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From Sun to Clock: Exploring the Interplay Between Circadian Rhythms and Systemic Lupus Erythematosus

Yin Yin [1]*

[1] Australian International School of Singapore, Singapore
*Corresponding author: yyyyinniyyyy@gmail.com

Abstract:

Systemic lupus erythematosus (SLE) has a complicated interaction with circadian rhythms, which influences immune function and disease activity. This study investigates the role of circadian dysregulation in SLE pathogenesis, specifically analysing changes in immune cell rhythms, sleep patterns, and nocturnal blood pressure in afflicted people. By deciphering this complex dynamic, researchers hope to gain new insights into SLE's underlying processes and potential treatment approaches. Tailoring therapeutic techniques to address circadian factors may offer promise for improving clinical results and quality of life in SLE patients. Overall, this study emphasises the importance of knowing the circadian component in autoimmune illnesses such as SLE, which opens new possibilities for individualised and targeted therapies to reduce disease burden.

Keywords: List the; keywords covered; in your paper.

1. Introduction

The circadian rhythm, or sleep/wake cycle, regulates sleep through homeostatic physiology. Circadian rhythm refers to a 24-hour internal clock which controls periods of alertness and sleep in reaction to light changes in our surroundings. The way the Earth rotates around its centre influences human biology and behaviour. This biological circadian clock developed to help humans adjust to changes in our surroundings, such as shifts in irradiation temperatures, and availability of food. Most living things have an internal clock called the circadian clock, which is essential for controlling several physiological and behavioural processes, most notably the sleep-wake cycle. All living things engage in sleep, which is characterised by a period of comparatively low stimulus reactivity. In rodents, complete lack of sleep results in death, and regular sleep of less than six hours per night is linked to shortened life spans, higher susceptibility to viral infections, and lower antibody titers following immunisation. As the circadian clock has such a significant influence on general health and wellbeing, it is important to take it seriously. Sleep and circadian rhythms have a complicated and possibly reciprocal interaction. On the other hand, transient sleep disturbances might impact peripheral organs like blood and lung that are subject to circadian rhythms. A closer look exposes the extensive effects of sleep and circadian rhythm disorders. Researchers may explore into understanding the function of circadian rhythms in modifying immunological responses during sleep, building on the investigation of previously unknown aspects of sleep regulation related to the immune system. Fruit flies and mice with more sleep after infection had a higher survival rate, but this conclusion is confounded by the fact that the increased sleep was caused by sleep restriction before to infection.[1] The discovery of neuron-specific protein (NUR), a molecule that regulates normal sleep homeostasis, is induced during infection, is required for the sleep increase, and has direct antimicrobial properties, establishes a clear mechanistic link between increased sleep and increased infection survival. NUR is normally created outside the brain, but its expression in the brain is low unless triggered by sickness or sleep deprivation. [2] The wide constitutive expression might be part of a baseline contribution to immune protection through the antibacterial characteristics of NUR, whilst increased brain expression may contribute to animal ability in response to sickness such as systemic lupus erythematosus (SLE). [2] The suprachiasmatic nucleus (SCN) [3] controls the circadian rhythm which orchestrates a multitude of physiological functions, including the sleep-wake cycle. Investigating the communication channels between SCN [4] and immune cells particularly located in the brain might provide useful insights. Studies that entail selectively manipulating the activity of immune cells in the brain during different circadian phases and observing the changes in

sleep patterns. However, the processes by which circadian rhythms interact with the immune system during sleep are less explored. [2]

