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The Impact of Sleep Deprivation on the Immune System in Shift-Working Nurses during Outbreak

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In Loving Memory of Late Professor Doctor ""Mohamed Refaat Hussein Mahran""

Abstract

Healthcare workers on the front line of COVID-19 face extended work hours with limited breaks, disruption of their sleep patterns, and an imbalance between the effort they put into their work and the rewards they receive. This has a negative impact on their ability to perform their duties, which is further exacerbated by the shortage of personal protective equipment (PPE), limited resources and inadequate infrastructure, as well as the fear of contracting the virus and spreading it to their families. Consequences of sleep deprivation include persistent insomnia, sleep problems caused by stress, and post-traumatic stress disorder. These changes in sleep patterns have a significant impact on mental well-being, leading to the development or continuation of worry, stress, and sadness, which in turn impairs the capacity to control positive and negative emotions. Having pre-existing sleep difficulties significantly increases the chance of developing and sustaining PTSD when people experience a major stressor like the COVID-19 epidemic. Simultaneously, the way a person manages their emotions related to worry throughout the day affects their ability to sleep at night, leading to ongoing sleep problems. These alterations in sleep and emotional management also impact the immune system. Sleep deprivation is often linked to chronic inflammatory illnesses as a result of disruptions in circadian rhythms, which may lead to potential psychophysiological problems and compromised neuroimmune-endocrine balance. This article aims to provide a comprehensive understanding of how sleep disorders impact the immune system and emotional regulation. It explores the phenomenological and neurobiological mechanisms behind these effects and offers insights into cognitive and behavioral coping strategies that health professionals can adopt to promote a healthier sleep pattern during the COVID-19 outbreak.

Keywords: Nurses, immunity, sleep deprivation, Covid-19 outbreak, immune system.

1. Introduction

The present severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for the continuing coronavirus disease 2019 (COVID-19)[1], has elicited a profound emotional response that impacts healthcare staff, individuals with symptoms, and the general public. Healthcare workers on the front lines of the COVID-19 pandemic face challenging work conditions, including shift schedules, long and demanding hours with limited breaks, disruption of their sleep patterns, and an imbalance between the effort they put into their work and the rewards they receive in terms of saving lives. These factors can negatively affect their ability to perform their duties effectively. Additionally, the lack of personal protective equipment, fear of contracting the virus, and concerns about infecting their family members further exacerbate the situation. One of the adverse consequences that have been documented is the occurrence of sleep problems.[2,3]

Research has shown the decline in immune function after emotional states linked to stress under challenging circumstances, such as natural disasters. Notably, sadness, anxiety, and loneliness have been

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identified as prominent affective states in these conditions.[4] The connection between emotional states and the immune response has been explained and linked to sleep disorders like insomnia and drowsiness caused by lack of sleep. This highlights the significant role of sleep in regulating emotions and its connection to immune regulation.[5-7]

Both emotional reactions and sleep disruptions may be associated with the ongoing COVID-19 epidemic, whereby the combination of isolation measures and increased workload impacts the well-being of healthcare personnel. Healthcare workers may experience a weakened immune response and reduced ability to respond to future outbreaks in the population affected by COVID-19 due to the stress, sleep deprivation, limited family contact, long working hours, and concerns about the future that they face.[8,9] These scenarios have already been investigated in different populations.[10-16]

Studies have investigated the connection between sleep and emotional regulation in the immune system. This connection has been described as changes in the way cells respond to growth signals, a reduction in the activity of natural killer cells, a decrease in the characteristics of T cells, and the influence of catecholamines on lymphocytes through the action of cortisol products produced by the hypothalamic adrenal system.[4] Yet to be examined is the phenomenon of case surges that have been seen in some nations, even in the presence of vaccination. These surges lead to the implementation of isolation measures and other precautions, resulting in the stabilization of stress and sleep disorder symptoms among healthcare professionals. This stabilization, in turn, leads to a decrease in immune response. Therefore, the preventive measures against stress and sleep become crucial and essential.[17]

The long-term effects of sleep disorders and sleep deprivation resulting from shift work patterns have been extensively studied and debated for many years.[18-21] Extensive researches has shown the potential for interventions to address sleep complaints. However, there is still a persistent lack of recognition by managers about the importance of sleep issues, as seen by the absence of governmental policies addressing sleep problems. Ironically, the COVID-19 pandemic underscored the significance of health professionals in confronting this crisis, while it also exposed the inadequate support provided to them. Cognitive-Behavioral Interventions, such as sleep hygiene, are considered the most effective non-pharmacological therapy for various sleep disorders and sleep deprivation.

