ORIGINAL ARTICLE

Psoriatic Insomnia: A Subjective and Objective Sleep Evaluation

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Psoriasis may affect patients' sleep. In order to examine this relationship, this study evaluated non-anxious and non-depressive patients with moderate to severe psoriasis before and after 6 months of systemic treatment. A prospective case-control study with 46 consecutive patients (mean age 51.1 ± 12.8 years, 18 women) and 24 age-, sex- and body mass index-matched controls (mean age 46.5 ± 15.4 years, 12 women) was conducted to assess sleep using both sleep questionnaires and actigraphy. Of psoriatic patients, 91.3% were poor sleepers, and 65.2% of the psoriatic patients presented insomnia symptoms, compared with 54.2% and 33.3% of the control group ($p < 0.001$, $p = 0.02$, respectively). Actigraphy showed that Total Sleep Time was shorter in patients, while 82.6% of the psoriatic patients had poor Sleep Efficiency, compared with controls ($p = 0.004$, $p = 0.03$, respectively). Patients' quality of life was associated with sleep disturbance ($p < 0.001$), and pruritus was negatively correlated with sleep duration ($p < 0.001$). After 6 months of treatment, patients' sleep pattern, according to actigraphy, had not changed significantly; however, they had insomnia for no longer than the control group ($p = 0.65$), whereas the above-mentioned correlations were non-significant after treatment. Psoriatic insomnia was improved after 6 months of systemic treatment. Actigraphy may be used as an objective tool to evaluate sleep in these patients.

Key words: actigraphy; insomnia; itching; pruritus; psoriasis; sleep; treatment.

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SIGNIFICANCE

Patients with moderate to severe psoriasis without anxiety and depression have reduced duration of sleep according to actigraphy, and present insomnia based on subjective sleep measurements. Psoriatic insomnia is improved after treatment of psoriasis based on subjective and objective evaluation of sleep. Early detection of psoriatic sleep disturbance may help to avoid the risk of depression that adversely affects the prognosis of psoriasis. Actigraphy may be used as an objective tool to evaluate sleep in these patients. The collaboration of dermatologists with a sleep specialist would be beneficial for the holistic management of long-term psoriasis with relapses and remissions.

Psoriasis represents a chronic autoimmune, pruritic dermatosis with relapses and remissions, which may be accompanied by arthritis affecting patients' quality of life and sleep health (1–4). Normal skin function is influenced by sleep, while healthy sleep exerts an immune-supportive function, promoting host defence against inflammatory insults (5). Sleep deprivation has been associated with alterations in innate and adaptive immune factors, leading to a chronic inflammatory state (6). Therefore, sleep could be an important parameter in the evaluation of skin disease. Although the relationship between other sleep disorders, such as obstructive sleep apnoea, has been studied in psoriasis (7–9), the majority of studies have not sufficiently examined the impact of psoriasis on both sleep quantity and quality. In addition, depression, which is common in psoriasis, is frequently associated with impaired sleep, usually insomnia (10–13). Evidence is very limited regarding the association of moderate to severe psoriasis and sleep health, particularly during exacerbation and remission. Furthermore, there only 1 study has evaluated sleep using actigraphy, which is an objective tool for sleep assessment, in psoriasis (14). Therefore, the aim of this study is to examine the influence of physical illness in sleep health, in non-depressive and non-anxious patients with moderate to severe psoriasis during exacerbation and remission (after 6 months of systemic treatment).

MATERIALS AND METHODS

Study participants

In this prospective case-control study, a total of 46 consecutive psoriatic patients (mean age 51.1 ± 12.8 years, 18 women) and 24 controls (mean age 46.5 ± 15.4 years, 12 women) at the Dermatology Department and the Outpatient Clinic and Laboratory Department at Attikon General Hospital, National and Kapodistrian University of Athens, Greece who met the study criteria were invited to participate from December 2018 to May 2019.

