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PSORIASIS (J WU, SECTION EDITOR)

Update on Sleep and Pulmonary Comorbidities in Psoriasis

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Abstract

Purpose of Review The purpose of this review article is to provide an overview of sleep and pulmonary comorbidities in patients with psoriasis and summarize important recent findings.

Recent Findings Evidence continues to show that patients with psoriasis experience greater chronic sleep impairment when compared to healthy counterparts. In addition to other comorbidities seen in psoriasis patients, including cardiovascular disease, obesity, and diabetes, obstructive sleep apnea and chronic obstructive pulmonary disease have increased frequency in this population.

Summary Sleep and pulmonary comorbidities in psoriasis contribute to disease burden and impaired quality of life in psoriasis patients. The evaluation of sleep comorbidities is complicated by the overlap with other comorbidities such as depression and anxiety. Regardless, there is strong evidence to indicate an elevated prevalence of insomnia in psoriasis patients. A causal relationship between psoriasis and insomnia has yet to be determined. There is moderate evidence to suggest increased risk of developing OSA in psoriasis patients, even when accounting for increased BMI. Most studies on sleep impairment in psoriasis patients have used self-reported data, of which only a portion has been validated. As such, there is a need to better evaluate sleep dysfunction in psoriasis patients. Regarding pulmonary comorbidities, psoriasis patients are more likely to smoke compared to the general population, which complicates evaluation of risk of COPD, lung cancer, and pulmonary infections in this population.

Keywords Psoriasis · Sleep · Pulmonary · Insomnia · Comorbidities

Introduction

Psoriasis is a chronic inflammatory skin disorder that affects approximately 3.2% of the US population [1]. It typically presents as erythematous, scaly, well-circumscribed plaques that can be painful and irritating, significantly impairing quality of life. Psoriasis is also associated with various non-dermatologic comorbidities, including cardiovascular disease, psoriatic arthritis, inflammatory bowel disease, and diabetes [2]. In recent years, interest in sleep and pulmonary comorbidities in psoriasis has garnered attention. This review summarizes important studies that have analyzed sleep and pulmonary comorbidities in psoriasis, including insomnia, narcolepsy, restless leg syndrome, obstructive sleep apnea (OSA), chronic obstructive pulmonary disease (COPD), lung cancer, and pneumonia.

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Sleep and Psoriasis

The relationship between skin and sleep is complex. Sleep and the circadian rhythm (sleep-wake rhythm) are regulated by interactions between the nervous, endocrine, and immune systems. Cytokines, as immune mediators, can regulate normal sleep patterns and alter sleep architecture as a result of infection and autoimmune disease by signaling the central nervous system (CNS) [3]. Psoriasis is predominantly mediated by an elevated Th1 cell response with resulting increases in IL-1, IL-17, IL-23, and TNF-alpha. Certain cytokines upregulated in psoriasis have also been identified as critical to modulating the circadian rhythm. IL-1, TNF-alpha, and IL-6, for example, peak during sleep in early morning and play a key role in physiological sleep-wake behavior. Patients with disorders of excessive daytime sleeping, such as narcolepsy, insomnia, and OSA, have demonstrated elevated IL-6 levels with sleep deprivation [4]. Furthermore, research in rheumatoid arthritis

patients has shown that TNF-alpha and IL-6 production by monocytes demonstrates a complex time-of-day-dependent association with sleep efficiency and slow-wave sleep amount. This suggests a feedback loop between sleep and cellular production of pro-inflammatory cytokines [5]. Based on these results, sleep dysfunction in other conditions driven by elevated immune activity, such as psoriasis, may not only be a symptom of such disease processes but also may be a direct contributor to disease pathophysiology.

The skin also plays a crucial role in regulating core body temperature (CBT), which is vital for sleep initiation. Both human circadian rhythm and the CBT cycle normally repeat as coinciding 24-h cycles [6]. Sleep occurs when CBT decreases during the nocturnal sleep phase and increases during the wake phase. Thus, disruption in skin homeostasis and, consequently, thermoregulation can result in sleep disturbance. Furthermore, pruritus, one of the most common disruptors of sleep in psoriasis patients, is also regulated by circadian mechanisms [7] as evidenced by a lowered pruritus threshold prior to sleep when cortisol levels decrease.

