

# Progress in Diseases Related to the Circadian Clock

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**Abstract.** The intricate set of molecular and cellular activities known as the circadian clock controls a number of physiological processes. These processes are essential for maintaining homeostasis and coordinating biological rhythms with the environment. Recent research has shown that disruption of the circadian clock is related to various diseases, including metabolic disorders, cardiovascular diseases, cancer, and neurological diseases. In particular, research related to metabolic disorders, such as diabetes, has gained significant attention due to the alarming increase in the number of individuals with diabetes worldwide. Since animal models have shown that an interruption of the circadian clock results in decreased glucose tolerance and insulin sensitivity, it is imperative to comprehend the molecular mechanisms underlying the circadian rhythm's role in the metabolism of glucose. By highlighting the importance of the circadian clock in the start of cardiovascular illness, recent research have revealed the biological clock's connection to the regulation of cardiac activity. As a result of the disturbance of the circadian clock being linked to an increased risk of cancer and a poor prognosis in cancer patients, research on the circadian clock has also drawn attention in the context of cancer. A deeper understanding of the molecular processes underlying the circadian rhythm and its role in disease etiology may lead to new treatment strategies and interventions.

**Keywords:** Circadian rhythm, diseases, mechanisms, treatments.

## 1. Introduction

The intricate set of molecular and cellular activities known as the circadian clock controls a number of physiological processes. Both preserving homeostasis and synchronizing biological rhythms with the environment depend on these activities. The disorder of biological clock is related to various diseases. Including metabolic disorders, cardiovascular diseases. Cancer and neurological diseases.

Metabolic illnesses, in particular 24diabetes, are one of the most well-known fields of research pertaining to the circadian clock. Due to decreased insulin secretion or activity, A long-term metabolic condition called diabetes is characterized by high blood glucose values. The dysfunction of  $\beta$ -cells leads to the development of diabetes. Given the alarming increase in the number of individuals with diabetes worldwide, it is crucial to comprehend the underlying causes of this trend. Circadian disruption is one of these elements that has been suggested as a role, with shift work, light pollution, jet lag, and excessive time spent on screens all having the possibility to be involved [1]. Studies using animal models indicate that disruption of the circadian cycle reduces insulin sensitivity and glucose tolerance. Therefore, a deeper comprehension of the molecular processes underlying the circadian rhythm and its function in glucose metabolism may result in new diabetes management strategies.

The biological clock is linked to the control of cardiovascular function in addition to metabolic diseases. The greatest cause of illness and mortality in the globe is cardiovascular disease. Recent research has demonstrated how crucial the circadian clock is in controlling cardiovascular function. For instance, it has been demonstrated that endothelial dysfunction and vascular disease are caused by the disruption of the circadian clock in animal models. Patients with disturbed circadian rhythms were reported to have a higher risk of cardiovascular disease development in a clinical trial [2]. In order to achieve better results, it is crucial to understand the fundamental role played by the circadian system in preserving healthy cardiovascular function as well as in the onset of cardiovascular disease.

Moreover, research on the circadian clock has drawn interest in the field of cancer. Many biological functions, including DNA damage repair, cell division, and apoptosis, discovered to be

controlled by the circadian clock. A poor prognosis for cancer patients and an elevated risk of the disease have been linked to circadian clock disruption. So, better understanding of the circadian clock's molecular mechanics and its function in cancer may result in new therapeutic approaches.

In conclusion, the circadian clock is an important mechanism that controls a number of physiological processes and has been connected to the emergence of certain illnesses. New therapeutic approaches and interventions may result from advances in research into the circadian clock's function in disease etiology. Therefore, the study's objective is to assess the state of the art in understanding diseases like metabolic, cardiovascular, cancer, and neurological conditions that are linked to the circadian clock.

