REVIEW ARTICLE

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Circadian Rhythm, Sleep, and Immune Response and the Fight against COVID-19

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ABSTRACT

Sleep is an imperative physiological aspect that plays a vital role in maintaining hormonal and humeral functions of the body and hence a healthy life. Circadian rhythms are daily oscillations in human activities and physiology that prepare human beings to better react to and anticipate challenges in the surrounding environment, which are a consequence of diurnal changes of day and night. The sleep/wake cycle is one of the most prominent manifestations of the circadian rhythm and communicates tightly with the immune system with daily oscillation of immunity. Sleep deprivation is now recognized as a common condition inherent to modern society, and it is detrimental to certain body functions, particularly immune function. The aim of this review is to explore the role of sleep in maintaining a healthy immune system during the COVID-19 pandemic. The review discusses sleep-regulatory substances that are linked to host defense mechanisms such as interleukin-1β, interleukin-6, tumor necrosis factor alpha, and interferon gamma. Cytokine levels also fluctuate with sleep/wake homeostasis and our review explores the relationship between sleep and cytokines and proposed therapeutics. The review will also cover sleep and immune response in children, adolescents, and healthcare workers, and finally it will touch on the effect of obstructive sleep apnea on immune response and the severity of COVID-19.

Sleep is a recurrent physiological state of bodily rest and reduced consciousness that serves multiple functions including the consolidation of memory and enhancing the immune defense.[1] It is tightly connected to the circadian system that regulates periodic changes in behavioral and physiological parameters. Sleep and the circadian system cooperate bidirectionally to organize immune functions in time and space via neuroendocrine and sympathetic effector mechanisms. Short sleep duration may depress the immune response.[2] Furthermore, sleep disturbances such as those occurring in patients with obstructive sleep apnea (OSA) may also cause cellular and humoral immune dysfunctions. COVID-19 infection is associated with elevated levels of inflammatory cytokines and that can be worsened by sleep deprivation and disturbances. Our aim is to explain the interaction between immune mechanism and sleep, and cover the effect of COVID-19 on children and healthcare workers (HCWs).

The circadian clock

Circadian rhythms are essential for a variety of phenomena ranging from microbial growth, plant growth and production, and human wake/sleep cycle. Circadian rhythms have a great influence on human sleep, locomotion, cognition, and feeding and drinking.[3] The regulation of circadian rhythms in humans is the function of suprachiasmatic nucleus, which is located in the hypothalamus and receives input from various sensors in the body. At sunset, the signal of the dimming light travels through a neural tract that runs from the retina to the suprachiasmatic nucleus, from which the information is transferred downwards to the preganglionic sympathetic neurons in the spinal cord and onto the superior cervical ganglia upwards to the pineal gland.[4] Melatonin, the sleep onset hormone, is then secreted into the bloodstream usually two to three hours after sunset to reach every organ in the body. Circadian rhythms can influence various biological rhythms such as hormone release, blood pressure, body temperature, and metabolism, and lasts approximately 24 hours.[5] Furthermore, circadian rhythms act as an internal timekeeping system permitting the cell to predict internal or external changes to perform its cellular activities at suitable times during the day.[6]

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Immune response and circadian rhythm

Immune cells are assigned either to the innate (unspecific; e.g., neutrophils, monocytes, macrophages, dendritic cells and natural killer [NK] cells), or the adaptive immune system (antigen-specific; lymphocytes [T-and B-cells]). In the oscillation of the sleep-wake cycle, leukocytes show robust diurnal rhythms with peak counts at night or during the day, depending on the cell type.[7] Leukocytes, such as naive CD4 T cells, monocytes, and neutrophils have nighttime maximum rhythms. These rhythms are regulated by cortisol that leads to an upregulation of the chemokine receptor CXCR4 and thereby facilitates the redistribution of these cells to the bone marrow, with a delay of approximately three hours.[8] On the other hand, leukocytes like cytotoxic NK cells have daytime maximum rhythms. These rhythms are regulated by epinephrine which promotes the release of these cells from the marginal pool by an immediate inhibition of adhesive fractalkine receptor signaling.[8] Furthermore, pro-inflammatory cytokines such as interleukin (IL)-1β, tumor necrosis factor alpha (TNF-α), interferon gamma, and IL-6 are generally thought to be as somnogenic with increased levels during the rest phase.[9] While anti-inflammatory cytokines, e.g., IL-10 and IL-4, have a negative effect on sleep and are high after waking.[10]

