Review / *Derleme*

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Sleep, the Immune System, and Inflammation: A Comprehensive Review and Update

Uyku, İmmün Sistem ve Enflamasyon: Kapsamlı Derleme ve Güncelleme

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Abstract

Neurotransmitters in the central nervous system, such as serotonin, noradrenaline, and dopamine, play important roles not only in sleep-wake cycle regulation and neurobehavioral modulation, but also in the regulation of immune system functions. Sleep and the immune system exhibit a bidirectional relationship. Beyond immune regulation, cytokines are involved in various other physiological processes, including memory, appetite, cognition, pain, fatigue, and sleep. Pro-inflammatory cytokines released from Th1 cells predominantly increase the duration of the non-rapid eye movement sleep stage and exert a pro-somnogenic effect. Other molecules such as nitric oxide and adenosine are also known mediators of sleep-immune interactions. During sleep, the production and release patterns of neurotransmitters and neurohormones undergo substantial changes, which are accompanied by alterations in immune cell functions and cytokine levels. In addition to circadian effects, sleep itself, and especially slow-wave sleep, modulates the expressions and levels of cytokines and hormones. Consequently, sleep disturbances, fragmentation, and disorders such as sleep apnea are associated with a significantly increased risk of developing cardiovascular disorders and cancer, driven by elevated inflammation.

Keywords: Sleep, immune system, cytokines, inflammation

Öz

Santral sinir sisteminde serotonin, noradrenalin veya dopamin nörotransmiterler, sadece uyku-uyanıklık döngüsü ya da davranışsal düzenlemede rol almakla kalmaz, aynı zamanda immün sistem ile ilişkili pek çok fonksiyonun düzenlenmesinde de önemli görev üstlenirler. Uyku ve immün sistem arasında iki yönlü bir ilişki mevcuttur. Sitokinlerin sadece immün sistem içerisinde değil, hafıza, iştah, bilişsel fonksiyonlar, ağrı, yorgunluk ve uyku gibi pek çok fonksiyonlarda görev aldıkları tanımlanmıştır. Özellikle Th1 hücrelerinden salınan pro-enflamatuvar sitokinler, çoğunlukla hızlı olmayan göz hareketli uyku, uyku evresinde artışa yol açarak, pro-somnojenik etki de gösterirler. Sitokinlerin yanı sıra, nitrik oksit ve adenozin gibi moleküllerin de immün sistem ve uyku aracılı etkileşimde rol oynadığı bilinmektedir. Uyku esnasında ise, hem nörotransmiterlerin ve nörohormonların salınım paterni değişir, hem de immün sistem ile ilişkili hücrelerin fonksiyonlarında ve sitokin seviyelerinde değişiklikler meydana gelir. Sirkadiyen etkilerin yanı sıra, uyku ve özellikle yavaş dalga uykusu hormon ve sitokin seviyeleri üzerinde etkilidir. Uykunun bozulması, fragmante olması ya da eşlik eden uyku apnesi gibi bozuklukların varlığında ise, enflamasyon artışı ile ilişkili kardiyovasküler hastalıklar ve kanser gelişim riskinde belirgin bir artış izlenir.

Anahtar Kelimeler: Uyku, bağışıklık sistemi, sitokinler, enflamasyon

Introduction

Every organ and physiological system within the human body relies on homeostatic mechanisms that are inextricably linked to immune and inflammatory functions. The cells mediating these functions interact continuously, utilizing a shared repertoire of peptides, neurotransmitters, and soluble molecules (1). Neurotransmitters such as serotonin, noradrenaline, and dopamine in the central nervous system (CNS) not only play a role in the sleep-wake cycle and behavioral regulation but also perform critical regulatory functions within the immune system (2-4). Immune system responses during inflammation are regulated by the "stress axis," which is formed by interactions among the hypothalamus, pituitary gland, and adrenal glands (5). Alongside this axis, various organs modulate the immune system (Figure 1). For example, skeletal muscle exerts an anti-inflammatory effect via myokines secreted into the circulation following sustained contraction during exercise (6). Lipopolysaccharides entering the bloodstream due to impaired gastrointestinal epithelial function can readily trigger