## **2. The disorder of circadian rhythm leads to diabetes**

### **2.1. Introduction of diabetes and circadian rhythm**

The purpose of the study is to investigate the influences of sleep disruption on diabetes [3] and the impact of disrupted circadian rhythms on insulin secretion in isolated pancreatic islets. The islets were stimulated with low and high glucose culture media, and insulin secretion levels were measured. The outcomes indicate that the insulin secretion levels in the OB and OB+CSD groups were higher than those in the C57 and C57+CSD groups after stimulation with either low or high glucose. After high glucose stimulation, the insulin secretion levels in the C57+CSD group and the OB+CSD group were decreased compared to the C57 group and the OB group, respectively. The findings suggest that circadian rhythm disruption can affect insulin secretion in isolated pancreatic islets. Moreover, research has found that obstructive sleep apnea (OSA) and social jet lag, which are both types of sleep circadian rhythm disruption (SCRD), may elevate the danger of type 2 diabetic mellitus (T2DM). Even after adjusting for other risk variables like age and obesity, OSA, which is characterized by increased sleep fragmentation and decreased sleep duration, has been demonstrated to increase the risk of T2DM. Moreover, T2DM development may be significantly influenced by various causes in addition to OSA, a complicated condition linked to chronic inflammation. When sleep-wake cycles are disturbed more frequently on rest days than on workdays, social jet lag—a less severe but more common variant of SCRD—occurs. T2DM is more common in people with social jet lag and a wake time difference between rest days and workdays of more than two hours. Shift employment and the prevalence of insomnia are both on the rise, and SCRD may be a significant risk factor in the growth in T2DM prevalence [4].

### **2.2. Mechanism of diabetes induced by circadian rhythm**

The timing of food consumption can alter the synchronization of the circadian rhythm; whereas the timing of breakfast may be influenced by genetics, the timing of lunch or dinner may be more heavily influenced by the environment. Due to the creation of adipokines by fat tissue—leptin being the first hormone identified—obesity might have further negative consequences on one's health. Leptin levels can drop and ghrelin levels rise as a result of sleep deprivation, making for less restful sleep. The metabolic syndrome can also be brought on by sleep apnea, however treatment can improve health. By preventing insulin release, melatonin, which has two receptors, can control blood sugar levels. By its connections to adipocyte development, gluconeogenesis, insulin production, and fat burning, SIRT1 can indirectly influence the metabolism of fats and carbohydrates. The CLOCK and BMAL1 genes help the body resist the effects of the metabolic syndrome. Hyperphagia, hyperlipidemia, hyperinsulinemic hyperglycemia, and sleep problems can all be caused by CLOCK gene abnormalities. Expression of BMAL1 can inhibit adipogenesis and promote lipogenesis [5].

### **2.3. Treatments of diabetes**

Semaglutide is a type 2 diabetes treatment that increases insulin production while decreasing glucagon release, hence lowering blood sugar levels. Moreover, it suppresses the need to eat, lowers appetite, and lessens a predilection for calorie-dense foods that are high in fat. The drug regularly

showed superior and maintained glucose control and weight loss compared to alternative treatments throughout the SUSTAIN clinical trial program, which included nearly 8000 type 2 diabetes individuals. Semaglutide was discovered to dramatically reduce the incidence of cardiovascular events when compared to a placebo or standard of care in the SUSTAIN 6 investigation, which comprised patients at high danger of cardiovascular disease. The hazard ratio was 0.74, and non-inferiority was implied by a  $P < 0.001$  value. Semaglutide is an effective therapy choice for people with type 2 diabetes because of its advantages for glycemic control, weight loss, and reduced cardiovascular risk. Several countries presently enable the once-weekly treatment of type 2 diabetes [6]. Weight gain can occur concurrently with the onset of type 2 diabetes mellitus (T2DM) and prediabetes in people with a genetic susceptibility. Studies have shown that caloric restriction can reduce T2DM symptoms in a dose-dependent manner, with over 80% of obese T2DM patients achieving remission after losing about 15 kg. Long-term weight loss maintenance, however, could be difficult. As obesity and T2DM are associated with poor brain glucose absorption, which lessens the satiating impact of eating carbohydrates, restricting carbohydrates may help maintain weight loss and maximize metabolic advantages. Together with calorie restriction and weight loss, increasing physical activity and fitness can aid T2DM remission. According to preliminary research, utilizing a precision dietary management technique that stratifies patients according to their baseline glycaemic status should improve dietary recommendations for carbohydrates, lipids, and dietary fiber, boosting weight loss maintenance and glycemic control [7]. It has been found that the 3Mdiet boosts the expression of clock genes, especially BMAL1, which is connected to improved insulin production and glucose metabolism. Also, by enhancing b-cell survival and reproduction, this increase may lessen the need for exogenous insulin therapy by improving b-cells' capacity to produce insulin in response to glucose. The 3Mdiet's reduced daily insulin dosage requirements and shorter duration of hyperglycemia could both be attributed to the upregulation of clock genes. After 12 weeks on the 3Mdiet, there was a 26-unit drop in total daily insulin dosage (TDID), which may be attributable to better b-cell secretory capacity [8].

