochondria due to high cortisol, hyperlipidemia, and chronic low-grade inflammation causes impairment of mitochondrial electron transport chain and subsequent decreased ATP production, oxidative phosphorylation uncoupling, and mitochondrial membrane potential dissipation (35,36). Therefore, damaged mitochondria cannot properly oxidize fatty acids, and lipotoxic metabolites such as diacylglycerol accumulate and impair insulin signaling (35).

Disturbances in the 24-hour cycle of HPA axis regulation result from chronic sleep deprivation, insomnia, or shift work and affect the relationship between the central suprachiasmatic nucleus (SCN) clock and the clocks of peripheral tissues (31,32). The disturbance is manifested in flat slopes of cortisol over 24 hours, higher evening cortisol concentrations, and changed Cortisol Awakening Response (CAR) in comparison with the normal morning cortisol peak and evening cortisol nadir (34, 33). Modeling systems biology emphasizes the importance of the right timing of cortisol secretion since the signaling of glucocorticoids depends on the moment of its secretion, and high cortisol in normally inactive periods disturbs metabolic processes (31). Phase 1 of the Progressive Pathological Continuum suggests temporary elevation of glucose synthesis and stress response due to acute sleep debt and circadian shift (33). Phase 2 includes persistent fatty acid release from adipose tissue, decreased GLUT4 in muscles, and gluconeogenesis in the liver due to prolonged circadian disruption (36). The final phase

is characterized by persistent low-grade inflammation owing to glucocorticoid receptor desensitization, oxidative stress, and subsequently causing failure of pancreatic beta cells, leading to Type 2 diabetes (32, 35).

Table 2. Effects of Cortisol Dysregulation on Insulin Signalling and Glucose Metabolism

Biological Pathway / Target	Primary Dysregulation under Circadian Disruption	Clinical & Metabolic Outcomes	Citations
Skeletal Muscle Glucose Uptake	Blocked IRS-1/PI3K/Akt phosphorylation and reduced transcription/translocation of GLUT4 transporters	Impaired peripheral glucose clearance and persistent postprandial hyperglycaemia	(35,32)
Adipose Tissue Lipolysis	Cortisol and catecholamines over-excitation of HSL/ATGL leads to free fatty acid overproduction	Insulin resistance due to ectopic lipid accumulation leading to diacylglycerols and ceramides interfering with insulin pathway	(36,35)
Hepatic Glucose Production	Activation of transcription by PEPCK and G6Pase along with glucagon and epinephrine stimulation	Excessive hepatic glucose production by inhibition of gluconeogenesis and glycogenolysis resulting in high fasting plasma glucose levels	(35,31)
Pancreatic beta-Cells & Mitochondria	Development from hyperinsulinemia to glucolipotoxicity/ER stress and mitochondrial ROS accumulation, and beta-cell apoptosis	Progression of beta-cell failure, JNK/IKK\beta inflammatory kinase activation, and development of Type 2 Diabetes	(35,32)

Circadian Misalignment and Hepatic Steatosis

Metabolic dysfunction-associated steatotic liver disease (MASLD) has become the most common chronic liver disease in the world. It occurs due to the excessive accumulation of triglycerides inside the hepatocytes. Due to that the normal metabolic balance becomes disturbed (37). Obesity, taking too many calories and insulin resistance are the main causes of MASLD. However, recent research shows that, when the circadian rhythm is disrupted, it also causes the MASLD (38). The liver contains a peripheral circadian clock which controls the glucose metabolism, lipid synthesis, fatty acid oxidation and overall energy regulation (39). Due to irregular sleep awake patterns, night shift work or eating unusual times, the circadian rhythm gets disrupted and that leads to metabolic disruption. Therefore, the liver cannot metabolize the fat. As a result, the fat starts to build up inside the liver cells and increase the risk of hepatic steatosis (8).