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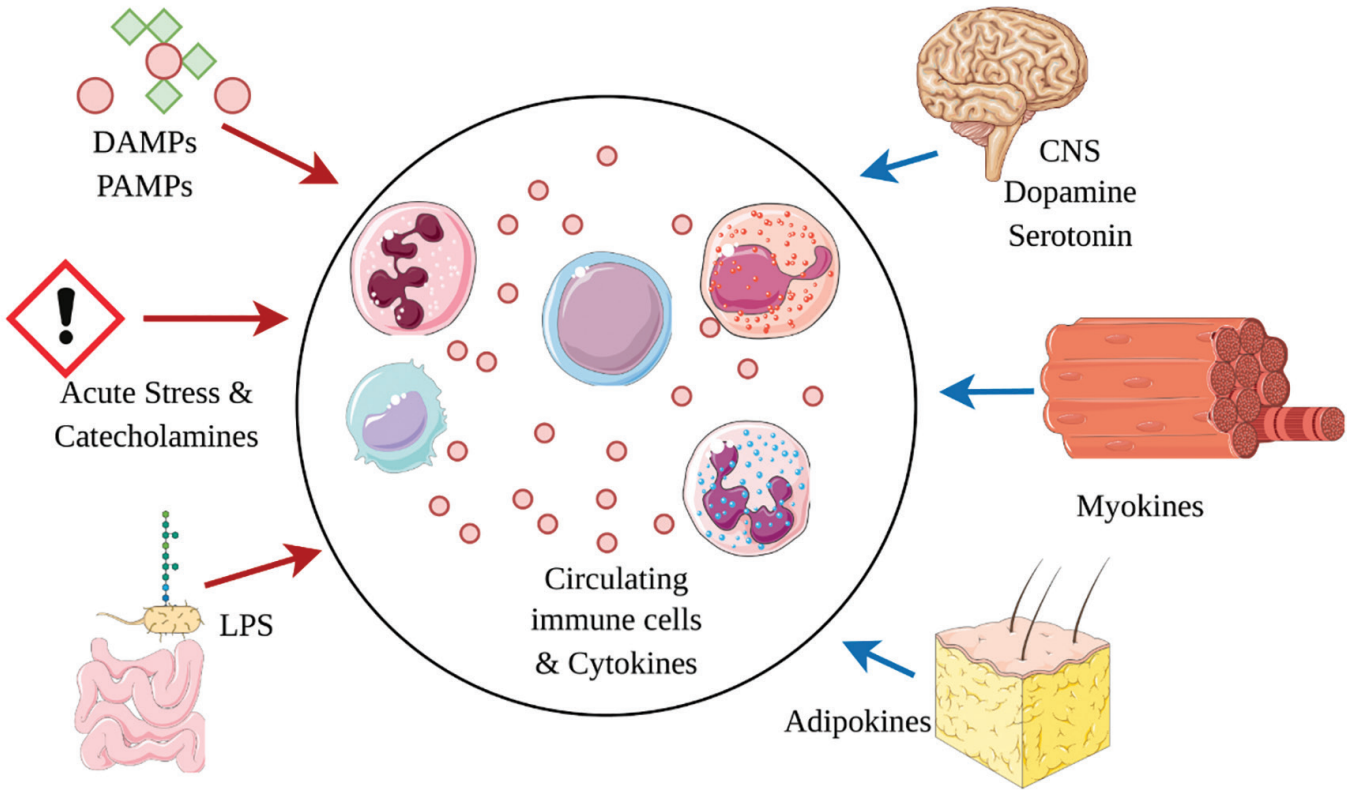

Figure 1. Regulators of circulating immune cells and cytokines. Peripheral inflammatory cues, including damage-associated molecular patterns, pathogen-associated molecular patterns, and bacterial lipopolysaccharide, as well as acute stress-related catecholamines promote immune activation and cytokine release (red arrows). In parallel, central and peripheral modulatory signals including central nervous system neurotransmitters (dopamine and serotonin), skeletal muscle-derived myokines, and adipose tissue-derived adipokines regulate and constrain immune cell function and cytokine profiles in a context-dependent manner (blue arrows). Some icons used in this figure were sourced from bioicons.com and are used under CC BY 3.0 and CC BY 4.0 licenses.
DAMPs: Damage-associated molecular patterns, PAMPs: Pathogen-associated molecular patterns, LPS: Lipopolysaccharide.

an immune response (7). Adipose tissue also suppresses immune function through the secretion of adipokines (8). Finally, immune-mediated molecules act across multiple areas of the CNS, including sleep-wake centers, exerting autoregulatory effects.