### **3. The disorder of circadian rhythm leads to cardiovascular function**

#### **3.1. Mechanism of cardiovascular disease induced by circadian rhythm**

The ANS and neurotransmitters such as catecholamines and acetylcholine have a significant immune regulation function, and vagus nerve stimulation can reduce ischemia-reperfusion injury. The SCN may affect lipid metabolism and increase the risk of cardiovascular disease by regulating the ANS abnormally. Additionally, fat cells signal to the central nervous system to regulate glucose homeostasis, which is important for obesity and type 2 diabetes. Circadian rhythm disorder may activate the sympathetic nervous system, inhibit the vagus nerve, and alter the ANS-related immune response and metabolic pathways, promoting ischemic heart disease through the ANS-immune-metabolic mechanism. In summary, the ANS plays a crucial role in the pathogenesis of ischemic heart disease in the context of circadian rhythm disorder, and understanding the mechanisms behind this can lead to new therapeutic strategies [9]. Also, animal studies have shown that disrupting the circadian rhythm through genetic modification or desynchronizing external stimuli can lead to cardiovascular disease, including cardiomyopathy, cardiac fibrosis, systolic dysfunction, and even cardiovascular death. Disrupted environmental cycles can make a disease worse after it has started. The molecular clock and circadian rhythms were first discovered in the 18th century, and significant advancements were made thanks to studies on the fruit fly, *Drosophila*, in the late 1960s. Many studies have been conducted on the mechanism of the clock, its regulatory loops, and the environmental influences that might synchronize the clock because there is a clear correlation between disrupted circadian rhythms and human physiology and disease. Molecular clock disruption can lead to atherosclerosis, insulin resistance, a slowed rhythmicity of blood pressure, a decreased release of neurotransmitters, and vasoactive hormones. By reestablishing synchronization through altering external inputs, cardiac dysfunction in animal models can be prevented. Animals with a severe dilated

cardiomyopathy that shortens life and altered metabolic, histological, and functional abnormalities are seen in Clock-mutant and Bmal1-knockout mice specifically for cardiomyocytes [10].

### **3.2. Treatments of cardiovascular diseases**

SIRT1 is a protein deacetylase that relies on NAD<sup>+</sup> and has protective effects on blood vessels. It enhances vasodilation, prevents inflammation, and suppresses foam cell formation. It also regulates the circadian clock and metabolism of energy through the activation of clock genes and the deacetylation of PER2 to affect transcriptional activity. Monocytes/macrophages, myeloid cells, and endothelial cells may all exhibit inflammatory responses when SIRT1 levels are reduced. SIRT1 and PER2 are inversely correlated, with PER2 adversely controlling SIRT1 transcription [11]. The ingestion of antihypertensive medications at bedtime is found to be more effective in controlling elevated blood pressure (BP) than in the morning. The Hygia Chronotherapy Trial discovered that by focusing on the circadian stage liable for aberrant sleep-time BP and dipping, administering hypertension drugs at bedtime dramatically lowers CVD mortality and morbidity. However, some studies deviate from these conclusions because of flaws in their conception and execution, such as the use of external clock hours and 24-hour ABPM in place of real biological time. Internal biological time is the foundation of the sciences of medical chronobiology, chrono pharmacology, and chronotherapeutics, and this foundation must be respected in practice to produce positive outcomes. Clinical medicine is not new to the idea or practice of chronotherapeutics, and it has demonstrated benefits in the treatment of a number of medical disorders [12].