SLE [5] is an autoimmune disease [6] that causes a breakdown in self-tolerance because of infections and cytotoxic environmental stressors that induce cellular damage. It is the most common type of lupus, resulting in significant inflammation and tissue loss in the affected organs. SLE primarily affects women, particularly around puberty and menopause. It may harm the bones, the epidermis, the brain, the lungs, the kidneys, even veins. Lupus does not have a cure, although pharmaceutical treatments and lifestyle changes can help keep it under control. When the immune system encounters self-antigens, it triggers both innate and adaptive responses, activating the IFN regulatory families, nuclear factor kappa B, and Mitogen-activated protein kinases. This activation boosts neutrophils, T lymphocytes, and B lymphocytes, causing abnormal gene expression in T cells [7, 8], promoting the production of inflammatory cytokines, autoreactive B cells, and tissue damage. The unregulated multiplication of activated B cells increases self-antigen presentation and autoantibodies, which perpetuates the autoimmune response. Recent research has found that the loss of mitochondrial topoisomerase I (TOP1MT) results in the release of mitochondrial DNA into the cytosol, activating the cGAS-STING innate immune system. SLE may range from moderate to life-threatening. The mortality rate was greater among the young people. The 5- and 8-year survival rates were 91%. [9]

One prominent end-organ manifestation of SLE is Lupus Nephritis (LN). which is a serious and potentially life-threatening kidney inflammation caused by SLE. [5] Lupus nephritis occurs when SLE affects the kidneys, leading to proteinuria, hematuria, and various levels of renal dysfunction. Although the circadian clock has been demonstrated to impact immune system responses and macrophage activity, its role in the development of SLE or LN has not been fully studied. In this review, we will briefly discuss the general pathobiology of LN and emphasise the present comprehension of the connection between clock cycle disturbances and SLE. [10]

2. The relationship between circadian rhythm and SLE

2.1 . The relationship of circadian rhythm and autoimmune system

Understanding how circadian rhythms influence the immune system can provide valuable insights into SLE [5], one of the most prevalent autoimmune diseases. The aetiology of autoimmune illnesses is multifaceted, with genetic, hormonal, and environmental influences all having a part. [11] Circadian rhythms have a major impact on the immune system, influencing autoimmune disorders via many pathways. To begin, circadian control regulates the function of immune cells, such as T cells and macrophages, via the rhythmic production of clock genes. Disruptions to these rhythms can dysregulate immune cell function, potentially triggering autoimmune responses. Second, circadian control includes the release of inflammatory cytokines including interleukin-6 and tumour necrosis factor-alpha, as well as anti-inflammatory compounds. Imbalances in these cytokines caused by circadian disturbance might lead to persistent inflammation, which is characteristic of autoimmune disorders. Finally, the circadian system controls the sleep-wake cycle and hormone release, such as cortisol and melatonin, both of which influence immune function. [12] Interruptions in these cycles, including that induced by inconsistent sleeping habits or working shifts, can decrease immune function and increase susceptibility to autoimmune diseases like SLE [5].

2.2 Evidence of circadian rhythm involvement in SLE pathogenesis

2.2.1 Sleep disruptions and SLE

Patients with SLE usually have sleep interruptions, which reduces their quality of life. [13] Research has shown that circulating immune complexes decrease during sleep, supporting the idea that the circadian rhythm controls immunological responses in SLE. Follow-up research discovered that getting fewer than seven hours of sleep each night was separately associated with an increased risk of developing SLE, indicating that circadian disturbance and sleep irregularities may play a part in the pathophysiology of SLE. [14] Blood pressure lost its overnight low in patients receiving glucocorticoid prednisolone for chronic glomerulonephritis and SLE; instead, it increased over the night and peaked in the morning. A hallmark of SLE/LN is dysregulated immunological responses, and changes in the circadian rhythm of immune cells can affect the course of events. [15] Sleep deprivation disrupted the normal cycle of regulatory T cells (Tregs) throughout a 24-hour period, affecting their function. This shows that changes to the circadian rhythm in SLE may affect Treg functioning.

