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Review

The bidirectional interactions between psoriasis and obstructive sleep apnea

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Abstract

Psoriasis is a chronic inflammatory skin disorder which can impair general routine activities and has been closely related to poor quality of life. Pruritus and scratching are frequently observed, occurring mainly during sleep and precipitating nighttime arousals. Indeed, sleep quality has been shown to be negatively affected in psoriatic patients, in a close relationship with stress exposure and immune response. Although psoriasis is known to impair sleep, leading to insomnia, its association with obstructive sleep apnea (OSA) is controversial. Similarly, OSA is considered a multifactorial inflammatory disease, characterized by intermittent hypoxia, sleep fragmentation and autonomic dysfunction, with important outcomes on the cardiovascular and metabolic systems. Importantly, immunological activities and pro-inflammatory cytokines play a prominent role in both OSA and psoriasis. Currently it is not clear whether OSA is a risk factor for psoriasis development or if psoriasis is a possible predictor of OSA. Thus, our main purpose is to provide an overview of this intriguing relationship and show the current link between psoriasis and OSA in a bidirectional relationship.

Introduction

The skin acts as a barrier between the body and the environment, interacting with thermoregulation, the circadian rhythm as well as the stress system.[1,2] Sleep and stress are closely related, sharing pathways that affect both the immune and central nervous systems and may constitute underlying mechanisms responsible, at least in part, for the pathogenesis of some skin diseases, such as psoriasis.[3] The central nervous system and the immune system present a bidirectional communication. If sleep is altered, there is a disruption in the immune response, which in turn is capable of inducing sleep changes.[4] Sleep disturbances, such as obstructive sleep apnea (OSA), increase the levels of proinflammatory cytokines.[5] OSA has been extensively studied in relation to metabolic and cardiovascular disease,[6] but has rarely been associated with dermatologic conditions. Indeed the interaction between OSA and psoriasis is complex and possibly linked by systemic inflammation.[7] Thus, it is reasonable to hypothesize that there might be a bidirectional relationship between one condition and the development of the other one. Taking into consideration the fact that poor sleep quality is correlated with skin dysfunction, and that OSA incidence is increasing over time in parallel with sleep deprivation,[8] the current study will discuss the bidirectional relationship between psoriasis and OSA, including aspects of etiopathogenesis of both disorders.

Obstructive sleep apnea

OSA is a prevalent sleep disorder affecting 2–33% of the general population, with a higher prevalence among males and a close association with obesity.[9,10] Over the last two decades, an increasing trend in OSA incidence has been reported.[8] Sleep fragmentation, intermittent hypoxia, hypercapnia, and intrathoracic pressure swings are the main factors associated with the pathophysiology of OSA and play an important role in the neurocognitive, metabolic, and cardiovascular consequences of the disease.[11–16] Evidence has confirmed the contribution of systemic inflammation as a mediator of some OSA-related outcomes such as atherosclerosis, endothelial dysfunction, and insulin resistance.[17–19] The chronic intermittent hypoxia, and possibly the sleep loss and fragmentation associated with OSA, increase the levels of C-reactive protein, tumor necrosis factor (TNF)-α, interleukin (IL)-6, and the activation of neutrophils and platelets, which are shown to be reversed or reduced after continuous positive airway pressure (CPAP) treatment.[20–25]

The inflammation process, which is activated in patients with OSA, seems to predispose them to develop

psoriasis. A longitudinal study by Yang *et al.*[26] found that in a sample of 13,513 subjects, 36 (0.3%) had developed psoriasis during the 3-year follow-up period, and it was much more frequent in those with OSA compared to non-OSA individuals. The logistic regression model showed that the risk of developing psoriasis during the 3-year follow-up period was 2.3 times higher for patients with OSA compared to the non-OSA group.

Psoriasis

Psoriasis is a common genetically determined, chronic, inflammatory skin disease characterized by rounded erythematous, dry, and scaling patches known to cause physical symptoms such as itch and pain.[27] It is a common autoimmune disease with a genetic basis with T cells involved in the inflammatory process, mainly T-helper 1 and 17.[28] Psoriasis tends to increase with age with most studies not showing differences between genders. The prevalence among adults varies according to the country, with, for example, 2.1% in Italy and 8.5% in Norway, but most countries report a prevalence above 1%.[29] One important outcome associated with psoriasis is the cardiovascular risk. A recent meta-analysis demonstrated that psoriasis is strongly associated with atherosclerosis, hypertension, and ischemic heart disease.[30] Moreover, psoriasis is also considered a risk factor for developing diabetes.[31] This is a disabling disease that causes overall negative impact in patients' lives,[32] including physical, social, and psychological impairment.[33,34] In addition, sleep is another behavior affected by psoriasis. Its evaluation should be considered and incorporated into several instruments used to evaluate the impact of the disease on quality of life.[35]

Psoriasis and obstructive sleep apnea: the chicken or the egg?