MASLD can develop when the body cannot control sugar and fat properly. Due to that fat accumulating in the liver and that leads to liver cell damage and inflammation. Insulin resistance is an important factor that causes excess fat to accumulate inside liver cells. When adipose tissue becomes resistant to insulin, lipolysis increases. This releases more free fatty acids into the bloodstream, which are then taken up by the liver and can contribute to hepatic steatosis (38). Insulin resistance can also promote hepatic de novo lipogenesis and reduce normal fatty acid oxidation. These changes lead to an imbalance between too much lipid being produced or delivered to the liver, compared with the liver's ability to use or remove it. Therefore, the extra fat mainly triglycerides build up inside the liver cells (39). If this accumulation continues the cellular system and mitochondria become stressed. So, the liver cells become damaged and inflammation can develop. Due to that, simple steatosis can progress to inflammatory liver disease.

The liver contains the peripheral clock which controls the fat and glucose metabolism in day and night. It includes lipid synthesis, fatty acid oxidation and regulation of blood glucose. This biological clock interacts with genes like CLOCK, BMAL1, PER, CRY and REV-ERBα. These genes work together and control genes which are responsible for the metabolism and maintain the metabolic balance (37). These clock genes also control downstream regulators of lipid metabolism. When the circadian rhythm of the liver is disturbed, it increases the activity of the SREBP – 1C and produces more fats and triglycerides. As a result, hepatic steatosis can occur (39). When the biological clock is disturbed the activity of the PPAR is also affected. Due to that fatty acid oxidation is also reduced. As a result, more fat is accumulated in the liver (8).

The circadian rhythm of the HPA axis is important for metabolic regulation because it controls the cortisol secretion. Under the normal conditions, cortisol concentration is high in the early morning to produce energy and then gradually decrease during the evening and night. When the normal biological timing is disturbed for a long time as an example, when sleep is disrupted, work schedules are irregular, the normal pattern of the cortisol can also become disturbed (8). Excess cortisol can promote hepatic gluconeogenesis, decrease insulin sensitivity in peripheral tissues, and stimulate lipolysis in adipose tissue. This increases the free fatty acids coming to the liver (40). When the cortisol signaling is

abnormal more fatty acids reach the liver. Then the liver converts them into triglycerides and stores more fat and causes hepatic steatosis.

When the body's biological clock is disrupted, it leads to insulin resistance, which promotes fat accumulation in the liver and increases the risk of hepatic steatosis. Insulin does not work properly in body fat, more stored fat is broken down and releases more free fatty acids into the blood. After that they reach the liver (38). This increased supply of lipids to the liver, in addition to increased de novo lipogenesis and decreased fatty acid oxidation, promotes triglyceride accumulation within hepatocytes (39). This relationship can develop into a vicious cycle. Excess fat accumulation in the liver can cause lipotoxicity, mitochondrial dysfunction, oxidative stress, and inflammation, which reduce the insulin sensitivity. At the same time the insulin resistance can increase the accumulation of the fat in the liver. As a result, liver fat and insulin resistance can worsen each other and lead to metabolic dysfunction and progression of MASLD.

Transition from steatosis to steatohepatitis and fibrosis hepatic steatosis is typically considered an early stage of MASLD. BUT due to the continued stress and inflammation, the liver becomes inflamed and damaged. This is a more advanced inflammatory stage that is called MASH and after that fibrosis occurs. Over time, lipid accumulation can lead to lipotoxicity which can be associated with mitochondrial dysfunction, increase the production of ROS and activate the inflammatory pathways (38). Due to these modifications the hepatocytes can damage and promote the releasing of pro- inflammatory cytokines as a result chronic inflammation can occur. The prolonged inflammation can activate the hepatic stellate cells and increase production and deposition of extracellular matrix components such as collagen and this can lead to fibrosis over time (41).

Human observational studies increasingly associate prolonged circadian disruption with hepatic steatosis, although the magnitude of this association varies across populations. The study which is done by the Correlation between shift work and non-alcoholic fatty liver disease among male workers in the steel manufacturing company of Korea evaluated 2,511 male steelworkers using abdominal ultrasonography and found that shift workers had higher odds of moderate-to-severe NAFLD than daytime workers, with the risk particularly increased among those exposed to shift work for more than 20 years (42). Similarly, the study which is done by the Night shift work and abnormal liver function is investigated 4,740 male workers and found that night-shift work was associated with abnormal liver function, including elevated serum alanine aminotransferase (ALT) levels, while non-alcoholic fatty liver disease was assessed using liver ultrasonography, providing complementary biomarker and imaging evidence (40). Importantly, the UK Biobank prospective analysis included 281,280 participants and identified 2,555 incident cases of NAFLD over a median follow-up of 12.1 years. Usual or permanent night-shift work was associated with an increased risk of NAFLD, with greater risk observed among individuals with longer and more frequent exposure to night-shift work (43). Similarly, the study which is done by Shift work and non-alcoholic fatty liver disease in young, healthy workers examined 45,149 Korean workers and reported an association between shift work and incident NAFLD among workers in their twenties, particularly among those with poor sleep quality (44).