Sleep deprivation and immune response

Several studies indicated that short sleep duration might depress cellular and humoral immunity.[11] There are daily rhythms in the changes of IL-1β and TNF-α concentration. Moreover, the expression of the messengerRNA of these molecules in the brain varies with the sleep-wake cycle. The highest levels correlate with high sleep inclination and both IL-1β and TNF-α messenger RNA expression increases in rats' brains during sleep deprivation.[12]

Previous studies on the influence of sleep on circulating concentrations of IL-2 and IL-6 had controversial findings. For instance, it has been found that sleep enhances the production of IL-2 by T cells,[13,14] while sleep deprivation leads to a decreased IL-2 production from stimulated lymphocytes under the influence of the hypothalamic-pituitary-adrenal axis.[15] Moreover, another study showed that five days of sleep deprivation decrease circulating IL-2 and IL-6, which is similar to the effects of acute sleep deprivation and psychological stress.[16,17] On the other hand, earlier studies indicated that nocturnal sleep deprivation leads to daytime (post-deprivation period) over-secretion of IL-6 in healthy subjects, and there is a negative correlation between nocturnal sleep and IL-6 release.[18] Thus, with good nocturnal sleep and a good sense of well-being, the next day are associated with decreased overall secretion of IL-6.[19] Nevertheless, we and others have clearly illustrated that patients with nocturnal sleep disturbance such as obstructive sleep apnea syndrome (OSAS) and pathologically increased daytime sleepiness and fatigue have elevated levels of circulating IL-6, which can activate the hypothalamic-pituitary-adrenal axis and lead to an increased production of cortisol and a depressive mood.[11,20,21] OSAS may be associated with inflammatory responses, including the upregulation of IL-1β, IL-6, and pro-Th2 immune responses, increased proliferative potential of NK and CD4 T cells, and a decreased capacity of neutrophils to phagocytose bacteria and produce reactive oxygen species.[11] More recently, a study showed that sleep restriction of five hours for one week may lead to decreased phagocytosis and NADPH oxidase activity in neutrophils and a decrease in the levels of CD4+ T cells, which is related to changes in the Th1-related chemokine (CXCL-9 and CXCL-10) balance.[22]

Impact of sleep deprivation on COVID-19 pandemic

Sleep deprivation is associated with an increased level of inflammatory cytokines including IL-6 and a decrease in CD4 T lymphocyte levels.[22–24] COVID-19 infection is associated with elevated levels of inflammatory cytokines including IL-6 and with lymphopenia.[25] Therefore, sleep deprivation might worsen these phenomena as it causes similar changes. Moreover, CD4 T cells are crucial in fighting infections including those caused by viruses, therefore their decrease in sleep-deprived patients suggests that sleep-deprived individuals are more susceptible to viral infections.[22] In fact, sleep deprivation for seven consecutive days was associated with increased susceptibility to rhinovirus causing common cold. Therefore, it is possible to hypothesize that sleep deprivation increases the susceptibility to SARS-CoV-2 causing COVID-19. Interestingly, a study found that poor sleep quality in hospitalized COVID-19 patients with lymphopenia was associated with a lower absolute lymphocyte count, reduced recovery rate,

and an increased requirement for intensive care unit (ICU) care.[26] More studies are required to clarify the effect of sleep deprivation on the pathogenesis of COVID-19 infection including its impact on treatments aiming to inhibit the inflammatory responses and the influence of hormones related to sleep such as cortisol and melatonin on COVID-19 pathogenesis, bearing in mind that these hormones have the capacity to decrease the inflammatory responses. Moreover, healthy sleep hygiene that adheres to circadian rhythm would help in fighting COVID-19 symptoms.

Sleep and the immune responses mutual effects during COVID-19

Multiple factors associated with sleep and immune responses might influence the infection with SARS-CoV-2 and are potentially affected by COVID-19. Among these molecules, we can identify IL-6 and melatonin.