Sleep interruptions are common among patients with SLE, which has a substantial influence on their quality of life. [16] Given SLE's characteristic dysregulated immunological responses, changes in immune cell circadian rhythms may have a substantial influence on illness development. Sleep deprivation has been shown to disrupt the regular cycle of regulatory T cells (Tregs) [17] over a 24-hour

period, compromising their critical immunoregulatory role. These data imply that changes in the circadian clock in SLE may have a negative impact on Treg function, underscoring the complex link between circadian rhythms, immunological dysregulation, and disease pathogenesis

2.2.2 Circadian rhythm and macrophage activity in SLE

Although the circadian rhythm controls macrophage activity and immunological responses, its part in the onset of SLE or LN is not well understood. Circadian rhythm effect on macrophage activity highlights its potential importance in the pathogenesis of both disorders. Macrophages activity is quite essential in SLE. Performing a critical function in the immune system, regulating inflammation and tissue homeostasis. Dysregulated macrophage activity has been linked to the pathophysiology of SLE, helping to perpetuate inflammatory responses and cause tissue damage.

Emerging data reveals that the circadian rhythm has a significant impact on macrophage activity, regulating activation, polarisation, and inflammatory cytokine production. Circadian control of macrophage activity is achieved by the rhythmic expression of clock genes, which coordinate molecular pathways that govern cellular functions. Disruptions in the circadian clock can impair macrophage function, resulting in abnormal immunological responses and inflammatory cascades that are linked to the pathophysiology of autoimmune diseases like SLE [5].

Furthermore, the dynamic interaction between the circadian rhythm and macrophage activity goes beyond internal cellular processes to include systemic aspects such as sleep-wake cycles and eating behaviour. Circadian signals, such as light-dark cycles and meal timing, can coordinate macrophage activity, improving immune surveillance and responsiveness to environmental stimuli. Circadian rhythm disruptions, like shift work or jet lag, can alter macrophage function, predisposing people to immunological dysregulation and inflammatory illnesses like SLE [5].

Given the critical role that macrophages play in the pathophysiology of SLE, understanding the effect of the circadian rhythm on macrophage activity has important therapeutic implications. Targeted therapies aiming at restoring circadian equilibrium and improving macrophage activity may provide new options for reducing autoimmune responses and slowing disease progression in SLE. By dissecting the complicated interplay between circadian cycles and macrophage activity, researchers might get a better knowledge of SLE aetiology and discover possible targets for precision medicine methods customised to individual patients.

2.2.3 Circadian rhythm and natural regulatory T cell (Treg)

In the complex terrain of SLE and lupus nephritis LN, regulatory T cells (Tregs) [17] play a significant role in immunological tolerance and self-regulation. Tregs serve an important function in suppressing abnormal immunological responses, maintaining peripheral tolerance, and avoiding autoimmunity. However, in the setting of SLE [5] and LN [18], dysregulation in Treg quantity, phenotype, and function contributes to immunological tolerance breakdown, driving autoimmune inflammation and tissue damage.

Studies have revealed Tregs' multidimensional function in SLE and LN pathogenesis, demonstrating both quantitative and qualitative changes in Treg populations in afflicted patients. While some studies indicate a numerical shortage of circulating Tregs in SLE patients, others emphasise functional abnormalities in Treg suppressive activity and stability. These anomalies in Treg biology promote uncontrolled autoimmune responses and lead to disease progression in SLE and LN.

The circadian rhythm has a significant impact on Treg biology, with accumulating data indicating regular fluctuations in Treg quantity and function over a 24-hour period in humans. Circadian signals, including light-dark cycles and feeding-fasting rhythms, coordinate Treg activity, enhancing immunoregulatory activities and ensuring immunological homeostasis. [19] Circadian rhythm disruptions, such as sleep problems or shift work, might impair Treg dynamics, reducing their suppressive ability and aggravating inflammatory responses in SLE and LN. [19]

Abnormalities in the circadian rhythm have been associated with the aetiology of SLE and LN, emphasising the complicated relationship between circadian rhythms and Treg-mediated immune control. Dysregulated circadian rhythms [20] can upset the balance of pro- and anti-inflammatory pathways, favouring autoimmune inflammation and tissue damage. This instability not only impairs Treg function but also influences the activity of other immune cell types, aggravating the autoimmune cascade in SLE and LN.