Inclusion criteria

The inclusion criteria for patients were: age > 18 years; presence of moderate to severe chronic plaque psoriasis according to the criteria of the European consensus for psoriasis (2) with Psoriasis Area Severity Index (PASI) > 10 or PASI < 10 but Dermatology Life Quality Index (DLQI) > 10. Patients were not on any treatment at the time of enrolment and they were either treatment-naïve or had previously received a biologic agent or other systemic therapy at least 6 or 3 months ago, respectively.

Exclusion criteria

Patients with additional dermatological or autoimmune diseases (e.g. systemic lupus erythematosus, lymphoma, pemphigus, atopic dermatitis, etc.) and disorders that may interfere with sleep were excluded. Other exclusion criteria included alcoholism, prescribed neuroleptics, anti-epileptics, dopamine antagonists, antidepressants, depression or anxiety disorders, shift work, malignancies, rheumatological disorders, and pregnancy.

Initial evaluations

A neuropsychiatric evaluation was performed assessing mental state and psychiatric illness, and using specific questionnaires (Hospital Anxiety and Depression Scale). A full medical history of psoriasis features was obtained, including the age of onset, disease duration, presence of Psoriatic Arthritis (PsA), history of previous use and number of systemic classical or biological treatments. The collecting data included weight, height, body mass index (BMI), blood pressure, tobacco smoking, presence of other comorbidities, such as systemic hypertension and diabetes mellitus type-2 (DM2), dyslipidaemia, thyroid disease, and concomitant medications. PASI and DLQI scores were employed to assess psoriasis severity and extent. A visual analogue score (VAS) was used for evaluation of pruritus at the time of presentation to the psoriatic clinic. Patients were also evaluated with sleep questionnaires and were instructed at baseline to use a wrist-watch sensor (actigraph) for 7 days, which measures sleep based on monitoring motion.

After 6 months of treatment, patients revisited the clinic for dermatological and sleep re-evaluation using the same methods. During this period, a consecutive volunteer control group of similar age, sex, and BMI without psoriasis ($n = 24$) was randomly selected from the Outpatient Clinic and Laboratory Department of Attikon General Hospital, National and Kapodistrian University of Athens, Greece among those who came for an annual check-up examination. Similar inclusion and exclusion criteria were applied to the control group. All participants in the study were examined for psoriasis and sleep disorders by a dermatologist (EP) and a sleep specialist (KV), respectively, during the same chronic period. All participants included in the study had the ability to provide informed consent.

Sleep assessment was performed using a multidimensional evaluation with validated sleep questionnaires and actigraphy, at baseline and after 6 months of systemic treatment. Sleep evaluation was performed using 3 self-sleep questionnaires, validated in Greece, and actigraphy. The Pittsburgh Sleep Quality Index (PSQI) is a standardized, self-rated questionnaire, which consists of 19 items that measure sleep quantity and quality during the last month (15, 16). Scores range from 0 to 21, with higher ratings indicating worse sleep. A score of 5 or more identifies clinically significant sleep complaints. Athens Insomnia Scale (AIS) was used to quantify the presence and severity of reports of insomnia during the last month. AIS has 8 items in a 4-point Likert scale that reflect the insomnia criteria of the International Classification of Diseases 10th Revision (ICD-10) (17, 18). The total score ranges from 0 (absence of any sleep-related problem) to 24 (severe insomnia). Scores of 6 or higher are suggestive of a diagnosis of insomnia. Epworth Sleepiness Scale (ESS) is an 8-item self-administered questionnaire used for rating, on a scale of 0–3, the likelihood of dozing (i.e. sleep tendency) in each of 8 daily situations (19, 20). The test yields a score of 0–24, with 0 indicating no daytime tendency for sleepiness and 24 indicating the most severe tendency for sleepiness. Excessive daytime sleepiness is commonly considered present whenever the ESS score is 10 or more. Objective sleep estimation was obtained using actigraphy with the Actiwatch Spectrum actigraph (Philips/Respironics, Murrysville, PA, USA), which measures daytime activity (21). This is a wearable digital wrist device approved by the US Food and Drug Administration (FDA). Total Sleep Time (TST) (in min) and Sleep Efficiency (SE%) (% of time in bed spent asleep) were scored automatically using the manufacturer's software. Data from the Actiwatch Spectrum were downloaded and analysed in Respironics Actiware 5 (versions 5.57 and 5.59). Subjects were instructed to wear the actigraph for 7 days, day and night on their non-dominant wrist at all times, except when submerged in water (e.g. bathing or swimming). At the end of the 7-day recording period, data were uploaded and analysed using the Sleep Analysis software, which provides algorithms to score sleep.

