Sleep, Immunological Memory, and Inflammatory Skin Disease

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Introduction

Despite the well-known advantages of adequate sleep for the human body, the impact of sleep on chronic inflammatory skin disease is underappreciated [1]. Psoriasis, atopic dermatitis, hidradenitis suppurativa, and vitiligo patients experience a greater prevalence of sleep dysfunction versus the general population [2–5], which likely contributes to their reduced health-related and overall quality of life [6–9]. Sleep dysfunction in these patients may also have repercussions regarding the development and progression of their chronic inflammatory skin disease, and the systemic comorbidities associated with them. This may be, in part, explained by the bidirectional relationship between sleep and the immune system, which we discuss below.

Impact of Sleep on the Immune System

Recent research supports the influential role that sleep behavior is capable of having on immune function. For example, sleep dysfunction following vaccination is linked to decreased antibody response [10], and short

sleep duration is shown to increase susceptibility to viral illness [11]. These outcomes may be in part related to the impact of sleep on immune memory formation. Slow-wave sleep (SWS), which is considered the deepest type of sleep occurring during non-rapid eye movement (NREM) sleep, promotes the redistribution of antigenic information in antigen-presenting cells (APCs) to T cells for long-term storage. SWS creates an ideal environment for immune cell memory formation by increasing growth hormone and prolactin and decreasing catecholamine and cortisol levels. These conditions promote an increased number and efficiency of APC and CD4+ T-cell interactions, broader recruitment of T-cell receptors on CD4+ T cells, and increased synthesis of pro-inflammatory cytokines, such as IL-17, which supports memory T-cell survival [12]. Sleep dysfunction could be disruptive to these neuroendocrine conditions, negatively affecting immune cell memory consolidation [13]. This may have some clinical relevance for the onset, maintenance, and progression of chronic inflammatory skin diseases, such as vitiligo and psoriasis, which are driven by aberrant memory T cells [14, 15].

Beyond its regulatory effect on immune cell memory formation, sleep has also been evidenced to affect the im-

immune system in other ways. Even just one night of sleep deprivation is seen to increase pro-inflammatory TNF- α concentration [16] and five days of sleep restriction can shift the Th1/Th2 ratio toward Th2, [17] potentially affecting Th2-mediated diseases such as atopic dermatitis. Future research would be helpful to assess whether the immunomodulatory effects of sleep impact the course of chronic inflammatory skin diseases. While disease severity is seen to correlate with poor sleep in psoriasis patients [18], it is unclear whether more severe disease leads to poor sleep or whether poor sleep leads to more severe disease, with both likely playing a role. The influence of sleep dysfunction on chronic inflammatory diseases has not yet been assessed in dermatology patients, but it has been explored in IBD patients. In murine models of colitis, chronic intermittent sleep deprivation was found to increase colonic inflammation and colitis severity [19], and in IBD patients, self-reported sleep quality demonstrated an inverse correlation with serum C-reactive protein levels [20].

Impact of the Immune System on Sleep

Sleep and the immune system are part of a bidirectional feedback loop. While sleep is suggested to have a regulatory effect on immune memory formation, immune system activity is conversely demonstrated to influence sleep parameters such as sleep latency, efficiency, and architecture. For instance, cytokines IL-1, TNF, IL-2, IL-4, IL-10, IL-13, IL-15 IL-16, and IL-18 have all been shown to harbor physiological sleep-modifying properties [21, 22]. In animal studies, biologic inhibition of IL-1 and TNF have been shown to reduce NREM sleep, and elevation of IL-1 and TNF have been shown to increase NREM sleep and reduce rapid eye movement (REM) sleep. This suggests a role for IL-1 and TNF in maintaining a balance between NREM and REM sleep, which affects the amount of SWS an individual experiences [22]. Prostaglandins have also been shown to affect sleep architecture and SWS, with acute aspirin (an inhibitor of prostaglandin production) administration reducing sleep efficiency, increasing nighttime awakenings [23], and decreasing SWS in healthy adults [24].