Studies evaluating sleep in psoriasis can be categorized into those that obtain subjective data from validated questionnaires, those that obtain subjective data via non-validated questionnaires, and those that obtain objective data via methods such as polysomnography (PSG) or actigraphy. A 2016 systematic review of the psoriasis and sleep literature found that less than 50% of studies meeting inclusion criteria utilized validated sleep measurements [8••]. In addition, only 16% of studies utilized polysomnography to evaluate sleep. Validated questionnaires that specifically examine sleep include the Pittsburgh Sleep Quality Index (PSQI), Berlin Questionnaire (for sleep apnea), Insomnia Severity Index (ISI), General Sleep Disturbance Scale (GSDS), the Functional Outcomes of Sleep Questionnaire (FOSQ), the Morningness-Eveningness Questionnaire (MEQ), and the Medical Outcomes Study Sleep Scale (MOS-SS).

Important recent studies examining specific sleep disorders in psoriasis are discussed below.

Sleep Comorbidities

Insomnia

Insomnia refers to sleep impairment that can manifest as a variety of symptoms including difficulty falling asleep, reduced quantity of sleep, increased nighttime awakenings, daytime sleepiness, irritability, depressed mood, and low energy. Insomnia in psoriasis patients is likely a result of various factors. Degrees of disease severity, itch, and concurrent depressive symptoms have been identified as some of the most consistent predictors of insomnia in psoriasis patients [9] [10]. Itch, which is observed in up to 84% of patients [11], has been typically studied in psoriasis using numerical rating scales such as the visual analog scale. Although more objective measures such as actigraphy or video surveillance have been utilized in atopic dermatitis to assess nocturnal itch [12], these approaches can be time-consuming and costly. High-quality studies in psoriasis patients utilizing these approaches have yet to be conducted. While pruritus is an important factor in sleep dysfunction in psoriasis patients, a combination of cytokine dysfunction, hypothalamic-pituitary-axis (HPA) dysregulation, and resultant hyperarousal prior to the initiation of sleep, depression, anxiety, pain, and somatic nervous system overactivity likely all play a role.

Insomnia is evident in 50 to 60% of psoriasis patients [8••], while insomnia in the general population is estimated to range from 10 to 20% [13]. Insomnia in psoriasis can be thought of as having two components: poor sleep quality and reduced sleep quantity. The Citizen Pscientist study, an analysis of over 3100 patients with psoriasis, found that sleep difficulty was significantly associated with psoriatic arthritis, female sex, obese BMI, co-occurring OSA, smoking, and psoriasis severity. Low sleep quantity was associated with obese BMI, OSA, psoriasis severity, and smoking [14]. In addition, over 38% of psoriasis patients reported receiving less than the minimum 7 h of sleep per night that is recommended by the American Academy of Sleep Medicine.

Studies evaluating improvement of sleep in psoriasis patients following treatment are limited. Two studies have shown improvements in MOS-SS in patients with chronic plaque psoriasis following treatment with adalimumab [15] and etanercept [16]. To our knowledge, studies utilizing non-TNF-alpha biologics to evaluate improvements in sleep have not been conducted thus far.

Obstructive Sleep Apnea

Obstructive sleep apnea is a sleep-related breathing disorder that is due to repetitive upper airway collapse, resulting in periodic apneic and hypopneic episodes. It is associated with older age, male sex, and elevated BMI. When defined as an apnea-hypopnea index (AHI) greater than or equal to 5, the estimated prevalence of OSA is 24% in men and 9% in women aged 30 to 60 [17]. Studies have suggested a bi-directional relationship between psoriasis and OSA. A 2016 review of 11 observational studies of OSA in psoriasis patients found a prevalence ranging from 36 to 81.8% [7]. One hospital-based case-control study using nocturnal polysomnography (PSG) found that the prevalence of psoriasis was elevated in OSA patients and that psoriasis was associated with OSA risk but not OSA severity [18]. Maari et al. used PSG to examine the efficacy of adalimumab on sleep patterns in patients with psoriasis and OSA. This study did not find an improvement in OSA symptoms following treatment [19]. A Danish nationwide prospective cohort study analyzed both risk of OSA in psoriasis patients and risk of psoriasis in OSA patients. The