Table 3. Studies on Shift Work, Circadian Disruption, and Fatty Liver Disease

Effect	Mechanism	Clinical Significance	Citation
Increased hepatic steatosis in shift workers	Prolonged disruption of normal sleep–wake and circadian rhythms may disturb hepatic lipid metabolism and promote triglyceride accumulation.	Shift workers had higher odds of moderate-to-severe NAFLD, with particularly increased risk after more than 20 years of shift-work exposure.	(42)
Abnormal liver biomarker levels	Night-shift work may contribute to metabolic dysfunction and hepatic injury, reflected by increased serum alanine aminotransferase (ALT).	Night-shift workers showed an association with elevated ALT, while ultrasonography provided evidence of fatty liver, linking circadian disruption with both biochemical and structural liver abnormalities.	(45)
Increased risk of incident NAFLD	Repeated and prolonged exposure to night work may produce persistent circadian misalignment, potentially disrupting metabolic regulation and hepatic lipid homeostasis.	In usual or permanent night-shift work was associated with increased risk of developing NAFLD; longer duration and greater frequency of night work were associated with higher risk.	(43)
Increased NAFLD risk in young workers with poor sleep quality	Circadian disruption combined with poor sleep may amplify metabolic disturbances that contribute to hepatic fat accumulation.	Among workers, shift work was associated with incident NAFLD in workers in their twenties, particularly those reporting poor sleep quality.	(44)

Current Evidence: From Circadian Disruption to Metabolic Disease

When the biological clock becomes disturbed the hormones and metabolism can affect and that leads to metabolic disease. Under the normal physiological condition, the central circadian clock which is located in the suprachiasmatic nucleus (SCN) synchronizes the peripheral clocks which are located in the liver, pancreas, adipose tissue and skeletal muscle. These synchronized clocks coordinate the hormone secretion, blood glucose control, and lipid metabolism (37). When the normal daily routines such as sleep, eating are disturbed, the central and the peripheral clock can not synchronize. This can disturb hormone regulation and metabolism (8).

The current evidence suggests that the circadian disruption can cause changes in hormones and metabolism. These changes can contribute to the development of MASLD. Under normal physiological conditions the HPA axis controls the body's cortisol secretion. Cortisol levels are normally highest in the early morning and gradually decrease throughout the day. Circadian misalignment can be caused by sleep deprivation, shift work, irregular eating schedules, and chronic jet lag. As a result, the HPA axis can become overactive and then causes over release of cortisol which leads to prolonged cortisol exposure (8). Excess cortisol promotes hepatic gluconeogenesis, reduces peripheral insulin sensitivity, and stimulates adipose tissue lipolysis, which leads to an increased release of free fatty acids into the blood (39). When too many free fatty acids enter the liver, they can convert it into triglyceride and store them inside the liver cells. This leads to hepatic steatosis.

Evidence from both experimental and clinical studies shows that circadian disruption is associated with metabolic problems. However, the strength of this relationship can differ depending on the people being studied and the study condition. Studies in animals have shown that disturbing the body's biological clock can cause problems with blood sugar, insulin, and fat metabolism which lead to fat accumulation in the liver (Mukherji et al., 2020). Studies in humans have found that people who work shifts, regularly do not get enough sleep, or eat at irregular times have a higher risk of obesity, insulin resistance, and MASLD. This suggests that disturbing the body's biological clock can have important effects on metabolism and health (Daniels et al., 2023). Researchers studied people who have obesity, type 2 diabetes, or MASLD. They found that these people also have disturbed metabolic rhythms and problems with liver function, which is what researchers have seen in experimental studies (8).