The relationship between the CNS and the immune system is highly integrated and bidirectional (9). Communication between these systems via cytokines and neurohormones was first suggested by Besedovsky et al. (10) in the 1970s (11). Subsequent studies have established that cytokines, once thought to operate exclusively within immunological boundaries as messengers between leukocytes, are actually pleiotropic regulators of memory, appetite, cognition, pain, fatigue, and sleep architecture (12). They can exert both pro- and anti-inflammatory, as well as somnogenic and anti-somnogenic effects. Moreover, they can also modulate circadian gene expressions (13).

In this review, we aimed to synthesize recent, clinically relevant literature on the interactions among sleep, the immune system, and inflammation, integrating experimental and human data to provide an updated framework for clinicians and researchers.

The Immune System as a Regulator of Sleep Architecture

The inflammatory response to invading pathogens or tissue injury fundamentally alters healthy sleep architecture, a phenomenon recognized clinically and biologically as "sickness behavior" (14). From an evolutionary perspective, sickness behavior—which includes lethargy, social withdrawal, loss of appetite, and increased sleepiness—is a highly conserved adaptive response designed to conserve energy and redirect metabolic resources toward mounting a robust immune defense. In general, pro-inflammatory cytokines exhibit pro-somnogenic effects, predominantly increasing the duration and intensity of non-rapid eye movement (NREM) sleep, while anti-inflammatory cytokines largely exert anti-somnogenic or wake-promoting effects (Table 1).

The interleukin (IL) 1 family represents a broad and complex network of cytokines comprising 11 different members that

exhibit both pro-inflammatory (e.g., IL-1α, IL-1β, IL-18, IL-33) and antagonistic or anti-inflammatory (e.g., IL-36Ra, IL-37, IL-38) properties (15). The profound relationship between IL-1 and sleep regulation was first identified in 1984, and its somnogenic impact is highly dependent on both the dosage and the circadian timing of administration. Under normal, healthy conditions, IL-1 levels fluctuate with the sleep-wake cycle, peaking at sleep onset. At low physiological doses, IL-1α and IL-1β can trigger sleep without inducing a febrile response, specifically enhancing the duration and electroencephalographic delta-wave intensity of NREM sleep. However, at higher, pathological doses mimicking a severe infection, IL-1 induces fever while simultaneously suppressing rapid eye movement (REM) sleep to prioritize deep, restorative NREM stages (12). The endogenous or exogenous inhibition of IL-1 signaling and the action of anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 inhibit NREM sleep (16,17).

IL-6 is another highly potent pro-inflammatory and pro-somnogenic cytokine. Elevated levels of circulating IL-6 are known to increase NREM and decrease REM sleep duration. IL-6 is linked to the circadian system, modulating the molecular transcription of the *Per1* gene, thereby bridging the immune response with the body's internal clock (18,19). A pivotal study investigated the administration of tocilizumab, a targeted IL-6 receptor inhibitor, to patients suffering from rheumatoid arthritis. The intervention resulted in significant, rapid improvements in sleep quality and a marked reduction in daytime sleepiness (20). The authors stated that these beneficial effects occurred independently of the decrease in disease activity. However, another comprehensive study failed to replicate such effects, instead reporting that tocilizumab was associated with poorer sleep quality (21).

Tumor necrosis factor alpha (TNF-α) shares similar somnogenic properties with the IL-1 family. Recognized for its sleep-promoting effects in 1987, TNF-α is essential not only to inflammation but also to apoptosis, neuroplasticity, and appetite regulation. The expression of TNF-α in the brain increases proportionally with the duration of wakefulness. Like IL-1 and IL-6, TNF-α enhances NREM sleep duration and intensity while causing a compensatory reduction in REM sleep duration, playing a central role in the homeostatic sleep drive (12,22).

Beyond the classical cytokine networks, nitric oxide (NO) and adenosine are also known to mediate interactions between the immune system and sleep. NO, which has important functions in various immunological and physiological processes, demonstrates a circadian pattern in brain tissue that parallels the homeostatic need for sleep; increased NO levels correlate with a heightened urge to sleep. Studies have shown that both NREM and REM sleep stage duration increased following the administration of NO or L-arginine (an NO precursor) (12,23,24). Adenosine is a nucleoside associated with increased homeostatic drive after a period of prolonged wakefulness. It is released from astrocytes during inflammation, especially as part of the cerebral response to lipopolysaccharides originating from the gastrointestinal tract. It exerts a sleep-enhancing effect by stimulating adenosine-1 receptors (25).