Psoriasis is known to impair sleep, but the association between sleep disturbance and this disease has not been entirely characterized. Patients can be evaluated by subjective or objective trials. Among subjective trials, quality-of-life questionnaires have been used to measure sleep quality,[32,33,36] and a number of hypotheses have been made about the factors involved in the relationship between sleep and psoriasis, including depression.[37] Indeed, psoriasis is associated with depression, which has also been shown to alter sleep through modulation of substance P.[38–40] Psoriasis may cause itching that impairs sleep, commonly affecting the trunk and extremities, and negatively affecting quality of life.[41] Scratching occurs predominantly during sleep stages N1 and N2 rather than N3, and precipitates arousals, leading to sleep fragmentation.[42] Pruritus and pain are considered predictive factors of poor sleep quality.[27,34] Callis Duffin *et al.*[27] reported that 49.5% of respondents stated that their psoriasis negatively affected sleep at least once per month. The same group revealed that psoriatic arthritis, lesion-related itch and pain, as well as emotional well-being are risk factors for the development of sleep disturbance in patients with psoriasis.

Gaikwad *et al.*[43] showed that stigma, shame, guilt, and various illness-related fears are contributors for sleep disorders in psoriatic patients. In particular, psoriasis is significantly associated with insomnia, a sleep disorder characterized by difficulty initiating or maintaining sleep as well as early awakenings.[35,44] Li *et al.*[45] performed a prospective analysis that identified an association between rotating night shift work and increased risk of psoriasis. However, another study showed that in patients with psoriasis vulgaris, excluding those with comorbidities such as OSA, restless leg syndrome, congestive heart failure, depression, and stress factors, psoriasis did not adversely affect quality of sleep.[46]

Regarding objective studies, the literature is scarce. Yang *et al.*[47] found that the respiratory disturbance index was greater in patients with psoriasis compared with controls, and there was decreased deep sleep in patients with psoriasis. Another study using polysomnography found that the frequency of OSA was significantly higher in patients with psoriasis, at about 55%, compared to the general population.[48] However, this study had some limitations, such as the lack of a control group, the small number of patients, and the lack of adjustment for body mass index (obesity). It is well-known that the prevalence of OSA is higher in obese patients and the prevalence of obesity is increased in patients with psoriasis.[10,49] Early studies indicated a greater prevalence of OSA in psoriasis than in control groups.[47,50] While studying groups of patients with psoriasis and chronic bronchitis, Buslau and Benotmane[50] demonstrated that apnea–hypopnea index was significantly higher in those with psoriasis compared to those with chronic bronchitis. Moreover, they found an improvement in the psoriasis of three patients with refractory psoriasis and concurrent OSA while on CPAP treatment, suggesting a role for sleep improvement and reduction of inflammation subsequent to nasal CPAP therapy in the treatment of psoriasis and its pathophysiology. On the other hand, Papadavid *et al.*[51] found that in general there was no correlation between psoriasis characteristics and OSA, although patients with psoriasis who were diagnosed with OSA through polysomnography presented more frequent snoring and lower sleep quality compared with those without OSA. Multivariable logistic regression models revealed that only body mass index and hypertension were associated with increased risk of

OSA, adjusting for psoriasis characteristics, age, and gender. However, in subgroup analyses, OSA correlated with duration of psoriasis (> 8 years) in women and with Framingham scores in men.[51] Another scenario in this relationship points to the fact that the activation of inflammatory pathways mediated by OSA may predispose people to the development of psoriasis, which was indicated by one epidemiological study.[26]

In addition to OSA, lack of sleep can also interfere with the immune system, promoting nocturnal secretion of cytokines, which may be considered another risk factor for psoriasis.[2,52,53] Thus, a bidirectional mechanism is suggested in which psoriasis might also be considered an indirect risk factor for sleep fragmentation, contributing to inflammation and, consequently, to OSA.[54,55] Other mechanisms have associated OSA to psoriasis pathogenesis. Evidence shows that not only is metabolic syndrome, which is characterized by hypertension, dyslipidemia, insulin resistance, and obesity, a risk factor for OSA,[34] but OSA itself can lead to metabolic syndrome.[34,56,57] Cyclic periods of high-frequency hypoxia–reoxygenation might increase the release of reactive oxygen species, which are considered key mediators in the development of hypertension and coronary artery diseases.[58] In contrast, components of metabolic syndrome enact a significant part in the pathogenesis of psoriasis.[34,59,60] Patients with cardiovascular disease, obesity, and psoriasis present higher levels of inflammatory mediators, e.g., TNF-α, intercellular adhesion molecule-1, E-selectin, and vascular endothelial growth factor, which perpetuate the inflammatory process and consequently the course of OSA and psoriasis.[54,55,61] In addition, the increase of the proinflammatory cytokine IL-17 observed in psoriasis is not only related to the pathogenesis of psoriasis but also to atherosclerotic vascular disease, which is considered a risk factor for OSA[34,62,63] and may play an important role in this OSA–psoriasis relationship.