Written informed consent was obtained from all study participants. The study was approved by Ethics and Scientific Committee of Attikon General University Hospital, Athens University School of Medicine (i.d. #559, 10/27-11-2018).

Statistical analysis

The comparison of study variables between case and control participants was conducted using χ^2-tests and *t*-tests or paired *t*-tests for categorical and continuous normally distributed variables, respectively. Mann–Whitney *U* and Wilcoxon signed-rank tests were used for continuous not normally distributed variables. The normality hypothesis was tested with the Shapiro-Wilk test. Spearman correlation coefficient (r) was used to detect associations of continuous or ordinal variables. Analyses were performed using the statistical package IBM-SPSS® version 25 for Windows (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Reported *p*-values are 2-sided, and a level of a=0.05 was considered significant.

RESULTS

Demographic and clinical characteristics of psoriatic patients pre- and post-treatment and healthy controls are shown in **Table I**.

Mean age and percentage of sex were similar in both groups. Compared with controls, patients with psoriasis did not present any significant differences regarding smoking status, BMI, hypertension, dyslipidaemia, or thyroid disease ($p > 0.05$). However, patients with psoriasis more frequently had DM2 than did controls (17.4% vs 0%, $p = 0.03$). Psoriasis patients presented statistically significantly higher median PSQI ($p < 0.001$) and AIS scores ($p = 0.002$). Based on the PSQI category score (PSQI≥5), 91.3% of patients with psoriasis and 54.2% of controls were classified as poor sleepers ($p < 0.001$). Based on the AIS category score (AIS≥6), insomnia symptoms were observed in 65.2% of patients, but in only 33.3% of controls ($p = 0.02$). ESS and daytime sleepiness, based on ESS ≥10, were similar in both

Table I. Baseline demographic and clinical characteristics of patients with psoriasis before and after treatment, and healthy controls (*n* = 70)

Variable	Psoriasis patients before treatment (*n* = 46)	Psoriasis patients after treatment (*n* = 46)	Control group (*n* = 24)	*p*-value[a]	*p*-value[b]	*p*-value[c]
Demographic parameters						
Age, years, mean±SD	51.1±12.8	–	46.5±15.4	0.18	–	
Sex, *n* (%)						
Male	28 (60.9)	–	12 (50)	0.38	–	
Female	18 (39.1)	–	12 (50)			
Clinical features						
Disease duration, years, median (IQR)	16 (11–20)		–	–	–	
Early onset of disease, *n* (%)	32 (69.6)		–	–	–	
Smoking status, *n* (%)						
Non-smokers	23 (50)	–	11 (45.8)	0.08	–	
Former smokers	3 (6.5)	–	6 (25)			
Current smokers	20 (43.5)	–	7 (29.2)			
BMI, kg/m^2, mean±SD	35.5±9.4	32.9±9.2	31.8±7.4	0.1	**0.001**	0.63
PASI, median (IQR)	11 (6.6–16)	4.6 (0.8–7.8)	–	–	**<0.001**	–
DLQI, median (IQR)	12 (7–15)	6 (4–8)	–	–	**<0.001**	–
VAS, median (IQR)	8 (6–10)	6.5 (3.3–8)	–	–	**<0.001**	–
Comorbidities						
Presence of PsA, *n* (%)	24 (54.2)	–	–	–	–	–
Arterial hypertension, *n* (%)	12 (26.1)	–	2 (8.3)	0.08	–	–
DM2, *n* (%)	8 (17.4)	–	0 (0)	**0.03**	–	–
Dyslipidaemia, *n* (%)	8 (17.4)	–	4 (16.7)	0.94	–	–
Thyroid disease, *n* (%)	12 (26.1)	–	4 (16.7)	0.37	–	–
Total comorbidities, *n* (%)						
0	22 (47.8)	–	13 (54.2)	0.17	–	–
1	14 (30.4)	–	11 (45.8)			
2	6 (13)	–	0 (0)			
3	2 (4.4)	–	0 (0)			
4	2 (4.4)	–	0 (0)			
Starting treatment with						
Methotrexate, *n* (%)	6 (13.04)	–	–	–	–	–
Anti-TNF-α (adalimumab), *n* (%)	12 (26.09)	–	–	–	–	–
Anti-IL, *n* (%)	10 (21.74)	–	–	–	–	–
Ustekinumab	9 (90)					
Secukinumab	1 (10)					
Apremilast, *n* (%)	18 (39.13)	–	–	–	–	–
Subjective measures of sleep, median (IQR)						
PSQI	15 (8–19)	10 (5–17)	7 (3.3–10)	**<0.001**	**<0.001**	**0.02**
AIS	8 (2–13)	4 (2–6)	5 (1–6)	**0.002**	**<0.01**	0.65
ESS	6 (5–8)	3 (2–6)	6.5 (3.3–11.8)	0.96	**<0.001**	**0.01**
Actigraphy Sleep Parameters						
TST, min mean±SD	379.8±86.1	342.1±71.5	432.1±55.4	**0.004**	0.98	**<0.001**
SE, % mean±SD	78.1±8.4	74.8±11.12	81.1±7.7	0.17	0.59	**0.04**
SE% ≤85%, *n*, (%)	38 (82.6)	14 (30.4%)	14 (58.3)	**0.03**	**0.04**	0.33