Table 1. Classification of cytokines according to their pro-/anti-inflammatory effects, pro-/anti-somnogenic effects, and their associations with the innate versus adaptive immune system (the effects of immune cell populations and certain interleukins (*) may be dose-dependent or, when administered exogenously may vary according to circadian rhythm).

Cytokines	Pro-somnogenic	Anti-somnogenic	Immune system
Pro-inflammatory	IL-1β* IL-1α* TNF-α TNF-β IL-6* IL-15 IL-18 NGF Neurotrophin-3 Neurotrophin-4 Interferon-α* Interferon-γ*	IL-1β* IL-1α* IL-6* Interferon-α* Interferon-γ*	Innate
	IL-2		Adaptive
Anti-inflammatory	Epidermal growth factor	IL-10 IL-1Ra Insulin-like growth factor* Soluble TNF receptor Soluble IL-1 receptor	Innate
		IL-4 IL-5 IL-13 Transforming growth factor-β	Adaptive

IL: Interleukin, TNF-α: Tumor necrosis factor-alpha, TNF-β: Tumor necrosis factor-beta, NGF: Nerve growth factor

The immune system and inflammation have sleep-regulating effects. Inflammation in response to a pathogen alters healthy sleep structure. The inflammatory process is highly complex, exerting its effects on sleep by interacting with both neurons and glial cells. Through these interactions, neuronal cellular pathways are activated, and localized inflammation arising in specific brain regions accelerates sleep onset. In other words, local inflammation in the brain naturally increases during sleep (26).

Neuroinflammation

Pro-inflammatory cytokines can cross to the CNS, interact with the brain's cytokine network, and contribute to the regulation of multiple behavioral functions (27). Cytokines released from activated monocytes and macrophages reach the CNS through three main routes: humoral, neural, and cellular. In the humoral pathway, entry occurs through regions with higher blood-brain barrier permeability, such as the choroid plexus and circumventricular organs. Within the brain parenchyma, activated endothelial cells promote the release of mediators such as NO, thereby driving the activation of specific brain regions. In the neural pathway, peripheral afferent fibers of the vagus nerve, upon stimulation by pro-inflammatory cytokines, relay signals to the nucleus of the solitary tract and the area postrema. Finally, in the cellular pathway, circulating pro-inflammatory cytokines—particularly TNF-α—can directly activate brain-resident monocytes and related myeloid cells, thereby contributing to the development of neuroinflammation.

Cytokines influence a wide range of physiological domains within the CNS. For example, their effects on the basal ganglia can modulate motivation and motor activity, whereas their impact on the anterior cingulate cortex can shape circuits related to mood and anxiety. Cytokines also regulate neuronal growth, neurogenesis, and synaptic plasticity through interactions with neurotrophic factors. In addition, they affect the metabolism of key neurotransmitters, including serotonin, dopamine, and glutamate, thereby contributing to mood regulation and sleep control. Neuronal metabolic activity leads to the release of "sleep-regulatory molecules" such as adenosine, NO, IL-1β, and TNF-α, which shift local networks toward sleep. These same mediators also act at larger circuit levels. For instance, microinjections of IL-1β or TNF-α into the anterior hypothalamus markedly increase total sleep time, while unilateral cortical cytokine administration increases ipsilateral slow-wave activity. Thus, the complex relationship between local networks and whole-organism sleep is coupled through shared cytokines and metabolites (28).

A broad range of cytokines participate in sleep regulation (27,29). Pro-inflammatory cytokines, particularly those associated with Th1 responses, often exert pro-somnogenic effects by promoting NREM sleep. Key pro-somnogenic mediators, including IL-1, TNF-α, and neurotrophic factors, activate intracellular inflammatory mediators such as nuclear factor κB (NF-κB) and increase the production of prostaglandin D2, adenosine, NO, and growth hormone-releasing hormone. This strengthens the homeostatic sleep drive and facilitates NREM sleep initiation. Pro-inflammatory cytokines also bias the balance between inhibitory and excitatory neuronal and glial signaling—mediated by gamma-aminobutyric acid and glutamate—toward sleep. Beyond their effects on homeostatic regulation, pro-inflammatory cytokines also influence circadian processes. They inhibit the effect of the *BMAL1–CLOCK* complex on the *CRY–PER* complex, further contributing to sleep initiation (29). Moreover, cytokines and neurohormones exhibit circadian rhythmicity. During wakefulness, the increase in cortisol (associated with increased CXCR4 expression) promotes the trafficking of naïve T helper cells toward the bone marrow (30). Similarly, the high levels of adrenaline during wakefulness facilitate the mobilization of cytotoxic natural killer cells from marginal pools into the circulation by reducing CX3CR1/CD11a signaling. During sleep, both neurotransmitter and neurohormone release patterns shift, accompanied by changes in immune cell function and cytokine levels.