The elevated levels of IL-6 during the infection with SARS-CoV-2,[27] might associate with the severity of the disease and its mortality.[28–31] The treatment of severe COVID-19 cases includes broad anti-inflammatory molecules like dexamethasone and anti-IL-6R drugs[28] such as tocilizumab and sarilumab. This reduces the application of mechanical ventilation and mortality in critical and severe cases of COVID-19.[32–35] IL-6 can affect the brain by blood-brain-barrier transport and volume diffusion.[36] Therefore, it can modulate the different processes implicated in sleep.[37] IL-6 has the capacity to bind to its soluble receptor (IL-6Rs) and induce signaling in cells that do not have IL-6R in a process called trans-signaling.[38,39] IL-6 induces the majority of its inflammatory effects through trans-signaling.[38,39] Although neurons might have low levels of IL-6R,[40] IL-6 can potentially affect them through trans-signaling. Interestingly, this trans-signaling is associated with the sleep process.[38,39] Different studies demonstrated the presence of association between high levels of IL-6 and other inflammatory markers such as TNF-α and C-reactive protein (CRP) with sleeping difficulties.[41–45] IL-6 was suggested to have a strong association with sleeping problems,[43] although IL-6 might have somnogenic effects at high levels during the rest phase. Hospitalized COVID-19 patients might develop psychological and neurological disorders.[46,47] This might be a direct pathological effect of SARS-CoV-2 itself as the virus might be present in the brain tissues. However, SARS-CoV-2 does not infect neurons.[48] This suggests that other factors associated with the pathogenesis of COVID-19 can affect the brain. IL-6 constitutes a potential factor that affects the brain and sleep during severe COVID-19 infections because of its effects on them. This corroborates with the fact that the anti-IL-6R drug tocilizumab abrogates the association of the psychological and neurological disorders in severe cases of COVID-19.[49,50] Interestingly, this effect is also observed with anakinra, an anti-IL-1β drug[49,50] and the psychological and neurological effects are associated with systemic inflammation occurring in severe COVID-19 infection.[49,50]

IL-6 might also affect the brain and sleep by an indirect mechanism. The high levels of IL-6 in severe COVID-19 might participate in inducing the differentiation of CD4-T cells to Th17 cells.[51,52] This can affect the ratio of Th17 to regulatory CD4 T cells (Tregs).[53] The modified Th17/Treg ratio might have an effect on the brain and therefore can potentially affect the sleep process centrally.[54]

Moreover, sleep itself can regulate the levels of IL-6; however, this effect is controversial.[19–22] Some studies reported that sleep deprivation is associated with decreased levels of IL-6,[19,20] and that would suggest that lack of sleep during COVID-19 infections might have a decreasing effect on IL-6 levels. However, the concentration of IL-6 in severe COVID-19 reaches high levels,[27] and it is unlikely that a decrease in IL-6 levels induced by sleep deprivation might affect these concentrations.[29–31] In contrast, the studies indicating the increase of IL-6 levels in sleep-deprived individuals[21,22] suggest that sleep deprivation associated with COVID-19 might increase IL-6 levels by installing a circle where the infection with SARS-CoV-2 leads to the increase of IL-6, which can induce sleep deprivation that contributes in increasing IL-6 levels and amplifying the inflammatory process.

Circadian and drugs used for SARS-CoV-2 treatment

Although melatonin is mainly produced by the pineal gland, it is also produced by other cells and organs such as the eyes, gastrointestinal tract, bone marrow, and lymphocytes.[55] Melatonin affects the immune responses and both anti-inflammatory and

enhancing effects were reported for it.[56] Beneficial effects were suggested for melatonin in some viral infections.[57] This provides a rationale for the potential therapeutic effect in the infection with SARS-CoV-2. A large study reported that high levels of melatonin were associated with a decreased potential of infection with SARS-CoV-2. This decrease was higher in the African American population (52%) compared to the general population (28%).[58]

Moreover, beneficial effects were also reported for melatonin in intubated COVID-19 patients.[59] Several trials that involve melatonin and its agonists are reported at clinicaltrials.gov. A small study suggested that treatment with 3 mg melatonin for two weeks was associated with rapid hospital discharge, improvement of pulmonary involvement and symptoms including dyspnea, fatigue and cough, and molecules associated with inflammation such as CRP.[60] Another pilot study suggested that treatment with 6 mg melatonin for two weeks was associated with higher symptoms recovery.[61] In addition, treatment with 3 mg melatonin for one week was associated with higher Leeds sleep evaluation questionnaire scores and oxygen saturation. This study did not detect an association with CRP, white blood cell count, and lymphocyte count.[62]

Moreover, circadian clocks regulate the pharmacokinetics and efficacy of many therapeutics, as several drug targets the proteins involved in drug transport and metabolism exhibit daily rhythmic expression.[63] Chronotherapy is an emerging therapeutic approach for COVID-19 and new drugs that are currently used in the treatment protocols for SARS-COV-2 have circadian properties.[64] Therefore, another aspect of COVID-19 management will be to understand the dosing-time dependency of drugs that inhibit SARS-CoV-2 and elicit any clinical improvement in infected patients. For instance, it has been shown that corticosteroids reduce mortality in hospitalized COVID-19 patients.[65]

Nevertheless, authors found that administration of prednisolone is more beneficial in the evening compared to the morning in other diseases like rheumatoid arthritis and that might be applicable for COVID-19 treatment.[65] However, there are no published clinical trials that have evaluated the circadian influence of prednisone or methylprednisolone against SARS-CoV-2, and therefore future studies should aim to explore this knowledge gap.