AIS: Athens Insomnia Scale (range 0–24); BMI: body mass index; DLQI: Dermatology Life Quality Index (range 0–30); ESS: Epworth Sleepiness Scale (range 0–24); IQR: interquartile range; PASI: Psoriasis Area Severity Index (range 0–72); PSQI: Pittsburgh Sleep Quality Index (range 0–21); SE: sleep efficiency; TST: Total Sleep Time; VAS: visual analogue scale (range 0–10).
p-value: [a]between cases and controls; [b]between pre- and post-treatment; [c]between patients post-treatment and controls. Statistically significant results are shown in bold.

groups ($p = 0.96$ and $p = 0.29$, respectively). Actigraphy-measured sleep analysis showed that TST was shorter in patients with psoriasis than in controls ($p = 0.004$) and 82.6% of psoriatic patients had poor SE (SE≤85%) vs 58.3% of controls ($p = 0.03$). Moreover, in subgroup analyses, female patients presented significantly poorer sleep quality based on the PSQI score ($p = 0.04$) and more insomnia symptoms based on AIS score ($p = 0.009$) than did male patients. Interestingly, patients with PsA presented a significantly higher median score of PSQI and AIS ($p = 0.02$ both) and significantly decreased TST than patients without PsA ($p = 0.008$). In patients before treatment, only DLQI was positively correlated with subjective sleep measurements, such as PSQI, AIS, and ESS ($p < 0.001$, $p < 0.001$, $p = 0.04$, respectively) adjusting for BMI and DM2. VAS was negatively correlated with actigraphic TST ($p < 0.001$).

After enrolment, patients started treatment with methotrexate (13.04%), anti-tumour necrosis alpha (TNF-α)/adalimumab (26.09%) and anti-interleukins (anti-ILs) (21.74%) agents (ustekinumab 90% and secukinumab 10%), and apremilast (39.13%) (Table I). All patients had statistically significant clinical improvement in all clinical aspects of psoriatic disease, including PASI, DLQI, and VAS ($p < 0.001$). The median scores of PSQI, AIS, and ESS were significantly improved after 6 months of treatment ($p < 0.001$, $p < 0.01$, $p < 0.001$, respectively). Also, the observed correlations between skin indices and sleep parameters were attenuated or disappeared after treatment.

No statistically significant differences were detected in actigraphic parameters before and after treatment ($p > 0.05$), with the exception of the percentage of patients who presented SE% less than 85% that was decreased after treatment ($p = 0.04$).

