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Circadian Regulation of the Immune System and Susceptibility to COVID-19

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Abstract. Circadian rhythms regulate essential physiological processes, including immune responses, and their disruption has been implicated in increased vulnerability to infectious diseases. The importance of circadian health has been highlighted by the COVID-19 pandemic, with studies showing that an infection from SARS-CoV-2 can disturb circadian regulation via changes in clock gene expression and the increase of systemic inflammation. Behavioral changes during the pandemic have worsened circadian inconsistency. Clinically, patients with COVID-19 often show sleep disturbances and changes in circadian biomarkers, which are associated to increasing disease severity and delayed recovery. Studies of mechanisms suggest that circadian disruption reduces antiviral immunity, enhances viral replication, and increases inflammatory responses, which leads to the deterioration of clinical results. Time therapy and other therapies based on circadian rhythms may be utilized after the connection between COVID-19 and these patterns has been established. Studies on such association, along with potential treatments that try to enhance patient health by restoring circadian rhythm, are focused on in this article.

Keywords: COVID-19; Circadian Regulation; Immune System.

1. Introduction

An intrinsic biological clock, the circadian rhythm, orchestrates numerous physiological and behavioral processes across 24 hours. Regulation of this rhythm is attributed to the hypothalamic suprachiasmatic nucleus (SCN), which synchronizes the functions of peripheral clocks distributed in various tissues and organs. Diminishing daylight triggers the retina to detect light reduction, subsequently relaying a signal to the SCN via a neural pathway. The signal is conveyed to the preganglionic sympathetic neurons in the spinal cord, passes via the superior cervical ganglia, and arrives at the pineal gland.

Immune responses are modulated by circadian rhythms, a critical factor. This factor alters immune cell migration, cytokine synthesis, and the manifestation of inflammatory mediators. Circadian rhythm disruption results in compromised immune defenses, thereby increasing susceptibility to infections, including COVID-19.

COVID-19, attributed to SARS-CoV-2, has instigated a global health emergency, marked by extensive illness and death. The virus predominantly impacts the respiratory system; however, severe instances frequently precipitate systemic inflammation, hyperactive immune reactions, and organ failure. Recent investigations suggest that circadian rhythms may have an effect on both the host immune system and the progression of COVID-19 [1]. Circadian rhythms dictate the timing of viral infection, replication, and immune activation, implying variability in the body's defense mechanisms across different times of day. Understanding the interplay between circadian regulation and the immune system is crucial for pinpointing those at heightened risk of severe disease and for optimizing therapeutic approaches.

A daily rhythm characterizes the immune system's functioning. Temporal peaks in leukocyte migration, cytokine secretion, and antigen presentation during active phases are essential for optimizing pathogen detection and immune response. Circadian genes, including BMAL1, CLOCK, and PER, modulate these processes to facilitate optimal immune system function [2]. The disruption

of this rhythm, due to shift work, jet lag, or irregular sleep patterns, may result in immune suppression or excessive inflammation. Severe COVID-19 outcomes are heightened in those with circadian misalignment.

Melatonin, a hormone regulated by the circadian rhythm, is essential for immune system regulation. Melatonin contributes to the suppression of inflammation and the reduction of oxidative stress, thereby preserving tissue integrity. Melatonin levels are diminished with circadian rhythm disruption, thereby compromising immune defenses and increasing the likelihood of severe COVID-19 [3].

Epidemiological data have revealed a strengthened link between circadian disruption and COVID-19 susceptibility. Literature indicates that shift workers and those with atypical sleep patterns are more prone to infection and more severe disease [4]. Individuals suffering from pre-existing circadian rhythm disorders or comorbidities, like obesity and cardiovascular disease, which are linked to circadian derangement, are at an increased risk for severe COVID-19.

By harmonizing treatment schedules with circadian rhythms, chronotherapy emerges as a promising strategy for enhancing COVID-19 patient outcomes. The effectiveness of vaccinations, antiviral therapies, and immune-modulatory treatments is contingent upon the timing of their administration, as research has shown. Circadian biology-informed treatment customization may foster increased immune responses and decreased adverse effects, as cited in [5].