Clinical Implications

For the population that is at risk with circadian disruption are the people who have night shifts, that group of people between the central circadian “clock” and daily behaviors, typical in night workers, impairs glucose tolerance, likely due to internal misalignment between central and peripheral circadian rhythm. Restricting meal timing to daytime during simulated night work prevents central-peripheral clock desynchronization and glucose intolerance in which we have to do early screening (26). Clinical framework for early screening of circadian disruption (sleep tracking, continuous glucose monitoring, and cortisol timing) to prevent transition to overt type 2 diabetes and metabolic dysfunction. One key player in this system is adipose tissue, or fat, which stores and releases energy. Changes in how this

tissue works can significantly impact our metabolic health. Adipose tissue is mainly responsible for energy storage alteration in the adipose tissue can cause pathology changes but also include changes in circadian rhythmicity. By the fact that circadian rhythm disturbances were linked to these metabolic disorders (46).

Future Directions

Chronotherapy timing drug delivery to match endogenous circadian rhythms represents a promising therapeutic avenue for metabolic disease. Future randomized controlled trials (RCTs) must systematically evaluate the time-of-day administration of glucocorticoid receptor (GR) antagonists, insulin sensitizers (e.g., metformin), and lipid-modulating agents (46). Synchronizing therapeutic administration with peak peripheral clock sensitivity or dampening nocturnal HPA hyperactivity could optimize drug efficacy while minimizing systemic adverse effects. Traditional laboratory markers of circadian phase such as Dim Light Melatonin Onset or serial 24-hour salivary cortisol collection are labor-intensive and impractical for continuous clinical surveillance. Applying penalized machine learning (PML) and deep learning algorithms to these continuous time-series streams allows for automated, non-invasive circadian phenotyping (47). The bidirectional gut-brain-liver axis is increasingly recognized as a central regulator of metabolic homeostasis. Circadian misalignment alters gut microbial diversity and rhythmic metabolite production, such as short-chain fatty acids (SCFAs) and secondary bile acids. Circadian misalignment alters gut microbial diversity and rhythmic metabolite production, such as short-chain fatty acids (SCFAs) and secondary bile acids (48).

Translocation of gut-derived lipopolysaccharides (LPS) under dysbiosis promotes low-grade systemic inflammation and hepatic Kupffer cell activation, exacerbating steatosis. Future work should examine how microbiome-targeted therapies (synbiotics, postbiotics, microbially-derived small molecules) can mitigate HPA stress hyperreactivity and preserve-hepatic metabolic rhythmicity (48). As AI continues to evolve, its integration into circadian physiology our understanding and management of time-dependent biology. Future research must focus on enhancing the precision, accessibility, and clinical utility of AI-based models for circadian rhythm prediction. One promising direction lies in the development of multi-modal, chronobiology-aware AI systems that incorporate diverse data streams, such as transcriptomic proles, wearable sensor outputs, environmental context, and behavioral patterns, to create holistic models of internal time. These systems could continuously adapt to individuals' changing physiology and lifestyle, enable in real-time feedback.

Strengths and Limitations of Current Evidence

The maintenance of metabolic homeostasis relies on the physiological pulsatility of cortisol, which follows a robust circadian rhythm to prime tissues for anticipated activity and nutrient intake (49). When the central circadian pacemaker in the suprachiasmatic nucleus (SCN) is uncoupled from environmental timing, the HPA axis exhibits phase-shifted or flattened secretory profiles. This disruption in glucocorticoid timing is detrimental; because insulin sensitivity is intrinsically clock-

controlled, aberrant nocturnal elevations in cortisol, a period typically characterized by low glucocorticoid exposure directly antagonize insulin signaling pathways (49).

Finally, a heavy reliance on cross-sectional observational data leaves findings vulnerable to residual lifestyle confounders, while short-term laboratory trials fail to capture the multi-year progression from acute HPA hyperreactivity to chronic conditions like Metabolic Dysfunction-Associated Steatotic Liver Disease (22). Controlled laboratory interventions primarily measure transient disruptions in glycemic control, limiting their capacity to model long-term tissue adaptation, epigenetic remodeling, or sustained metabolic deterioration. "Furthermore, behavioral factors associated with misalignment, such as "social jetlag" and late-night caloric intake, exacerbate this state by sustaining sympathetic outflow and HPA-axis activation This chronic stress response blunts insulin's antilipolytic effects in adipose tissue, leading to an increased flux of non-esterified fatty acids (NEFAs) to the liver.