Further studies are also needed to examine the effect of circadian and sleep on the efficacy of vaccination in general and specifically for COVID-19 vaccination. Improving sleep quality and its circadian timing can potentially play a role in improving vaccination outcomes.

Sleep disturbances in children and adolescents during the COVID-19 pandemic

Children and adolescents require good quality sleep to ensure their well-being, adequate growth, and puberty development. Sleep disturbances are not infrequent in children. With the modern lifestyle of social media and increasing time spent on electronic devices, more and more children are suffering from sleep disturbances according to the American Academy of Sleep Medicine in 2014.[66] The spectrum includes difficulties falling asleep, maintaining sleep, and/or waking too early. In children before the COVID-19 pandemic, this prevalence was as high as one in four children.[67,68]

The COVID-19 pandemic has affected all age groups although initially it was thought that children have mild disease with subsequent mutations and different strains, children have been reported to develop significant morbidities. It can cause serious severe symptoms and even death. SARS-CoV-2 can also cause neurological complications in children, such as shortness of breath, myalgia, stroke, and encephalopathy. These problems are highly linked with cytokine storm and proinflammatory responses, which can alter the physiology of the blood-brain-barrier and allow the virus to enter the brain.[69]

Sleep disturbances during COVID-19 illness and post-infection have been reported widely for adults and there is significant literature describing all aspects of this important topic. However, in children the studies are limited. The COVID-19 pandemic has influenced sleep patterns in all age groups. Although there are few reports of positive influence many have reported negative effects. Liu et al,[70] in a study showed that almost 70% of the adult sample had poor sleep quality, with higher sleep latency and poor efficiency. It was noted for children aged 4–12 years the main issue was initiating and/or maintaining sleep, and for the 0–3 years group increased nocturnal awakenings. The authors have also found that sex and having a child with sleep disturbances significantly predicted parents' sleep problems. The lockdown during the COVID-19

pandemic has been linked to both positive and negative changes in children's sleep, specifically in terms of shifting sleep and wake times, increased nightmares, or increased sleep duration.[70,71] While the delayed onset of sleep and later bedtime, which worsened during COVID-19, can be considered a sign of worsened sleep, in instances where children previously had insufficient hours of sleep, this may be considered a positive outcome.[70] The positive or negative effects on sleep may be influenced by screen time, available social opportunities, physical activity levels, nutrition and diet, and increased flexibility in daily schedules.[71–73] During the lockdown, the negative impact of these factors was intensified due to the limited time and opportunities for children to play and socialize.[71] New research has demonstrated that poor sleep is also associated with reduced social interaction, by way of low mood.[74]

In addition to parent-specific challenges, sleep quality in parents and children demonstrates bidirectional associations, such that parents' poor sleep and stress affect the child and vice versa.[75–77] This can be exacerbated by disrupted circadian rhythms from inconsistent routines and lifestyle changes during the pandemic. A systemic review showed a longer duration of sleep time, an increase in sleep latency, and daytime sleepiness. However, it is still unknown if the adverse changes to sleep patterns and bedtime routines seen during the lockdown will have any long-term consequences for children's sleep and daytime functioning.[78]

A UK study that involved 17 000 school-aged children and adolescents during COVID-19 restrictions, sleep patterns consistent with adolescent delayed sleep phase were observed, with longer sleep times for secondary school students. Perceived deteriorations in sleep quality were associated with reductions in happiness and interpersonal functioning, highlighting the importance of including sleep measures in adolescent well-being research.[79]

COVID-19 infection and the effect on the immune system of children

In general, COVID-19 infection in children causes mild and recoverable symptoms, however, it can cause serious severe symptoms and death. The cytokine storm and proinflammatory responses are linked to severe morbidities. In severe COVID-19 infection, there is a high risk of acute respiratory distress syndrome and multiorgan dysfunction and this has been attributed to the cytokine storm or substantial pro-inflammatory response.[80] In some instances when cytokine expression is not elevated in peripheral blood immune cells, type I interferon expression plays an important role.[80,81] Proinflammatory cytokines associated with SARS-CoV-2 include interferon gamma, TNF-α, vascular endothelial growth factor, monocyte chemotactic protein-1/C-C motif chemokine ligand (CCL)-2, ILs (IL-1Rα, IL-1β, IL-7, IL-8, and IL-10), granulocyte colony-stimulating factor (G-CSF), basic fibroblast growth factor, granulocyte-macrophage colony-stimulating factor, induced protein-10/CXCL10, macrophage inflammatory protein-1α/CCL3, macrophage inflammatory protein-1β/CCL4, and platelet-derived growth factor.[82]