A study of the molecular pathways linking circadian rhythms with immune regulation will yield valuable insights into their impact on disease progression. Temporal analysis of immune activation, cytokine secretion, and circadian gene expression in COVID-19 patients may pinpoint new therapeutic avenues. The integration of circadian-based treatment strategies into clinical trials may yield essential evidence for the betterment of patient care.

2. Mechanisms of Circadian Rhythm Alteration in the COVID-19 Outbreak

The association between SARS-CoV-2 and circadian rhythm disruption is via biological and behavioral pathways. These disruptions influence immune function regulation, possibly leading to increased disease severity [4].

2.1. Viral Alteration of the Host's Circadian Clock

SARS-CoV-2 alters circadian rhythm regulation, predominantly by disrupting core clock genes. The mammalian circadian clock is sustained via an autoregulatory feedback loop that incorporates the genes BMAL1, CLOCK, PER1/2, and CRY1/2, operating through a transcription-translation process. These genes' disruption impairs circadian regulation, including immune responses, hormone secretion, and metabolic balance [2].

Circadian regulators within lung cells demonstrate transcriptional profile alterations induced by SARS-CoV-2. Suppression of BMAL1 expression is evident post-infection. BMAL1 functions as a dual regulator, influencing both circadian rhythm and antiviral immunity via interferon-stimulated genes. Inhibition might enhance viral replication and weaken the immune system [6].

Furthermore, evidence supports the neurotropic capability of SARS-CoV-2, leading to infection of neurons in human brain organoids and transgenic mice with human ACE2 [7]. The SCN, within the hypothalamus, is the architect of the central circadian rhythm; the virus may impair its function through neural invasion. Disruption may instigate sleep-wake cycle disturbances, hormonal imbalances, and widespread desynchronization.

Herpes and hepatitis viruses are implicated in the alteration of the host's circadian system. Pathogens elevate replication efficiency through the manipulation of clock genes, suggesting circadian manipulation as a widespread strategy [6]. The trajectory of SARS-CoV-2 may lead to chronobiological disruptions in infected subjects, akin to other pathogens. SARS-CoV-2's pattern

may be akin to that of other pathogens, thus contributing to chronobiological disruptions in infected subjects.

2.2. Inflammation-Mediated Circadian Dysregulation

Cytokine levels, notably IL-6, TNF-α, and IL-1β, are elevated in COVID-19, indicating systemic inflammation [1]. Circadian genes' regulation is notably affected by inflammatory mediators. An intimate relationship exists between the immune system and circadian rhythms, with inflammation being a disruptor of circadian regulation.

By inhibiting the transcription of essential circadian components, such as CLOCK and BMAL1, IL-6 disrupts the feedback loop necessary for circadian rhythm maintenance [8]. TNF-α, in a manner akin to others, interferes with circadian regulation in peripheral tissues, thereby causing systemic dysrhythmia. The inflammatory feedback loop not only diminishes sleep quality but also hinders immune response coordination.

COVID-19 triggers the NLRP3 inflammasome, a pivotal inducer of cytokine storms and tissue damage in severe instances. Circadian-regulated melatonin modulates NLRP3 activity and mitigates oxidative stress. The disruption of melatonin secretion in COVID-19 patients is associated with inflammation and circadian rhythm disruption. Reduced melatonin levels are linked to more severe COVID-19 outcomes, as indicated by research [9].

Temporal coordination failure in the immune system results in diminished pathogen recognition and elimination capabilities. Reduced Toll-like receptor expression and diminished immune cell migration, both associated with circadian misalignment, weaken the body's defense mechanisms against infection and prolong viral survival.