## **4. The disorder of circadian rhythm leads to cancer**

### **4.1. The relationship between circadian rhythm and breast cancer**

There is mounting evidence that the circadian clock and cancer are strongly correlated on a number of levels. Gene expression has a 24-hour rhythmicity due to the transcription-translation feedback loops (TTFLs) that make up the molecular clock in mammals. The clock-controlled genes (CCGs) and their regulators are expressed as a result of the BMAL1: CLOCK heterodimer in the body, in contrast to the nucleus where PER1/2 and CRY1/2 regulate transcriptional activity. The phosphorylation of these clock proteins by kinases is controlled by the degradation of PER1/2 and CRY1/2, which releases repression in response to BMAL1: CLOCK transcriptional activity. ROR and REV-ERB interact with the BMAL1 promoter's RORE promoter region to control the transcription of BMAL1 [13]. Breast cancer risk is enhanced when circadian rhythms are disrupted, such as through shift employment, according to epidemiological studies. Many cancers, including breast cancer, have been linked to the disruption of circadian rhythms. Findings show that less aggressive breast tumors frequently maintain a functional circadian clock, but more aggressive forms frequently exhibit decreased or erased rhythmic clock gene expression. When the circadian network is disturbed, tumor-suppressing activity may be lost, and cells may become more oncogenic and tumor-permissive. Breast cancer development and poorer prognoses have been linked to clock gene alterations and expression patterns. For instance, while low levels of PER1 and PER2 expression are connected to the onset of breast cancer and worse prognoses, high levels of CLOCK and CRY1 downregulation are associated with the progression of breast cancer stage. Several single-nucleotide polymorphisms and genotypes of CLOCK, CRY1, PER2, and TIMELESS have also been connected in studies on breast cancer chances. Additionally, studies on breast cancer have found that TIMELESS is overexpressed in comparison to healthy breast tissue, and more severe cases of the disease have been linked to hypomethylation of the gene's promoter. Our results demonstrate the importance of maintaining a healthy circadian network and imply that changes to the circadian clock may increase a person's risk of breast cancer [14].

#### **4.2. Mechanism of breast cancers induced by circadian clock**

In reaction to darkness, the pineal gland releases the hormone melatonin, which helps organ systems synchronize for the circadian rhythms dormant phase. Cortisol, on the other hand, peaks in the morning. The time of melatonin production in the evening is currently used as a benchmark for identifying a person's circadian phase. It is believed that melatonin dysregulation has a role in the development of cancer because melatonin affects anaerobic glycolysis, DNA repair, and angiogenesis. Breast cancer models have demonstrated that while higher melatonin inhibits tumor growth, light-induced melatonin suppression results in an increase in blood glucose. Breast cancer models have demonstrated that in women with ER+ (estrogen receptor-positive) breast cancer have associations between tumor growth and the greatest levels of evening melatonin as well as lower nighttime melatonin. Melatonin may also inhibit the manufacture of estrogen by the CRY-interacting protein TIMELESS, which controls the development of breast cancer cells through sphingolipid metabolism.