Based on psoriasis severity, patients with severe psoriasis presented more significant improvements than patients with moderate psoriasis in ΔPASI score ($p = 0.002$)

and in their sleep quality (expressed as difference in SE% before and after treatment, $p=0.014$). This study also found that patients on biologic agents (anti-TNF-α and anti-ILs) presented more pronounced significant improvements in ΔPASI ($p<0.001$) and ΔDLQI ($p=0.001$) scores than patients on apremilast and methotrexate. Regarding treatment, patients treated with methotrexate and biologic agents (anti-TNF-α and anti-ILs agents) presented more significant improvements in TST ($p=0.001$), SE% ($p=0.002$) and AIS score ($p<0.001$) than patients treated with apremilast. However, the current study did not have adequate statistical power to adjust these findings with severity of psoriasis. Patients with more than 2 comorbidities had similar improvements in all sleep parameters before and after treatment ($p>0.05$).

Finally, Table I also depicts sleep characteristics in treated psoriatic patients and healthy controls. Although treated patients still presented significantly higher PSQI than controls ($p=0.02$), they had improved AIS score without any significant difference in AIS of healthy controls ($p=0.65$). According to actigraphic sleep data, treated patients still presented a significantly decreased TST and SE%, ($p<0.001$ and $p=0.04$, respectively). However, there was no statistically significant difference between the percentages of patients and controls who presented SE% <85% ($p=0.33$). In all statistical analyses, there was no relationship between subjective and actigraphic sleep parameters ($p>0.05$).

DISCUSSION

This study shows that patients with chronic severe to moderate psoriasis without anxiety and depression developed restricted sleep duration according to actigraphy as well as insomnia symptoms based on the AIS score. Insomnia symptoms were improved during disease remission after 6 months of systemic treatment. Evidence has shown that sleep integrity in patients with psoriasis can be adversely affected by itching (22). Up to 65% of patients with psoriatic present pruritus, which exhibits mainly nocturnal exacerbation due to aberrations in regulatory skin mechanisms, exerting a detrimental effect on sleep pattern (23). Indeed, in this study, VAS was negatively correlated with TST, with pruritus acting as the link between sleep restriction and active psoriasis. Women and patients with PsA were more vulnerable to sleep disturbance. Apart from the relationship of itching and decreased sleep quantity, we have shown that disturbed sleep had a negative impact on patients' quality of life, since DLQI presented a positive correlation with subjective sleep measurements.

Sleep restriction is accompanied by an increased inflammatory burden, which may complicate to a greater extent the pathogenesis of psoriasis (24). Moreover, sleep deprivation and psoriatic symptoms, both being stressful factors, could present synergistic effects, counteracting the hypothalamus-pituitary-adrenal axis and facilitating psoriatic flares (25). In addition, the mortality and morbidity of these patients may be worsened further because of poor sleep quantity and quality due to the elevated risk of cardiovascular disorder (26) and the accompanying disturbance of mental status (26). Regarding the psychological burden of psoriatic patients, there is a debate in the literature as to whether their non-restorative sleep is a consequence of the dermatological disease or the result of underlying depression (27). Psychiatric studies have shown that insomnia over a cumulative period may predict depression more consistently than depression predicts insomnia with the latter being indicative of a greater risk of subsequent psychiatric distress (29, 30). Furthermore, the subsequent amplified chronic inflammatory status could play a prominent role in the pathogenesis of depression (29, 31). Hence, the prognosis of psoriatic disease may be complicated by insufficient sleep because of the potential risk of developing depression (32, 33). However, in the current research, we studied non-anxious and non-depressive psoriatic patients; thus the lack of sleep could be attributed to the inflammatory nature of psoriasis (34).