The integration of chronobiology and endocrinology has shifted metabolic research from static hormone snapshots to dynamic, temporal signaling. Glucocorticoids exhibit ultradian and circadian oscillations, with target-tissue sensitivity gated by local clocks. Circadian misalignment flattens cortisol profiles, overriding peripheral clock control in adipose and hepatic tissues to promote systemic insulin resistance and de novo lipogenesis (49).

Furthermore, the literature frequently conflates pure circadian misalignment with sleep restriction or fragmentation, independent HPA-axis activators (50). Finally, a heavy reliance on cross-sectional observational data leaves findings vulnerable to residual lifestyle confounders, while short-term laboratory trials fail to capture the multi-year progression from acute HPA hyperreactivity to chronic conditions like Metabolic Dysfunction-Associated Steatotic Liver Disease (22).

Conclusion

Modern lifestyle factors such as shift work, irregular sleep, abnormal eating patterns and exposure to artificial light frequently disrupt human circadian rhythms. The central pacemaker in the SCN coordinates endocrine functions throughout the body by staying synchronized with peripheral tissue clocks and external environmental factors. When the circadian cycle is disturbed, the HPA axis becomes dysregulated. This chronic HPA axis impairment alters hormone regulation, ultimately driving systemic metabolic disturbances.

The misalignment of the sleep-wake cycle can cause disruption in cortical rhythm and lead to insulin resistance. Prolonged hypercortisolemia leads to decrease the sensitivity of insulin receptors in the tissues due to dysfunction of IRS-1 and PI3K, causing decreased transcription of GLUT4 and glucose uptake in peripheral tissues. Simultaneously, chronically high cortisol levels cause down-regulation of glucocorticoid receptors on immune cells, resulting in cortisol resistance and decreased anti-inflammatory control. This dysregulation activates inflammatory cascades (such as JNK, IKK-β), worsening insulin insensitivity, creating a loop of chronic inflammation and insulin resistance.

Circadian disruption also plays an important role in pathogenesis and progression of MASLD. The peripheral clock within the liver is regulated mainly by nutrient signals and core clock genes (CLOCK,

BMAL1, PER, CRY, REV-ERBα). Excessive cortisol release by the HPA axis due to irregular circadian cycle also plays a role in developing MASLD. Altogether they work as a system that controls metabolic balance of the liver. Disruption of these factors suppresses PPARα, which gradually destroys healthy lipolysis rhythm, leading to insulin resistance. As a result, lipolysis increases its activity in an uncoordinated way, liberating more free fatty acids into the bloodstream. Simultaneously, elevated SREBP-1c activity leads to acceleration of lipogenesis in the liver, causing more fat building up within the hepatic tissue. Together with systemic insulin resistance, this imbalance between excessive hepatic fat accumulation and reduced lipid clearance causes steatosis. Moreover, the more disrupted day-night pattern is, the more severe liver disease becomes.

Preclinical and clinical evidence confirms that circadian disruption significantly impairs metabolic health, leading to insulin resistance, obesity, and MASLD. Although the strength of these effects varies across study populations and experimental conditions, findings consistently show that irregular sleep and eating patterns disrupt metabolic rhythms and compromise liver function. To mitigate the risks, shift workers should follow a strict daytime eating schedule to help preserve the normal regulation of the HPA axis, maintain balanced glucose and lipid pathways and prevent development of insulin resistance, which leads to diabetes type 2 and hepatic steatosis later on. Additionally. chronotherapy and AI-guided monitoring should also be considered in people with disrupted circadian rhythm to help realign endogenous hormonal cycle without causing further imbalance homeostasis.

Despite these findings, some limitations still remain. The study protocols are varied from animal models to human laboratory setups, making it difficult to apply laboratory results directly to real-world settings. Additionally, studies often blur the line between pure circadian misalignment and the effects of sleep loss or stress response. Finally, short-term trials and observational data makes it challenging to establish a clear cause-effect relation or to observe how short-term stress shifts into acute HPA hyperactivity or long-term conditions like MASLD over time.

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