study found that when patients with obesity or diabetes were excluded, the fully adjusted incidence rate ratios (IRRs) for risk of sleep apnea in psoriasis patients were 1.36 (95% CI, 1.21–1.53), 1.53 (95% CI, 1.08–2.18), and 1.98 (95% CI, 1.50–2.61), for mild psoriasis, severe psoriasis, and psoriatic arthritis, respectively [20•]. Furthermore, when OSA patients with obesity or diabetes were excluded, the fully adjusted IRRs for developing psoriasis were 1.36 (95% CI, 1.21–1.53), 1.53 (95% CI, 1.08–2.18), and 1.98 (95% CI, 1.50–2.61), respectively [20•]. Another study examining incidence of psoriasis in PSG-confirmed OSA patients found that OSA patients had an increased risk of developing psoriasis or psoriatic arthritis when compared to age and sex-matched controls (HR 2.3; 95% CI, 1.13–4.69) [21]. The study did not, however, distinguish between the incidence of psoriasis and psoriatic arthritis.

Other Sleep Disorders (Narcolepsy, Restless Leg Syndrome)

In their systematic review of sleep comorbidities in psoriasis patients, Gupta et al. included studies that evaluated narcolepsy and restless leg syndrome (RLS) [7]. The prevalence of RLS in three studies examining psoriasis or psoriatic arthritis patients ranged from 15.1 to 18%, compared to a baseline prevalence of 5 to 10% in European and North American populations. Gupta et al., however, report a high risk of bias in all three studies. In addition, the review also examined one study ($n = 156$) looking at the prevalence of inflammatory disorders in narcolepsy patients, with diagnosis confirmed with PSG followed by either multiple sleep latency test (MSLT) or measuring hypocretin-1 levels. The prevalence of psoriasis in this study cohort was 1.3% [7] [22]. Given that psoriasis prevalence generally ranges between 2 and 4%, there does not appear to be a strong association between narcolepsy and psoriasis, although definitive conclusions cannot be drawn without additional studies.

Pulmonary Comorbidities

Chronic Obstructive Pulmonary Disease

COPD is a chronic respiratory condition characterized by airway inflammation and obstruction with resultant damage to pulmonary alveoli, airways, and vasculature. It can be further sub-categorized into chronic bronchitis, emphysema, and chronic obstructive asthma. The most significant reportable preventative risk factor for the development of COPD is smoking, with smokers having a 3.8-fold higher risk of developing COPD when compared to never-smokers (95% CI, 2.7–5.3) [23]. Psoriasis patients are at elevated risk of being both former and current smokers [24]. A retrospective cohort study using NHANES survey data found that psoriasis patients were more likely to have COPD (12.2% vs. 5.9%, $p < 0.001$) and to be smokers (59.7% vs. 45.2%, $p < 0.001$) [25]. In a 2013 systematic review and meta-analysis of psoriasis and smoking, Armstrong et al. found that there is an increased prevalence of smoking among patients with psoriasis and an increased incidence of psoriasis among smokers [26]. Yeung et al., in a 2013 UK cross-sectional, population-based study, found higher prevalence of chronic pulmonary disease (unspecified) in psoriasis patients (adjusted OR 1.08; 95% CI, 1.02–1.15) when compared to non-psoriatics after adjusting for age, sex, and follow-up duration [27].