After 6 months of systemic treatment with mainly biological agents, patients were not only improved in terms of physical illness and daytime sleepiness, but also manifested an improved sleep recovery, with insomnia being ameliorated, in comparison with the control group. Furthermore, during the remission of psoriasis, the observed pretreatment correlations between severity skin indices and sleep parameters were attenuated, reinforcing the hypothesis of the association between physical symptoms and sleep inadequacy. Systemic treatment of psoriasis may diminish the overall inflammatory burden (34) by improving sleep, while it might reduce the risk of depression (35). Previous studies have reported that treatment with biological agents in rheumatoid arthritis is associated with reduced rates of insomnia (36). A sleep benefit has also been reported with adalimumab and etanercept after 3 and 6 months of anti-psoriatic treatment, respectively (37, 38); however, these studies had not used a multidimensional sleep evaluation with actigraphy and validated sleep questionnaires. Thus, based on reliable sleep measurements, the recognition of sleep reduction in this group of psoriasis may reflect the disease severity spectrum and the cost-effectiveness of systemic treatment. It is important to mention that, in the current study, those patients with more severe psoriasis had more significant improvement in sleep quality according to SE%, and psoriatic patients on biologic agents presented more significant improvement in sleep parameters and insomnia compared with patients treated with apremilast. Although the current study sample size was small in order to permit subgroup analyses with adequate statistical power, these differences could be attributed to the most profound inflammatory impact of severe disease on sleep and the

best treatable effect with anti-TNF and anti-ILs in those patients with severe disease. A further explanation would be that sleep disturbance, especially insomnia, may be observed in some patients treated with apremilast (39, 40).

Patients with active psoriasis had restricted sleep quantity according to actigraphic sleep measurements, presenting poor sleep quality and insomnia symptoms based on the validated sleep questionnaires of PSQI and AIS, respectively. Nevertheless, psoriatic insomnia was improved during remission compared with controls. The observed discrepancy and inconsistency between subjective sleep perception and sleep estimation by actigraphy before and after treatment could be attributed to the combination of: (*i*) the presence of insomnia which affects patients' sleep perception; (*ii*) the different aspects of sleep that are captured by objective and subjective sleep assessment tools; and (*iii*) the short period for the reassessment of a long-term systemic inflammatory skin disorder, which may influence the cognitive status of patients.

Strengths and limitations

The current study had several strengths, including mainly its prospective and well-controlled design. Another major advantage is that we used a variety of diagnostic tools to examine the participants' attributes of sleep quality, sleep quantity and daytime tendency for sleepiness (Actiwatch Spectrum actigraph, PSQI, AIS and ESS). More importantly, sleep evaluation was the primary outcome and was assessed with a multidimensional approach before and after psoriasis treatment. Nevertheless, this study has some limitations, such as the small number of participants. Due to the small sample size and the low statistical power, this study not able to perform subgroup analyses adjusting for important confounders. Furthermore, although a complete neuropsychiatric evaluation was performed to exclude patients and controls with anxiety and depression, the study did not assess other parameters affecting sleep, such as the use of electronic devices before sleep, physical activity and social parameters.

Conclusion

Overall, non-anxious, non-depressive patients with moderate to severe psoriasis and psoriatic arthritis have decreased sleep duration according to actigraphy, and present insomnia symptoms. Psoriatic insomnia is improved during the remission of psoriasis after treatment based on subjective and objective sleep evaluation. It is recommended, whenever possible, to use multiple evaluations of sleep, and to examine the consistency of the results yielded by different methods in different periods, considering the dynamics of sleep pattern during treatment. Actigraphy is a reliable instrument to signal the shortage of sleep duration in psoriatic patients, especially in those with severe disease, contributing to the early detection of sleep disturbance. The ultimate goal would be to avoid the risk of depression that may adversely affect the prognosis of psoriasis and to improve the quality of life in psoriatic patients. Dermatologists should keep in mind that VAS and DLQI scores, which are patient-centred indices of psoriasis severity, may be tools predictive of sleep disturbance, especially in patients with severe psoriasis. The collaboration of dermatologists with a sleep specialist would be beneficial for the holistic management of long-term psoriasis with relapses and remissions. Further larger, well-designed prospective studies are required to confirm these findings, and to explore the impact of psoriatic insomnia and its management on the risk of depression, which significantly affects the burden of psoriasis and patients' quality of life.

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