Natural daylight and artificial light at nighttime

Environmental stimuli, particularly the absence of natural darkness at nighttime, are crucial for the production of melatonin, a hormone that plays a vital role in regulating biological rhythms, sleep, and many cellular, tissue, and organ activities. The 24-hour light/dark cycle of nature provides important time signals to the body's main biological clock, known as the suprachiasmatic nuclei (SCN) of the hypothalamus and pineal gland. These signals help the body achieve internal synchronization of the duration and timing of the circadian time structure (CTS).[22]

Artificial Light at Night (ALAN) exposure can disrupt the circadian system, affecting both the molecular clocks that regulate cellular activities and the synchronization between our daily behavior patterns and the solar day. This exposure also reduces the secretion of melatonin, delays the onset of sleep, and increases alertness. These disruptions can lead to circadian misalignment, which can have negative effects on psychological, cardiovascular, and metabolic functions.

In the industrialized world, 24-hour activities are essential for ensuring public safety and health, and they often provide economic benefits. Shift work disorder (SWD) is a condition that affects a specific group of shift workers, caused by a disruption in their internal body clock (circadian misalignment) as defined by the International Classification of Sleep Disorders. Shift workers suffer from substantial adverse health effects and a reduced standard of living.[23]

Sleep and immunity

The correlation between sleep and immunity has been a topic of debate for more than 2000 years. Hippocrates, for instance, noted the occurrence of drowsiness during the progression of a sudden infection.[18,20] Currently, we have knowledge that the connection between sleep and immunity is created through anatomical and physiological foundations.[20] Neurons, glial cells, and immune cells communicate with each other using shared intercellular signals, including hormones, neurotransmitters, cytokines, and chemokines.[20,21] It is established that all lymphoid tissue is innervated and receives pro-inflammatory cytokines, such as IL-1β and TNF-α.[24] These cytokines and their receptors are expressed in certain areas of the brain and play a role in regulating various physiological and behavioral processes, including the sleep-wake cycle.

Experimental study suggests that TNF-α and IL-1, two types of cytokines, have the ability to regulate sleep, independent of their ability to cause fever. For instance, when IL-1 and TNF-α are administered in a laboratory setting, they induce slow oscillations that closely resemble non-rapid eye movement (NREM) sleep in people.[24] Administering IL-1 decreases the strength of excitatory signals in the rat hippocampus, while introducing TNF in the sensory cortex promotes an increase in slow-wave sleep in these animals.[25,26] The IL-1 and serotonergic pathways exhibit mutual interaction. 5-HT modulates the expression of IL-1 mRNA in certain brain areas. Conversely, IL-1 enhances the release of 5-HT in the

hypothalamus. Additionally, the administration of IL-1 directly into the dorsal raphe nuclei causes non-rapid eye movement (NREM) sleep. Therefore, it is evident that sleep can also impact the immunological response.