It has also been reported that higher levels of insulin-like growth factor II are found in the skin and blood of patients with psoriasis with chronic inflammation.[64] In fact, insulin-like growth factor II is linked to diabetes and hyperlipidemia in both animal and human models. It promotes epidermal proliferation and is implicated in atherosclerosis development, body fat mass modulation, and lipid metabolism in mice.[60,64,65] Therefore, it characterizes an indirect mechanism that makes psoriasis a risk factor for OSA.

Our group has shown that sleep loss in a psoriatic animal model leads to exacerbation of psoriasis through immune system modulation.[2] In this study, we found that mice with psoriasis submitted to sleep deprivation increased skin kallikrein-5 and kallikrein-7 activities as well as systemic IL-1, IL-6, and IL-12 cytokines and corticosterone levels, in addition to a significant decrease in the anti-inflammatory cytokine IL-10.[2] Indeed, sleep has an important influence over psoriasis through immune and stress system modulation.[66,67] It is known that the increase of these chemical messengers alters brain and behavioral processes, including sleep.[68] The central nervous system is able to detect peripheral immunological activation through the stimulation of nerve fibers by circulating cytokines that permeate the organs and the blood–brain barrier.[4] Cytokines are synthesized and released in the central nervous system by both neurons and glia, and neurons immunoreactive to IL-1 and TNFα are located in brain regions involved in sleep–wake cycle regulation, such as the hypothalamus and brainstem. Proinflammatory cytokines in particular promote non-REM sleep, whereas anti-inflammatory cytokines inhibit non-REM sleep.[69] Given that OSA causes sleep fragmentation, this condition might worsen psoriasis evolution. Moreover, psoriasis causes itching and pain, leading to sleep fragmentation or deprivation, which in turn is able to induce immune system activation.[27,70]

Ekstedt *et al.*[56] reported increased cortisol levels in patients with higher frequency of microarousals, while Spiegel *et al.*[71] found raised concentrations of this hormone in patients presenting sleep debt.[56,71] This is a self-cycling mechanism given that sleep loss activates the hypothalamic–pituitary–adrenal (HPA) axis, leading to increased secretion of cortisol, which plays a major role in the onset of wakefulness.[56,72] OSA leads to increased cortisol levels due at least in part to the sleep fragmentation and hypoxia-induced stress, and frequent cerebral arousals during apneic events generally activate the HPA axis.[58]

As cortisol interacts with the immune system, stressful events could contribute to the maintenance and exacerbation of chronic inflammatory diseases such as psoriasis. For example, cortisol activates skin mast cells, alters the barrier function of skin, and upregulates proinflammatory cytokines, which in turn might exacerbate the severity of psoriasis.[73–76] However, the literature has also demonstrated altered HPA axis activity and immune function in patients with psoriasis. Richards *et al.* found significantly lower serum cortisol levels in response to an acute experimental social stressor for patients with psoriasis, classifying their psoriasis as being stress-responsive.[77] Hypocortisolism might indicate lower responsiveness of the HPA axis in patients with psoriasis, which might be the result of chronic exposure to stress and prolonged hyperactivity of the HPA axis.[78] In these cases, this blunted HPA activity might lead to an immune overactivity with increased inflammatory responses as a consequence of the diminished suppressive effect of the low level of cortisol and maintain, and perhaps reveal, the autoimmune inflammatory state characteristic of psoriasis.[77,78,79]

Both the increase and decrease of cortisol levels could lead to psoriasis exacerbation. Our group demonstrated that augmented corticosterone levels in mice with psoriasis subjected to paradoxical sleep deprivation is associated with disease progression and increased systemic inflammation.[2] It remains to be clarified whether OSA, causing sleep fragmentation and intermittent cycles of hypoxia–reoxygenation, may lead to HPA axis activation or an altered response in human patients with psoriasis. Figure 1 summarizes the overall relationship between OSA and psoriasis, giving importance to several mechanisms based on the literature review.