CX3CR1 signaling is also critical for microglial activity and the maintenance of neuroimmune homeostasis. CX3CR1, a receptor predominantly expressed on microglia in the CNS, follows a circadian rhythm that dictates microglial morphology and their surveillance of neuronal synapses. Healthy sleep-wake cycles ensure the proper regulation of this signaling, facilitating synaptic pruning and preventing excessive neuroinflammation. However, sleep disruption can impair CX3CR1-mediated pathways, leading to aberrant microglial activation and a shift toward a pro-inflammatory state. Consequently, nocturnal sleep serves as a fundamental regulator of the brain's internal immune environment through these specific molecular checkpoints (31).

Beyond the CNS, nighttime sleep also reshapes peripheral immune trafficking between the circulation and lymphoid tissues. Lower cortisol levels during sleep compared to wakefulness facilitate the egress of T helper cells from the bone marrow into the circulation and their subsequent homing to lymph nodes (30). Thus, circulating T helper cell levels are higher during nocturnal sleep. In contrast, lower adrenaline levels promote redistribution of cytotoxic natural killer cells from the circulation to marginal pools, resulting in lower circulating natural killer cell counts during sleep.

These changes in neurohormonal tone and immune cell distribution translate into substantial alterations in cytokine profiles. Decreases in cortisol and adrenaline/noradrenaline reduce anti-inflammatory cytokine production by monocytes, particularly IL-10. Conversely, increases in growth hormone and prolactin are accompanied by marked rises in pro-inflammatory cytokines released from monocytes and dendritic cells, including IL-6, TNF-α, and IL-12. Collectively, these shifts contribute to a more pro-inflammatory milieu in the brain during sleep, consistent with enhanced nocturnal neuroinflammatory activity.

Effects of Sleep on the Immune System

Circadian rhythms shape the secretion profiles of many hormones and cytokines. Sleep—especially slow-wave sleep—exerts an additional, state-dependent influence on their circulating levels (32). During this sleep phase, a significant increase in growth hormone and prolactin secretion is observed,

as well as a decrease in cortisol levels. Comparisons with nocturnal wakefulness demonstrate that this is a true "sleep" effect rather than merely a "night" effect (30). Catecholamine levels also decrease during sleep compared to periods of nocturnal wakefulness, particularly during the REM sleep phase. Consequently, sleep increases TNF-α and IL-12 production while suppressing IL-10 production via its modulation of neurohormonal levels. Conversely, IL-6 production is controlled solely by circadian effects. Indeed, comparisons with nocturnal wakefulness reveal no additional effect of sleep.

As discussed above, a decrease in cortisol and epinephrine/norepinephrine levels and an increase in growth hormone, prolactin, and melatonin levels occur during healthy sleep via the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (33). When sleep is disrupted, increased cortisol levels suppress pro-inflammatory gene transcription by stimulating glucocorticoid receptors, directly inhibiting pro-inflammatory mediators such as NF-κB through protein-protein interactions and increasing anti-inflammatory gene transcription. As a result, Th1 cell counts and interferon (IFN) levels decrease, while Th2 cell count and IL-10 levels increase. The grand sum of these effects is the anti-inflammatory effect associated with the adaptive immune system.

In the presence of sleep disruption, fragmentation, or comorbid sleep disorders such as sleep apnea, sympathetic nervous system activation occurs. This causes an increase in epinephrine/norepinephrine levels, which normally decrease during healthy sleep. As a result, β-adrenergic receptors (such as ADRB2) in leukocytes are stimulated, increasing pro-inflammatory *IL-1β, IL-6* and *TNF* gene transcription and suppressing anti-inflammatory *IFN* gene transcription. This leads to susceptibility to infection and poor vaccine response. Sleep disruption also negatively impacts the innate immune system. Similarly, CNS activation and the stimulation of leukocyte β-adrenergic receptors increase NF-κB secretion, resulting in the production of IL-6 and TNF-α. The interaction between the brain and peripheral tissues enables the brain's modulating effect on the immune system, whereas inflammatory activity reciprocally affects neural processes and sleep patterns. Disruption of this dynamic is associated with increased inflammation and heightened risk of cardiovascular diseases and cancer.