In their systematic review and meta-analysis of over 3200 patients with psoriasis in 4 observational studies, Li et al. found a pooled odds ratio of COPD in patients with psoriasis versus control to be 1.90 (95% CI, 1.36–1.2.65). In addition, an even stronger association was noted in a sub-analysis of severe psoriasis patients (OR 2.15; 95% CI, 1.26–3.67) [28]. Another systematic review and meta-analysis of seven case-control and cross-sectional studies comparing over 300,000 psoriasis patients with controls found a pooled odds ratio of COPD in patients with psoriasis versus controls of 1.45 (95% CI, 1.21–1.73) [29]. However, only one study adjusted for smoking as a confounder when analyzing psoriasis patients with COPD compared to healthy controls [30]. Dreiher et al. found that psoriasis patients who were current smokers had an increased prevalence of COPD (OR 5.56; 95% CI, 4.95–6.24) and that psoriasis was associated with COPD even after controlling for confounders including age, sex, smoking, obesity, and socioeconomic status (OR 1.27; 95% CI, 1.13–1.42), although the strength of association decreased following adjustment [30]. The study also found that when comparing smokers with psoriasis and smokers without psoriasis, the odds ratio for having COPD was 1.34 (95% CI, 1.17–1.55), indicating that psoriasis still elevated the risk of COPD even when controlling for smoking. Thus, psoriasis may be an independent risk factor for the development of COPD regardless of smoking status.

Of note, one study using a Taiwanese national cohort of psoriasis patients examining the most prevalent comorbidities found in psoriasis showed a distinct clustering of hypertension and COPD [31]. Another study using a French registry of moderate-to-severe psoriasis patients found that patients with co-occurring COPD, which predisposes patients to pulmonary infection, led to a preferred use of etanercept or ustekinumab over adalimumab by providers [32].

Lung Cancer

Lee et al. examined cancer incidence in nearly 900,000 psoriasis patients using the Korean National Insurance Service (NHIS) database. Over a follow-up period of up to 8 years, they found an elevated risk of lung cancer (HR 1.159; 95% CI,

1.110–1.210) in psoriasis patients when compared to age and sex-matched controls and adjusting for diabetes, hypertension, dyslipidemia, income level, and place of residence [33]. In addition, the risk of developing lung cancer increased further (HR 1.405; 95% CI, 1.208–1.633) when examining severe psoriasis patients specifically. However, the study did not collect information on the use of immunosuppressive medications, smoking status, alcohol use, obesity, or family history of cancer and therefore did not incorporate these potential confounders in its analysis. A 2016 population-based cohort study in the UK that included nearly 200,000 psoriasis patients over a 6-year follow-up period found an elevated risk of lung cancer after adjusting for smoking, age, and sex in the overall, mild, and severe psoriasis groups, respectively (HR 1.15; 95% CI, 1.03–127), (HR 1.12; 95% CI, 1.01–1.25), and (HR 1.62; 95% CI, 1.16–2.28) [34]. However, after performing a sensitivity analysis that included only patients who had never smoked, the association was lost in the overall (HR 0.98; 95% CI, 0.76–1.25), mild (HR 0.97; 95% CI, 0.75–1.24), and severe psoriasis group (HR 1.18; 95% CI, 0.44–3.17). Thus, smoking is an important confounder when assessing risk of lung cancer in psoriasis patients, and future studies should incorporate such analyses. Interestingly, when comparing an age and sex-adjusted model for lung cancer including only patients classified as current smokers, a positive association between psoriasis and risk of lung cancer across all study groups persisted [34]. Thus, the relationship between lung cancer and psoriasis is likely highly complex given that non-smokers do not appear to have an increased risk of developing lung cancer, but current smokers with psoriasis do, even when compared to current smokers without psoriasis. In general, age-appropriate malignancy screening is recommended in psoriasis patients. For lung cancer, this involves annual low-dose computed tomography (LDCT) in adults aged 55 to 80 who have a 30 pack-year history of smoking and currently smoke or have quit within the last 15 years [35].