Prior research has examined the impact of sleep on the human immune system by studying the long-term effects of sleep deprivation on different immune parameters. This includes observing how diseases that disrupt sleep, such as insomnia, circadian rhythm disorders, and shift work, affect immune function.[27-31] The aforementioned research have yielded intriguing findings. Several studies have indicated that short-term deprivation (50-64 hours) is linked to a transient rise in the activity of natural killer cells (NK), as well as an increase in the number of T-CD4+ lymphocytes, CD8+ cells, monocytes, granulocytes, and NK cells. [26,27,28,31] However, other research on partial sleep, specifically early night or late night sleep, and chronic sleep deprivation, which are more commonly observed in clinical settings, have showed contrasting results. These studies have found a decrease in the activity of NK cells and the counts of CD 16+, CD 56+, CD 57+ cells, as well as IL-2 levels.[25,29,30,32] These lymphocytes, involved in innate immunity, play a crucial role in protecting against viruses, intracellular bacteria, and tumor cells.[33,34,35]

In a study conducted by Axelsson *et. al*.,[36] the objective was to examine the effects of partial sleep deprivation over a period of five days on the production of inflammatory cytokines and the balance between Th1 and Th2 cells in healthy individuals. The researchers observed a temporary decrease in IL-2 levels and the IL-2/IL-4 ratio, which persisted until the fifth day of sleep deprivation.

In their study, Fondel *et. al*.[32] assessed the immunological activity in individuals who slept less than seven hours (referred to as short sleepers) and compared it to individuals who slept between seven and nine hours (referred to as normal sleepers). They recorded a 30% reduction in the activity of NK cells (p 0.01) and a 49% increase in the activity of T-lymphocytes triggered by PHA (phytohemagglutinin), regardless of plasma cortisol levels.

In a study conducted by Sakami *et. al*.[37], the immune response in individuals with insomnia was investigated, specifically focusing on the balance of effector response. The researchers noticed a shift in the Th1/Th2 immune response, favoring the Th2 response. This shift was characterized by a decrease in the secretion of IFN-γ and a decrease in the IFN-γ/IL-4 ratio in individuals with insomnia. The researchers determined that sleeplessness leads to a modification of the immune system's functioning, characterized by a dominant suppressive Th2 response.

Savarde *et.al*.[38] conducted a comparison between a group of patients suffering from insomnia and a group of individuals who are deemed to have good sleep quality. They noticed a notable disparity: a higher quantity of TCD3+, TCD4+, and TCD8+ lymphocytes as well as total lymphocytes in the group of individuals who sleep well in comparison to those who suffer from insomnia.

In a recent study conducted by Prather[39], 164 healthy subjects were exposed to rhinovirus in an experimental setting. The study used pulse actigraphy to measure sleep duration. The results showed that individuals who had less than six hours of sleep before exposure were four times more likely to become sick (OR=4.50; 95% CI: 1.08–18.69 for less than 5 hours, and OR=4.24; 95% CI: 1.08–16.71 for 5-6 hours) compared to those who had more than seven hours of sleep (OR=1). This significance persisted even after controlling for characteristics such as smoking, gender, levels of neutralizing antibodies, physical activity, and alcohol intake.

The Nurses' Health research-II was a longitudinal research conducted from 2001 to 2005, with a population of almost 56,000 nurses in good health. The study revealed that insufficient sleep (<5 hours), as well as negative perception of sleep or excessive sleep (>9 hours), were associated with a 1.39 (95% confidence interval: 1.06–1.82) and 1.38 (95% confidence interval: 1.04–1.84) times higher risk of developing pneumonia, respectively. These findings remained significant even after accounting for variables such as age, body mass index, and smoking.[40]

Research has shown that a decrease in sleep is linked to certain alterations in the immune system.[31-36] During acute deprivation, there is a brief stimulation of the immune system, however the clinical implications of these findings are now unknown. Further investigation is required to address these inquiries.**36-38** The aforementioned studies indicate that both partial and protracted deprivation are associated with a higher susceptibility to respiratory infections, particularly those caused by viruses.[39,40] Possible factors contributing to this phenomenon include compromised innate immunity, as evidenced by decreased activity of NK cells (CD16+, CD56+, CD57+), and a decline in Th1 effector cellular response, which is crucial for the activation of TCD4+ lymphocytes in favor of a more regulatory Th-2 response.[25-30]

The relationship between circadian rhythm, immunity, and immunological memory

The human circadian rhythm is regulated by the suprachiasmatic nucleus (SCN), which acts as the neurological master clock. Additionally, peripheral clocks are found in nearly every cell, including immune system cells. The SCN enables all tissues and cells to predict and swiftly react to environmental changes, including light, temperature, and the potential danger of being exposed to pathogens in the environment. It regulates and synchronizes a variety

of behavioral, physiological, and biochemical processes.[41-43]