Final considerations

The current review showed that there is an important interaction between sleep and psoriasis. Patients with psoriasis present significant alterations in sleep architecture such as decreased slow-wave sleep and increased sleep fragmentation, which have been associated as independent factors for inflammation-related mechanisms linked to high cardiometabolic risk. In addition, the immune system alterations that accompany psoriasis and characterize it as a chronic inflammatory disease may predispose patients with psoriasis to sleep disorders such as sleep apnea. Some evidence shows that patients with psoriasis are indeed at higher risk of developing OSA. However, there is also some contradictory data, revealing that OSA may increase risk of psoriasis due to the inflammatory environment that links both conditions. As a limitation, the current work has considered the bidirectional relationship between OSA and psoriasis with a hypothetical bias. Possibly, if more studies are undertaken to look at treatment of both diseases in a prospective framework,

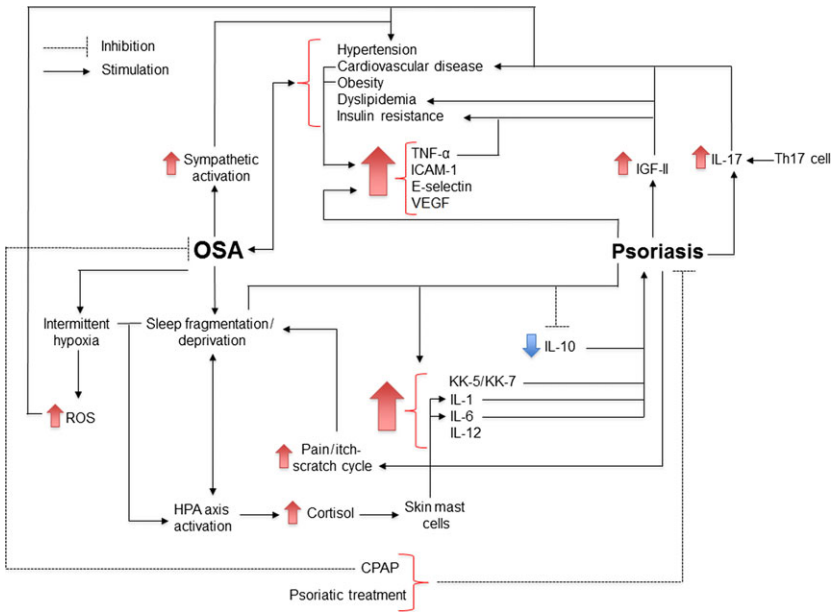

Figure 1 How do sleep apnea and psoriasis interact? Interaction occurs via many intermediate pathways. Comorbidities such as metabolic syndrome (hypertension, obesity, dyslipidemia, insulin resistance) and cardiovascular disease predispose to obstructive sleep apnea (OSA) and vice versa by means of several mechanisms, such as the secretion of cytokines and sympathetic activation. Psoriasis also leads to the same comorbidities, and they share the secretion of various mediators such as tumor necrosis factor (TNF)-α, intercellular adhesion molecule (ICAM)-1, E-selectin, and vascular endothelial growth factor (VEGF), perpetuating the inflammatory process. Moreover, psoriasis leads to an increase in insulin growth factor (IGF)-II levels and interleukin (IL)-17, which are involved in the pathogenesis of both metabolic syndrome and cardiovascular disease. Psoriasis provokes itching and pain and consequently induces sleep fragmentation/deprivation. On the other hand, OSA is characterized by intermittent hypoxia, which increases generation of reactive oxygen species (ROS) and sleep fragmentation/deprivation, both of which are associated with hypothalamic–pituitary–adrenal (HPA) axis activation and augmented cortisol levels. Elevated cortisol may worsen psoriasis via activation of mast cells and secretion of IL-1 and IL-6 proinflammatory cytokines. Sleep loss in psoriatic animal model leads to increased skin kallikrein-5 and kallikrein-7 activities, elevated systemic IL-1, IL-6, and IL-12 levels, and a significant decrease in IL-10. Such changes in immune system modulators exacerbate psoriasis. Finally, patients with psoriasis and concurrent OSA under psoriasis treatment may experience an improvement in the former disease while on continuous positive airway pressure (CPAP) treatment

we may observe a bidirectional relationship between psoriasis and OSA. As sleep has an important impact on physiological and psychological domains, it is highly relevant for both basic and clinical researchers in dermatology to be aware of this intriguing relationship between sleep and psoriasis, as it can help to promote a better quality of life in the patients and guide management of the disease.

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