Sleep exerts a distinct effect on leukocyte trafficking beyond circadian timing. Although circulating leukocytes show robust day–night rhythms, controlled human studies demonstrate that nocturnal sleep itself acutely lowers blood counts of monocytes, natural killer cells, and major lymphocyte subsets compared with sustained nocturnal wakefulness, consistent with redistribution from the blood to tissue/lymphoid compartments (33,34). This sleep-related reduction extends across multiple T-cell populations. In detailed phenotyping, sleep uniformly decreased the numbers of diverse CD4+ and CD8+ T-cell subsets during the night relative to nocturnal wakefulness (35). Sleep selectively enhances the migratory potential of several T-cell subsets toward CCL19, a key chemokine for lymph node homing. This effect can be reproduced using plasma from sleeping participants and is dependent on growth hormone and prolactin signaling (36). Complementing these physiological observations, evidence from recent human data suggests that sleep disruption or deprivation can shift innate immune composition, with reversible increases in non-classical ($CD14^{low}CD16^{+}$) monocytes, supporting the view that insufficient sleep biases leukocyte distribution toward a more inflammatory profile (37).

Sleep, especially slow-wave sleep, works in cooperation with the circadian system to ensure the formation of an adaptive immune response. Changes in anti- and pro-inflammatory mediators and hormone levels first initiate an adaptive immune response in the lymph nodes. Following the entry of antigens into the body, they are retained by antigen-presenting cells (APCs) and presented to Th cells. IL-12 produced by APCs stimulates Th1 cells and activates antigen-specific Tc cells, which initiates antibody production by B-cells (30). In the first half of the night especially, the pro-inflammatory state created by the circadian system and slow-wave sleep—driven by increased growth hormone and prolactin secretion and the suppression of cortisol—lays the groundwork for this pathway, which establishes long-term immune memory against the antigen. Growth hormone, prolactin, and IL-12 increase the Th1 immune response at the cellular level. The neurobehavioral changes of the adaptive immune system take place in the lymph nodes through coding, consolidation, and recall phases, similar to what occurs in the brain. Thus, sleep provides memory against infections in both the brain and the peripheral immune system (30). In addition, cytokines released from Th1 cells are also known to induce slow-wave sleep in a positive feedback loop (as discussed above).

Natural killer cell activity in the innate immune system begins to increase in the first hours of sleep and reaches a peak in the second half of the night. Neutrophil and monocyte cell levels also increase with sleep duration (38). IL-5 and IL-6 levels also peak during sleep, especially during the REM sleep phase. In the event of a mismatch between daylight hours and the endogenous circadian clock, or in any situation that disrupts the healthy sleep architecture, an initial increase in cortisol levels occurs via HPA axis activation. Consequently, contrary to what occurs during healthy sleep, increased production of both pro- and anti-inflammatory cytokines is observed in the peripheral blood and the CNS, thereby initiating an inflammatory immune response.

Sleep Diseases and Inflammation

Disruption of sleep structure and shortening of total sleep time cause inflammation and inflammation-related disorders such as cardiovascular diseases, arthritis, diabetes mellitus, and some cancers (33,39,40). Sleep deprivation causes spontaneous activation of the cellular innate immune system and the release of inflammatory cytokines (e.g., IL-6 and TNF-α) from monocytes as a result of the aforementioned effects on the HPA axis. It also activates proteins involved in signaling and transcription, creating an inflammatory microenvironment that poses an increased risk for disease development. These effects may be reversible following correction of sleep deprivation (33,34).