The cells of the innate and adaptive immune system also exhibit circadian expression, which may be observed as fluctuations in the blood count and in the peripheral lymphoid organs. This expression is also evident in lymphocyte proliferation and in the levels of cytokines in the blood.[26,44-47] In humans, it has been established that the number of T cells in the blood decreases before the peak of morning cortisol, while the opposite impact has been observed during the early evening period. Sleep, in conjunction with the circadian system, is recognized to govern immunological activities. However, it is challenging to differentiate the specific impact of these two regulatory mechanisms.[44,45]

Empirical research consistently demonstrates that IL-12 levels rise specifically during slow-wave sleep, primarily due to the activity of pre-myeloid dendritic cells. These cells serve as the primary precursors for mature antigen-presenting cells (APCs). Furthermore, monocytes exhibit a decrease in IL-10 and IL-4 levels during slow-wave sleep, which promotes a Th1/Th2 balance that favors the Th1 response.[48,49] The activation of Helper T cells relies on the synthesis of IL-12 by APCs, as established in previous research.[50] The sleep pattern characterized by inflammation during the early part of the night is counteracted by a Th2 response during the latter part of the night, when REM sleep is dominant.[48] Sleep promotes the activation of Th1 cells, the production of C3a, and the movement of immune cells from the bloodstream to the secondary lymphoid organs. These processes enhance the likelihood of interaction between antigen-presenting cells (APCs) and naïve T cells and B lymphocytes, leading to the formation of an immunological synapse. These mechanisms contribute to the development of a more effective immunological memory during sleep. The relationship between sleep and adaptive memory has been examined in recent studies and has confirmed the hypotheses described before.[39,51]

Prather *et.al*.[39] conducted a prospective study including 125 individuals to assess the impact of sleep on the strength of the immune response to a viral antigen, specifically the Hepatitis B virus. The researchers found that getting less than 6 hours of sleep per night, as determined by a sleep diary and autography, was linked to a decrease in the effectiveness of the B virus vaccine. This decrease in effectiveness was detected even after receiving three doses of the vaccine, including a catch-up immunization in the sixth month.

In a study conducted by Langet *et.al*.[51], they compared two groups of healthy subjects who received immunization for the Hepatitis A virus. One group slept after immunization, while the other group stayed awake. The researchers found that sleep in the first group led to a significant increase in the number of specific Th1 cells and IgG1 antibodies to the virus. This increase was observed from the 8th to the 52nd week of follow-up. They determined that slow-wave sleep was accountable for this supplementary effect.

The relationship between sleep deprivation, emotional regulation, and the immune system

The immune response safeguards the body against potentially deleterious chemicals or pathogens. The literature has used several research to support the significance of sleep in relation to the immune response and the notable impact of sleep deprivation on its regulation.[52,53] One aspect of this relationship is that during sleep, specifically during deep slow-wave sleep (stage N3), the consolidation of long-term memory plays a crucial role in the immunological memory. This consolidation allows the immune system to remember its response to specific pathogens. Additionally, during the REM state of sleep, there is also consolidation of other specific memory threads, which is related to emotional regulation. This process is associated with a decrease in adrenergic loads, which promotes immune function.[54] Sleep deprivation and heightened stress responses can disrupt this process, rendering the body susceptible to harmful effects, including those on the respiratory system. Research has demonstrated that even brief periods of sleep deprivation can increase susceptibility to common colds, which is attributed to compromised adaptive immunity.[55,56]

Another crucial factor to emphasize is the strong correlation between sleep deprivation and two elements of our immune response. An example of such a component is innate or non-specific immunity, which refers to the defensive system that one is born with and acts as the first line of protection in the immune response. The second component is associated with acquired, adaptive, or particular immunity. The immune system consists of specialized cells and systemic mechanisms that protect against infections, while also developing immunological memory and tolerance to antigens.[52,53]