#### **4.3. The association between liver cancer and circadian rhythm**

Liver cancer is the third most prevalent cause of cancer deaths overall and the second biggest reason for cancer fatalities for men, based on a 2010 study. Moreover, it is a cancer that ranks sixth in the world. The most frequent primary liver cancer, hepatocellular carcinoma (HCC), is frequently linked to chronic hepatitis B or C infection, cirrhosis brought on by alcohol consumption, or aflatoxins. Obesity, fatty liver without alcoholism, and changes in the circadian clock all connected to an expanding number of HCC cases (NAFLD). The hallmark of NAFLD is an excessive accumulation of fat in the liver, which harms it, causes inflammation and regeneration, and then advances to non-alcoholic steatohepatitis (NASH), the stage that occurs before fibrosis and cirrhosis, both of which are risk factors for HCC. Many animal models of circadian disruption, including mice models with knocked-out circadian genes, have been used to show that circadian disturbance has a pro-tumorigenic effect. Alterations in the genetic and epigenetic makeup of the clock genes can also cause cancer in a number of mutant and knockout animal models. Neuronal PAS domain protein 2 (NPAS2), a crucial circadian molecule that is increased in HCC, aids in the survival of cancer cells. Cholestasis and issues with the sympathetic nervous system are brought on by circadian disruption, this then causes the constitutive aldosterone receptor to become active. A CAR that is overexpressed may promote the development of liver tumors, accelerating the transition from NAFLD to NASH and, ultimately, to HCC. Those with irregular sleep patterns, such as night shift workers or those who have sleep dyspnea, which is a risk factor for many metabolic illnesses, including cancer, are more likely to have NAFLD and obesity [15]. These connections have motivated scientists to investigate if cancer and the circadian clock are related in some way through physiological and genetic studies in animal models. Because of the controversial link between the circadian clock and cancer, the idea of using the circadian rhythm being an objective in treatment for cancer is being looked into by experts.

#### **4.4. Treatment of targeting circadian rhythms:**

It is unclear if the presence of clock genes, which control the body's internal circadian rhythms, in breast tumors with various clinical characteristics denotes a lack of rhythmic peaks or a constitutive downregulation of circadian regulators. According to ER, PR, and HER2 status, different alterations in clock gene expression were discovered to correlate with different prognostic patterns, while PER1, PER2, PER3, and CRY2 were found to be linked to extended metastasis-free survival. These modifications could be brought on by molecular adjustments brought on by elements linked to the progression of breast cancer. For instance, nighttime light inhibits nocturnal melatonin signaling, which impacts breast cancer cell proliferation and metabolism and leads to resistance to tamoxifen and chemotherapy. Radiation therapy, which is essential for treating breast cancer, is similarly affected by circadian rhythms. Circadian disruption has an influence on the heart, which is more susceptible to damage during radiation therapy, leading to cardiac dysfunction and increased fibrosis. According to clinical studies, the timing of radiation therapy has an effect on the results, and circadian factors and clock genes control the cell cycle, which affects how the body reacts to radiation therapy.

A promising strategy for enhancing radiation therapy's efficacy in the treatment of breast cancer is chrono radiotherapy, which involves scheduling radiation therapy in accordance with circadian rhythms [14].

#### 4.5. The relationship between circadian rhythms and cancer treatment

Nuclear hormone receptors REV-ERB and REV-ERB, which regulate circadian rhythms, have been found to have high selectivity for a variety of malignancies and low toxicity. Moreover, melatonin therapy has had positive results with hepatocellular cancer (HCC). Moreover, electroacupuncture has been demonstrated to control the circadian rhythm of HCC mice, which may be used to rectify abnormal gene expression in HCC models. The principal chemotherapeutic treatment for HCC, cisplatin-DNA adducts, are repaired by circadian genes, raising the possibility that the most effective drug delivery regimes could be improved. According to studies, there is a strong correlation between BMAL1 expression and the clinical results of melanoma patients taking immune checkpoint inhibitors. The treatment of HCC must also include immunotherapy [16].

### 5. Conclusion

In conclusion, the circadian clock is a critical regulator of numerous physiological processes and has been connected to the emergence of a variety of illnesses. According to a recent study, the disturbance of the circadian clock has been connected to a variety of illnesses, like metabolic disorders, cardiovascular diseases, cancer, and neurological issues. New therapeutic approaches and interventions may result from a better understanding of the circadian clock's biological underpinnings and its purpose in disease etiology. For instance, synchronizing external stimuli and timing of drugs can help avoid the onset or progression of disorders affecting the circadian clock. In addition, abnormalities of the circadian clock can be treated with both non-pharmacological approaches including light therapy, calorie restriction, and exercise as well as pharmacological approaches like melatonin, orexin, and Nobiletin. In conclusion, it is essential for creating fresh therapeutic approaches and enhancing patient outcomes that research into the circadian clock and its part in disease etiology continues.

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