2.2.4 Circadian clock genes affecting SLE

Researchers investigated the impact of genetic clock protein duplication on SLE induced by medicines or occurring spontaneously. The result revealed that animals missing circadian regulator 1-2 (CRY1 and CRY2) [21] had greater levels of antinuclear antibodies and increased complement precipitation in glomeruli. Moreover, deficits in CRY proteins [22] have been shown to speed up B-cell development in the abdominal cavity and the spleen, perhaps causing systemic consequences. This research suggests that clock proteins have wider functions in addition

to CR control and indicates their involvement in SLE.
In addition to the fascinating discoveries about genetic clock protein duplication and its implications for SLE, new research has shed light on the involvement of the COL1A2 and DOCK2 [23, 24] genes in SLE. Studies have found a negative connection between COL1A2[26] expression levels and glomerular filtration rate (GFR) in LN patients [reference required]. This implies that higher levels of COL1A2 [23] may worsen renal impairment, worsening the prognosis for those with LN or SLE. Conversely, research has indicated that DOCK2a gene implicated in immunological modulation, may protect the kidneys of LN [19] patients [24,25,26] Understanding the complex interplay between these genetic variables and renal function might provide useful insights for the development of tailored therapeutics aiming at maintaining kidney function and reducing the burden of LN [19] in SLE. [5,27]

3. Therapeutic implications of circadian rhythm and potential invention

Several lifestyle adjustments, including scheduled meals, sleep, and activity, have been studied for their safety and efficacy in achieving optimal circadian health. Lifestyle changes targeted at improving circadian health show potential as supplementary therapy methods for people with systemic lupus erythematosus. Scheduled meals, for example, have been proven to influence the body's internal clock and metabolic processes, which may affect immune function and inflammatory responses. Clinicians who incorporate regular mealtime into SLE [5] therapy strategies may help regulate circadian rhythms and reduce disease activity. Similarly, improving sleep habits, such as adhering to consistent bedtime and wake-up hours, might improve circadian synchronisation and overall health outcomes in SLE patients. Individuals with autoimmune disorders such as SLE frequently experience sleep disruptions, which are linked to increased disease activity and symptom severity. As a result, establishing sleep hygiene measures and treating underlying sleep disturbances may be a viable path for reducing SLE-related symptoms and improving quality of life.
Physical exercise has emerged as a modifiable lifestyle factor with significant consequences for circadian health and immunological function in SLE patients. Regular exercise has been demonstrated to impact circadian rhythms by enhancing clock entrainment and regulating inflammatory pathways. Exercise therapies in SLE patients have shown to improve disease activity, tiredness, and quality of life. Clinicians can improve circadian health in persons with SLE by combining individualised exercise programs into complete treatment strategies. Furthermore, participating in outdoor physical activities during daylight hours might assist regulate circadian rhythms by increasing exposure to natural light, which acts as an important entertainment trigger for the internal clock. Hence, supporting regular physical exercise as part of SLE management may have several benefits for circadian health and disease outcomes.

4. Summary

In conclusion, the complex link between in circadian rhythms and SLE highlights the possibility for new treatment approaches and management measures. The bidirectional impact of disturbed circadian rhythms on SLE pathogenesis highlights the necessity of managing sleep difficulties and chronobiological dysregulation in SLE patients. Furthermore, understanding the molecular processes behind this interaction opens up new opportunities for targeted therapies and personalised medical techniques. We may enhance health outcomes and quality life outcomes for individuals with SLE by including chronotherapy and lifestyle adjustments into their overall treatment plan. Continued study in this area offers tremendous potential for improving our understanding of SLE pathophysiology and creating therapeutic strategies tailored to each patient's circadian profile.

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