The impact of sleep deprivation on the adaptive immune system

When studying the connection between sleep deprivation and the adaptive immune response, researchers have found that the hypothalamic-pituitary-adrenal axis plays a crucial role. This axis is responsible for distributing glucocorticoid hormones in the bloodstream, which then regulate gene expression in almost all cells of the body. Sleep deprivation leads to the activation of glucocorticoid receptors in leukocytes, which in turn induces a significant inhibition of antiviral gene programs.[52,53]

Sleep deprivation leads to the activation of the sympathetic nervous system (SNS), which releases norepinephrine in primary and secondary lymphoid organs, as well as in other major organ systems such as vascular and perivascular tissues, and various

peripheral tissues. It also stimulates the adrenal glands, causing the release of epinephrine. Both neuromediators activate leukocytes and adrenergic receptors, such as ADRB2, to inhibit the genetic antiviral response gene programs (IRG interferon response). This inhibition is mediated by regulatory factors of IRF interferons, as described by Wilder-Smith *et.al.* [52] and Irwin [53].

Additional research has shown a connection between sleep and the initiation of the production of growth hormone, a process that takes place during the first phase of the night. This hormone has a role in enhancing the growth and specialization of T lymphocytes and stimulating the function of type 1 cytokines.[52,53] Based on the information provided, sleep deprivation leads to a decrease in the release of growth hormone and inhibits the response of Genetic antiviral interferon (IRG), which is controlled by IRF regulatory factors. This imbalance affects the ratio of Th1 to Th2 cells, resulting in reduced production of IFN in Th1 cells and increased production of interleukin-10, also known as IL-10. The hypothesis is that the inhibition of the adaptive immune response may increase vulnerability to infectious illnesses and reduce the effectiveness of vaccinations.[52,53]

The impact of sleep deprivation on innate immunity

Following a lack of sleep, the sympathetic nervous system (SNS) produces norepinephrine in the main and secondary lymphoid system, which in turn increases the adrenal production of epinephrine.[52,53] Both neuromodulators enhance the activation of ADRB2 leukocyte adrenergic receptors and trigger inflammatory responses. These responses are controlled by nuclear factors (NF)-κB and intrinsic circuits, which are responsible for detecting microbes through pattern recognition receptors (PRR), including the Toll-like-4 receptor (TLR4). These actions activate the expression of genes that cause inflammation by using NF-κB transcription factors and producing proinflammatory cytokines including interleukin (IL)-6 and tumor necrosis factor-α (TNF-α).[52,53]

The brain maintains homeostasis by regulating inflammatory activity via the integration of internal and external information. Additionally, it has the ability to impact brain function and modify internal equilibriums, with sleep being particularly susceptible to these effects.[52,53] Hence, the occurrence of sleep dysregulation may lead to an elevated susceptibility to inflammatory factors, which in turn can contribute to the development of cardiovascular disease, cancer, and psychiatric problems.[29] The emotional system's role in this triad is where the link becomes apparent, and simultaneously, these elements have been identified as mortality factors for the transmission of SARS-CoV-2.[58-61]

Conclusion

The health professional's vocation during the pandemic entails a surge in workload and disruption of sleep patterns, leading to sleep loss and heightened stress levels. Stress and its deprivation have a reciprocal connection that is closely tied to the immune system and the control of emotions. This connection leads to an elevation or occurrence of sleep disruptions, emotional disturbances, and the emergence of susceptibility to immunological issues.

According to the literature, these issues can be prevented by implementing strategies before and after work. This will help reduce the mentioned problems and develop more effective coping mechanisms for both the COVID-19 pandemic and future challenges. The primary goal in developing this book was to provide tangible strategies that have been effective in comparable scenarios and adapt them to the current situation for healthcare professionals. Another objective was to guarantee that in future scenarios, when confronted with comparable challenges, these tools may serve as the foundation for enhancing the well-being of healthcare workers during times of crisis. This is why the working group convenes and this method is being introduced to healthcare professionals.

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