Data regarding the immune response in children with COVID-19 infection is limited. However, the high CRP and IL-6 levels in children, suggest that the proinflammatory state in children may be like that in adults with COVID-19 infection.[69]

Effect of sleep disturbance on health care personnel

Studies investigated the influence of atypical work schedules on HCWs sleep in the context of the COVID-19 pandemic. It has been shown by several studies that there is an association between shift work and poor sleep quality among HCWs.[83–86] One study found that in models adjusted for age, sex, profession, and country, individuals working nights shifts were 1.81 times more likely to sleep less than six hours per day than those who were not working night shifts.[63] Furthermore, HCWs were subjected to longer working hours during the pandemic and consequently inadequate sleep.[87] Many studies around the world have documented an increased prevalence of anxiety and feeling of hopelessness among frontline HCWs.[88] Nurses in ICU and emergency department reported more psychological stress and lack of support from organizations and coping strategies. Similar complaints were reported from physicians in direct contact with COVID-19 patients.[89] They also reported exhaustion and higher stress levels compared to their colleagues in non-COVID-19 wards. Other HCWs reported lack of personal protective equipment, heavy workload, and lack of community support.[90]

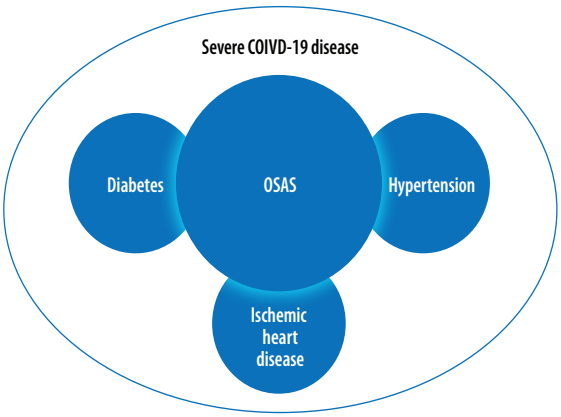

Figure 1: Association between obstructive sleep apnea syndrome (OSAS) and severe COVID-19 disease.

OSAS and COVID-19

OSAS is a common sleep-breathing disorder affecting around 2–4% of the world population.[91] It is characterized by repetitive obstruction of the upper airway during sleep associated with desaturation. OSAS is also associated with excessive daytime sleepiness and impairment of cognitive functions.[92] Several studies indicated that OSAS is associated with hypertension, ischemic heart diseases,[93] and impairment of glycemic control, and these comorbidities are associated with unfavorable outcomes of COVID-19 disease. Studies have shown that about 70% of OSAS patients are obese and the opposite is also true (i.e., 40% of obese patients have OSAS). Studies have shown that OSAS is linked to pneumonia severity, it can increase aspiration and may compromise the efficacy of the defensive cough reflex. COVID-19 patients with OSA are at a higher risk of ICU admission, mechanical ventilation, and poor disease outcome.[94]

Several mechanisms are responsible for higher rates of disease complications in patients affected by OSAS [Figure 1]. We have indicated earlier that patients with severe OSAS have impaired immune response. OSAS may be associated with inflammatory and pro-Th2 immune responses, increased proliferative potential of NK, and CD4 T-cells.[14] The changes in lymphocytic cells phenotypes associated with OSAS may also contribute to systemic inflammation.[95] Furthermore, OSA can become a risk factor for ICU admission and it is associated with higher concentration of plasminogen activator inhibitor-1, a component of the coagulation system correlated with increased risk for acute vascular events.[96] OSAS and obesity (hypoventilation) are associated with hypoxemia, which can be a worsening factor in the hypoxemia of COVID-19 pneumonia. It shows that OSAS may cause ventilatory compromise, which would impair ventilation in patients with COVID-19 disease.[97] A supine position may cause lower airway obstruction and reduced forced vital capacity in obese patients with OSAS.[98]

CONCLUSION

Sleep and immune response are connected through the circadian clock. Sleep disturbances and deprivation may depress the immune response to invading antigens like SARS-CoV-2. Proper sleep hygiene will keep the balance of humeral and cellular functions, which are required for better immune response to the disease and could help in recovery. There are multiple factors that modulate sleep and immune responses and that might influence the severity of COVID-19. IL-6 and melatonin are two of the main molecules among these factors. The relationship between sleep and immune response may also have a role in the severity of COVID-19 in children and adolescents and that could be similar in the adult population. OSA is a common sleep disorder and has a potential role in poor outcomes of COVID-19 disease and it interacts with other known risk factors such as hypertension and diabetes.

Disclosure

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