Altered cytokine gene expressions were also reported in experimental models featuring short-term sleep fragmentation (41). A significant increase in *IL-1β* gene expression levels in adipose tissue, myocardium, and specific brain regions (the hypothalamus and hippocampus) has been observed, as well as an increase in *TGF-β1* gene expression levels in the same brain regions. Studies in humans have further demonstrated that the regulation of immune-associated signaling pathways is impaired after partial sleep restriction. Changes in sleep structure due to altered cytokine levels, especially the decrease in NREM sleep duration, may also explain subsequent daytime fatigue and excessive sleepiness (42,43). A significant proportion of fatigue complaints, which are highly prevalent in multiple sclerosis (an immune-mediated neurodegenerative disorder), are associated with these negative inflammatory effects on the brain and sleep cycles (44,45). The persistent nature of some of these effects seems to be important in triggering pathological processes such as inflammation-related cardiovascular disease. Gastrointestinal conditions such as metabolic syndrome or inflammatory bowel diseases can also manifest or exacerbate due to the inflammatory processes associated with sleep disorders (46,47). In addition to increased inflammation, sleep restriction has also been shown to play an important role in the development of cancer (48). Ultimately, considering the regulatory role of sleep on the immune system, it is evident that sleep deprivation poses a significant risk for the development of numerous diseases by triggering inflammatory cascades. Acute sleep deprivation leads to an increase in pro-inflammatory cytokines and enlargement of the perivascular spaces, which also indicates glymphatic dysfunction (49). Prolongation of this process and chronic glymphatic system involvement is known to trigger the long-term development of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease (50).

The coronavirus disease 2019 (COVID-19) pandemic significantly highlighted the intersection of sleep medicine and infectious disease. While the pandemic itself triggered a surge in insomnia—largely driven by heightened levels of anxiety and depression—evidence consistently demonstrated that pre-existing sleep disturbances were associated with higher susceptibility to infection and more severe clinical courses. Specifically, patients with short sleep duration and insomnia exhibited higher rates of hospitalization and poorer prognoses (51,52). Furthermore, sleep deprivation was linked to diminished antibody responses and a higher incidence of fatal acute respiratory failure in COVID-19 cases (53). In this context, it has been reaffirmed that a healthy sleep is one of the most basic requirements for having a properly functioning immune system. Recognizing the highly integrated, bidirectional relationship between sleep and the immune system sheds light on the pathophysiology of various diseases. Furthermore, it highlights the clinical necessity of routinely assessing sleep health and implementing corrective interventions in both the prevention and treatment of disease.

Inflammatory Diseases and Sleep

In addition to the higher risk of developing immune and chronic inflammatory diseases in those with sleep disorders, the reverse is also true: sleep-related disorders are more common among patients with immune-mediated inflammatory diseases (54). A recent review comparing disease groups such as inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, psoriasis, and fibromyalgia with control groups revealed higher rates of disturbed nocturnal sleep, insomnia, restless legs syndrome, and sleep apnea in patients with inflammatory diseases. Given the complex etiopathogenesis of sleep disorders, it can be said that although the magnitude of risk varies across specific disease groups, the overall prevalence of sleep disorders remains significantly elevated in these populations.

Beyond the primary inflammatory drivers, specific clinical manifestations of immune-mediated diseases further complicate the sleep architecture through multifactorial pathways. Insomnia is frequently exacerbated not only by the systemic inflammatory load but also by comorbid chronic pain and depressive symptoms prevalent in these patient populations. Furthermore, anatomical and structural changes directly influence sleep-disordered breathing. For instance, rheumatoid arthritis may predispose patients to obstructive sleep apnea through temporomandibular and cricoarytenoid joint involvement (55). Similarly, the systemic nature of inflammatory bowel diseases, often accompanied by concomitant obesity or iron deficiency, can independently trigger sleep apnea or restless legs syndrome, respectively (56). Consequently, these disease-specific findings create a complex clinical picture where inflammatory activity and physical symptoms synergistically degrade sleep quality.

Conclusion

In conclusion, the relationship between immune-mediated inflammatory diseases and sleep disorders is characterized by a sophisticated, bidirectional interplay where dysregulated sleep architecture and chronic inflammation reinforce one another. Beyond the higher prevalence of sleep disturbances in these populations, the evidence suggests that poor sleep quality acts as a potent driver of disease progression, potentially worsening clinical outcomes and diminishing treatment efficacy. Recognizing sleep not merely as a quality-of-life issue but as a core physiological component of immune homeostasis is essential for modern clinical practice. Consequently, integrating sleep health assessments into the management protocols of inflammatory diseases—and targeting these shared neurobiological pathways—represents a critical frontier for improving both patient prognosis and the overall burden of chronic immune-mediated conditions.

Footnotes

Authorship Contributions

Concept: U.T., G.B.Ş., Design: U.T., G.B.Ş., Data Collection or Processing: U.T., G.B.Ş., Analysis or Interpretation: U.T., G.B.Ş., Literature Search: U.T., G.B.Ş., Writing: U.T., G.B.Ş.

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