2.3. Exploring Three Modulators of Circadian Rhythm Disturbance

Apart from biological influences, the COVID-19 pandemic has precipitated substantial shifts in behavior and the environment, resulting in disruptions to circadian rhythms. Lockdown measures, isolation strategies, and the shift to remote work and schooling have caused modifications in the daily routines of billions across the globe [10]. These alterations have resulted in diminished physical activity, increased screen time, and decreased natural light exposure, collectively affecting the circadian rhythm adversely.

The human circadian system is primarily modulated by light exposure as a zeitgeber. Insufficient daylight and excessive artificial blue light exposure at night can cause a delay in the circadian rhythm and inhibit melatonin synthesis [11]. During lockdowns, a significant number of individuals reported later bedtimes, increased sleep latency, and lower sleep quality [10].

A large-scale survey in Argentina exhibited extensive circadian misalignment during the pandemic. The study participants reported on later bedtimes, disrupted sleep schedules, and poorer sleep efficiency. These effects were more pronounced in individuals with high stress, low physical activity, and diminished daylight exposure [12].

Pandemic-induced psychological stress exacerbates circadian disruption via uncertainty, social isolation, and economic instability. The hypothalamic-pituitary-adrenal (HPA) axis is activated by chronic stress, leading to cortisol elevation [13, 14]. In typical conditions, cortisol follows a daily rhythm; chronic stress, however, disrupts this rhythm, contributing to reduced circadian integrity [15].

Environmental and behavioral alterations, though not virus-induced, intensify the discussed biological disruptions. Concomitantly, they impose a multifaceted strain on the circadian system, potentially compromising psychological and immune resilience amidst COVID-19 infection.

Circadian rhythm alterations in COVID-19 patients are attributed to a confluence of direct viral impacts, inflammation-mediated alterations in gene expression, and pandemic-induced

environmental or behavioral alterations. Disruption of circadian regulation by these factors can subsequently impact immune function, sleep quality, and disease outcomes.

3. Clinical Findings of Circadian Rhythm Alteration

References are cited in the text just by square brackets [1]. (If square brackets are not available, slashes may be used instead, e.g. /2/.) Two or more references at a time may be put in one set of brackets [3, 4]. The references are to be numbered in the order in which they are cited in the text and are to be listed at the end of the contribution under the heading *References*, see our example below.

3.1. The Patient's Sleep Problem Description

Sleep disturbances, stemming from circadian rhythm disruptions, are associated with immune system impairment and an increased susceptibility to infections, such as COVID-19. Sleep disturbances are a frequent manifestation of circadian misalignment, with the COVID-19 pandemic's stress and anxiety exacerbating the issue. COVID-19 patients commonly report issues including insomnia, fragmented sleep, and excessive daytime sleepiness, which may impair immune responses and recovery [16, 17].

The immune function is modulated by sleep, and its impairment, especially due to sleep deprivation and irregular sleep patterns, results in compromised immune cell activity and cytokine synthesis. Disruption of circadian rhythms results in diminished synthesis of essential immune mediators, such as NK cells and T cells, which are crucial for the initial defense against viral infections [1]. The susceptibility of individuals with immune deficiencies and sleep disturbances to COVID-19 and severe symptoms is exacerbated. Regular sleep-wake patterns are linked to an enhanced immune system and greater infection-fighting ability.

Circadian rhythm alterations, particularly in shift workers and those with irregular sleep, are associated with an enhanced risk of viral infections. The presence of disrupted sleep-wake cycles is associated with compromised immune responses, which are conducive to more frequent infections and extended recovery periods [4]. In the context of COVID-19, a rapid immune response is crucial; thus, maintaining a stable circadian rhythm may be beneficial in preventing infection and severe disease outcomes.

3.2. Abnormal Biomarkers

Alterations in circadian rhythms concurrently impact multiple essential biomarkers essential for immune function. A biomarker, cortisol, is a hormone that contributes to the body's stress response [18]. Cortisol concentrations, in standard physiological conditions, adhere to a circadian rhythm, with a morning peak and a gradual decrease throughout the day. It has been established that sleep deprivation and circadian misalignment alter cortisol secretion, negatively affecting immune responses [19]. The dysregulated inflammatory response observed in COVID-19 patients is linked to alterations in cortisol rhythm.