Pneumonia

The evaluation of pneumonia in psoriasis warrants attention as infection is the second-leading cause of death in psoriasis patients, and treatment with biologic agents often involves discussions with patients about infection risk [36] [37]. A Taiwanese population-based cohort study of over 14,000 psoriasis patients that examined risk of pneumonia requiring hospitalization during a 3-year follow-up period found an elevated risk in both mild psoriasis patients (HR 1.36; 95% CI, 1.09–1.70) and severe psoriasis patients (HR 1.68; 95% CI, 1.12–2.52) after adjusting for propensity score, which was used to balance demographic and comorbidities between psoriasis and non-psoriasis cohorts, including hypertension, diabetes mellitus, COPD, renal failure, liver diseases, neurological diseases, rheumatologic diseases, alcohol use disorder, and tobacco use disorder [38]. Of note, the study cohorts were defined based on previous use of systemic therapy. The mild cohort included patients who had previously only used topical therapies, and the severe cohort included patients who had used systemic therapy. As a result, the authors could not conclude if increased risk of pneumonia in psoriasis is due to disease severity or concurrent use of immunosuppressive medication in severe psoriasis. Kalb et al. utilized the Psoriasis Longitudinal Assessment and Registry (PSOLAR) to evaluate the risk of all serious infections in psoriasis patients currently receiving or eligible to receive systemic or biologic therapy. After reviewing over 22,000 patient-years, pneumonia was found to be the second most common serious infection following cellulitis. In addition, infliximab and adalimumab exposure were each associated with an increased risk of serious infection, including pneumonia requiring hospitalization, while treatment with ustekinumab or etanercept was not [37]. Dommasch et al. conducted a comparative cohort study of over 107,000 psoriasis patients who were new users of systemic therapies that included acitretin, adalimumab, apremilast, etanercept, infliximab, methotrexate, and ustekinumab. The study found that when compared to methotrexate, ustekinumab had a lower risk of pneumonia (pooled HR 0.53; 95% CI, 0.32–0.88) [39]. In addition, the study also determined that when compared to adalimumab, etanercept had a lower risk of pneumonia (pooled HR 0.62; 95% CI, 0.42–0.91) [39]. Providers should ensure that psoriasis patients receiving systemic therapies should be appropriately vaccinated and be educated on standard disease prevention practices. Live vaccines should, however, be avoided immediately prior to initiating any immunosuppressive therapy and during therapy.

Conclusion

We have reviewed the most commonly studied sleep and pulmonary comorbidities associated with psoriasis. In addition to previously studied comorbidities such as cardiovascular disease, obesity, metabolic syndrome, and diabetes, we found that an increased association between insomnia and OSA is well established in the psoriasis literature. Furthermore, data suggest that COPD, pneumonia, and lung cancer may be more frequent in psoriasis patients, although elevated rates of smoking and increased risk of obese BMI, among other lifestyle and genetic factors, may play a role.

Regarding sleep comorbidities, there is a lack of objective sleep data in studies analyzing sleep comorbidities in psoriasis. However, numerous studies of self-reported data have demonstrated that psoriasis patients suffer from sleep difficulties. Future studies should focus on accumulating formal data through means such as PSG. The potential bi-directional

nature of sleep dysfunction and psoriasis mediated by cytokines warrants further exploration. Inflammatory markers such as IL-6, IL-17, and TNF-alpha have been implicated independently in psoriasis as well as in psoriasis comorbidities, including cardiovascular disease and metabolic syndrome. The role of these inflammatory markers in relation to sleep dysfunction and psoriasis and the elucidation of their common pathways have yet to be definitively identified.

Future studies should focus on the effects of treatment on sleep and pulmonary comorbidities associated with psoriasis. In addition, providers should regularly counsel patients on sleep impairment and encourage healthy lifestyle practices, including exercise and avoiding tobacco use, while treating psoriasis patients. It has been reported that only 43% of primary care physicians routinely inquire about sleep, compared to 80 and 79% who routinely discuss exercise and healthy diet, respectively [40]. Practicing dermatologists should be empowered to inquire about sleep impairment and encourage patients to also discuss with primary care providers. Utilization of tools such as sleep diaries may be useful for patients to better track sleep symptoms and provide documentation of sleep impairment to facilitate these discussions.

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Compliance with Ethics Guidelines

Conflict of Interest Dr. Tina Bhutani is a PI for Janssen, Merck, Celgene, and Regeneron and an advisor for Abbvie and Eli Lilly. Drs. Reddy, Myers, Brownstone, Thibodeaux, and Chan declare that they have no conflict of interest.

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