The effects of chronic inflammation on sleep patterns have been explored in IBD and RA, with anti-TNF therapy leading to significant improvements in self-reported sleep quality in IBD [25] and RA patients [26, 27] and polysomnography-assessed sleep parameters in RA patients [28–30]. In one of these studies, TNF inhibitor

therapy resulted in reduced sleep latency and increased sleep efficiency and REM sleep in RA patients independent of joint pain [29]. In another study, IL-6 inhibitor therapy in RA patients resulted in better self-reported sleep quality independent of disease activity [31]. The abundance and timing of IL-6 and TNF accumulation have also been shown to influence sleep efficiency in RA patients [32], further suggesting an independent effect of cytokine levels on sleep behavior. This may be at play in linking hypertension and sleep dysfunction as well, as high blood pressure (which is associated with chronic inflammation) may be predictive of future insomnia in older adults [33].

In dermatology, we typically think of sleep disruption as a consequence rather than a cause of primary skin pathology, such as nocturnal pruritus in atopic dermatitis patients or pain with psoriatic arthritis in psoriasis patients. The increased prevalence of obesity, depression, and low quality of life in dermatology patients likely causes sleep dysfunction in this population as well. While the above studies suggest that an overactive immune system could be one of the factors contributing to sleep dysfunction in chronic inflammatory disease patients, future studies controlling for comorbid sleep-disturbing factors are necessary to determine the degree to which immune dysregulation alters sleep in dermatology patients. A useful population in which to study this could be vitiligo patients, as they exhibit an increased prevalence of sleep-disturbing parasomnias (sleep walking, nocturnal enuresis, night illusions, sleep terrors, and nightmares) [2], but do not characteristically suffer from pain or itch common to other skin diseases. Depression and low quality of life, common in vitiligo patients, would have to be accounted for.

Sleep and Our Immune System in Skin Disease

Given the relationship between sleep and the immune system and the robust correlation of sleep dysfunction with many skin diseases, sleep dysfunction could be contributing to chronic inflammation in certain skin diseases via its effect on immune memory. Memory T cells direct inflammation and autoimmunity and have been implicated in atopic dermatitis, contact dermatitis, vitiligo, and psoriasis, among others [34–36]. More recent evidence implicating tissue-resident memory T cells in vitiligo [37] and psoriasis [38] further supports the notion that many skin diseases are indeed “immune memory diseases” [32, 34, 35].

Sleep dysfunction is also strongly linked to several dermatologic comorbidities, especially cardiometabolic [39] and psychiatric disorders [40] in which chronic inflammation is implicated as well [41–43]. Individuals that get less than 5 h of sleep a night, on average, have a 2- to 3-fold greater risk of anxiety or depression compared to those who get 7 h of sleep a night [40]. Getting less than 5 h of sleep a night is further correlated with high BMI, obesity, diabetes, hypertension, hypercholesterolemia, heart attack, and stroke [39]. Notably, these comorbidities are associated with skin conditions that have a high prevalence of sleep dysfunction, such as atopic dermatitis [44], psoriasis [45], and hidradenitis suppurativa [46]. Poor sleep may play some role in driving the development of these comorbidities in dermatology patients, possibly through immune modulatory effects or others. In fact, psoriasis patients with a comorbid sleep disorder have been seen to have a higher risk of ischemic heart disease (HR 1.25, 95% CI 1.22–1.28) and stroke (HR 1.24, 95% CI 1.16–1.33) compared to psoriasis patients without a comorbid sleep disorder, supporting the role of sleep in augmenting the relationship between psoriasis and one of its major comorbidities, cardiovascular disease [47].

Conclusion

While understanding the effect of sleep on immune memory is preliminary, exploration of this relationship within the context of skin disease could lead to pathogenic and therapeutic insights. The repercussions of this may not only improve recognition of environmental conditions capable of triggering or maintaining aberrant or autoreactive T cells in skin disease, but may also help encourage dermatologists to emphasize sleep hygiene in

their practice. The therapeutic potential of this may lead to improved management of one's skin disease as well as reduced risk of developing cardiometabolic and psychiatric comorbidities. This may help improve dermatology patients' quality of life and also reduce patients' morbidity and mortality, which is largely a consequence of cardiometabolic disease in psoriasis [48], hidradenitis suppurativa [49], and atopic dermatitis [50]. Potential modalities to be explored in future clinical trials include cognitive behavioral therapy and mindfulness exercises to manage sleep dysfunction in chronic inflammatory skin disease patients [51].

Key Message

Sleep affects immune memory, which plays an important role in many chronic inflammatory skin conditions.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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