Cytokine levels, akin to cortisol, are regulated by circadian rhythms, being essential small proteins for immune function. Evening hours are associated with the peak expression of cytokines like TNF-α and IL-6. Disruption of circadian rhythms can modify these patterns, leading to cytokine overproduction or underproduction [20]. Dysregulation of inflammation may lead to the cytokine storm, a common manifestation in severe COVID-19 [21]. Increased IL-6 and other pro-inflammatory cytokine levels are associated with adverse outcomes in COVID-19, encompassing respiratory failure and multi-organ dysfunction.

Patients with severe COVID-19 frequently exhibit heightened CRP biomarkers. Circadian rhythm disruptions have been demonstrated to elevate CRP levels, which may exacerbate systemic inflammation associated with COVID-19 [22].

3.3. Analysis Regarding Gene Expression Profiles

The circadian system orchestrates the expression of a range of genes engaged in immune system regulation. Circadian genes, notably BMAL1, PER1, and CLOCK, regulate the temporal coordination of biological processes, such as immune responses [2]. Disruptions in circadian rhythms, stemming from irregular sleep or shift work, can result in modified gene expression and compromised immune function in combating infections.

Findings show that disruptions in circadian rhythms are associated with modifications in the expression of genes linked to inflammation and immune cell responses, including IL-6, TNF-α, and IFN-γ [1]. The alterations exacerbate the inflammatory response in COVID-19, particularly during immune dysregulation. The escalation of pro-inflammatory cytokines results in a hyper-inflammatory state, known as a cytokine storm, a pivotal factor in severe COVID-19 complications [21]. The cytokine storm, a hyper-inflammatory phenomenon due to the upregulation of pro-inflammatory cytokines, is a principal cause of severe COVID-19 [21].

Stabilization of immune-related gene expression via synchronized circadian rhythm may potentially decrease inflammation and mitigate the severity of COVID-19. Circadian regulation emerges as pivotal in combating viral infections, especially amidst global pandemics like COVID-19.

4. The Impact of Circadian Rhythm Disruption on Disease Onset Pathways

4.1. Viral Susceptibility's Impact on Pathogenicity

Circadian rhythms are pivotal in modulating immune system function; disruptions to these rhythms can profoundly impact an individual's susceptibility to infections, including COVID-19. Circadian misalignment, exacerbated by shift work, irregular sleep, and jet lag, is thought to compromise the immune system, augmenting the risk of infection. In the COVID-19 scenario, where a swift immune response is crucial for viral replication control, circadian disruptions can compromise the body's defense efficacy.

Individuals exhibiting irregular sleep-wake cycles frequently demonstrate compromised immune function, featuring diminished NK cell activity and defective cytokine production, notably TNF-α. Immune deficiencies correlate with an increased risk of COVID-19 and its severe manifestations. Alternatively, maintaining a regular sleep-wake pattern bolsters immune efficacy and lessens the chance of infection.

4.2. Components of Disease Severity

The severity of diseases like COVID-19 is amplified by circadian rhythm disturbances. Circadian disruptions amplify disease severity through the exacerbation of an exaggerated immune reaction. Cytokine storms are associated with a notable upregulation of pro-inflammatory cytokines, notably IL-6 and TNF-α [1, 20]. Cytokines precipitate tissue injury, multi-organ dysfunction, and respiratory collapse in severe COVID-19 instances. Cytokine synthesis is amplified by the interaction of circadian misalignment and sleep disturbances, which exacerbates inflammation and elevates the risk of complications. Circadian misalignment, when paired with sleep disturbances, increases cytokine synthesis, which worsens inflammation and heightens the risk of complications.

CRP levels, a systemic inflammation indicator, are increased in those with circadian misalignment, and this is linked to poorer COVID-19 prognosis [22]. Circadian rhythm disturbances impair the body's capacity for tissue repair and inflammation regulation, thus extending recovery and enhancing the risk of complications. The adherence to a regular circadian rhythm may aid in diminishing inflammation and enhancing clinical outcomes in viral infections, including COVID-19.

4.3. Potential Interventions

The profound impact of circadian rhythm disruptions on immune function and disease severity has ignited a growing interest in interventions designed to realign circadian rhythms, thereby improving immune responses and lessening disease burden. The exploration of chronotherapy [5], which synchronizes treatments with the body's circadian rhythms, has been undertaken as a potential therapeutic strategy for enhancing COVID-19 recovery outcomes. Furthermore, the implementation of interventions, including timed dim and bright light exposure in the evening, may aid in reestablishing circadian alignment and improving the immune system's ability to ward off infections [23].

5. Conclusion

Amidst the COVID-19 pandemic, the disruption of circadian rhythms, our internal body clock, became a focal point. Routines' alterations, stress escalation, and the virus's effects collectively precipitated sleep disruptions and biological rhythm changes. Research demonstrates disruptions are associated with heightened COVID-19 symptoms and modified disease progression, encompassing recovery.

The regulation of sleep, immune function, and metabolism is contingent upon circadian rhythms. These functions are directly connected to our infection-fighting prowess. Immune system efficacy is compromised when rhythms are disrupted, potentially due to poor sleep, irregular schedules, or stress. In dealing with diseases like COVID-19, the issue is exacerbated due to the pivotal role of the body's inflammatory response. Circadian rhythm disruption amplifies inflammation, thereby complicating the recovery process. Disruptions in sleep and circadian rhythms may exacerbate the susceptibility to viral infection, as a compromised immune response diminishes the efficacy of defense mechanisms.

The pandemic, in tandem with its physical impacts, compelled individuals to adopt new schedules, thereby further compromising their circadian rhythms. The implementation of lockdowns, social distancing, and home-based employment has transformed daily routines, influencing sleep, light exposure, and lifestyle. The change was more deleterious for those with greater stress and uncertainty. The synergistic effects of chronic stress and irregular sleep patterns have been associated with a compromised immune system's capacity to fight illness. Disruptions impacted individuals and the healthcare system, necessitating management of the virus's direct effects and circadian imbalance consequences.

The association between circadian rhythms and COVID-19 extends beyond physical health, influencing mental well-being as well. The psychological challenges of the pandemic exacerbated circadian disruptions, leading to a harmful cycle [24]. Sleep disturbances stemming from mental health issues can compromise the immune system, thereby exacerbating the severity of illnesses. Enhancing circadian health may facilitate improved recovery from COVID-19 and bolster mental resilience amidst stressful periods. Consolidating regular routines, particularly uniform sleep patterns, balanced light exposure, and stress control, may be pivotal in advancing recovery.

The pandemic has highlighted the importance of reevaluating the management of circadian health across a wider spectrum. Slight modifications to everyday practices, like establishing regular sleep cycles, maximizing daylight exposure, and minimizing evening screen exposure, can greatly reduce disease risk. Enhancing circadian health within public health endeavors may yield enhanced outcomes for COVID-19 and other health issues, including heart disease, diabetes, and mental health disorders, all interconnected with circadian rhythm disruptions. Enhancing circadian health within public health endeavors may yield enhanced outcomes for COVID-19 and other health issues, including heart disease, diabetes, and mental health disorders, all interconnected with circadian rhythm disruptions.

The correlation between circadian rhythm disturbances and COVID-19 highlights the imperative of understanding and nurturing our biological clocks amidst health crises. The pandemic has made apparent the significant ties between sleep, immune function, and overall health with the body's

regulatory rhythms. The incorporation of circadian science into healthcare strategies is anticipated to elevate patient care, transcending COVID-19 recovery to encompass preparation for impending health challenges. Harmonizing therapeutic interventions, lifestyle adjustments, and public health protocols with the body's intrinsic rhythms potentiates the body's resistance to illness and accelerates healing.

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