Received: 8 September 2023 | Accepted: 11 January 2024

DOI: 10.1111/ddg.15373

ORIGINAL ARTICLE

Burden of impaired sleep and its improvement through topical treatment in psoriasis and atopic dermatitis

Caroline Mann[1] | **Matthias Dreher**[2,3] | **Jan-Niklas Rothschmidt**[1] | **Petra Staubach**[1,3]

[1]Department of Dermatology, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

[2]Division of Rheumatology and Clinical Immunology, Department of Internal Medicine I, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

[3]University Center for Autoimmunity, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

Correspondence
Caroline Mann, MD, Department of Dermatology, University Medical Center of the Johannes Gutenberg University, Langenbeckstrasse 1, 55131 Mainz, Germany.
Email: caroline.mann@unimedizin-mainz.de

Summary

Introduction: Patients with chronic inflammatory skin diseases often suffer from sleep disturbances. However, objective data on sleep architecture, especially to evaluate potential overall influences under therapy, are lacking.

Patients and methods: Pilot study on sleep quality changes including psoriasis and atopic dermatitis patients before and 2 weeks after intensive topical treatment. In addition to disease activity rating, patient-rated outcomes for itch severity and sleep quality and polygraphy was performed before and after topical therapy.

Results: 14 psoriasis, eleven atopic dermatitis patients (10 female, 15 male) with a mean age of 49 years were included. Disease activity scores (EASI and PASI) were significantly reduced with topical therapy after 2 weeks ($p < 0.001$). Pruritus intensity (NRS) showed a significant influence on deep sleep, which resolved after therapy. Insomnia severity significantly decreased ($r > 0.50$, $p < 0.05$) and daytime sleepiness showed a significant reduction in 40% of patients. N3 (deep sleep) and REM sleep significantly improved, showing a strong effect ($r > 0.50$). The apnea-hypopnea index decreased in one of four patients independent of the individual BMI.

Conclusions: Through polygraphy, we demonstrated impaired sleep patterns in psoriasis and atopic dermatitis patients with itch as a relevant factor and beyond that, rapid sleep improvement under 2 weeks of topical treatment.

KEYWORDS
atopic dermatitis, psoriasis, sleep, topical therapy

INTRODUCTION

Patients with chronic inflammatory skin diseases suffer from impaired sleep and fatigue.[1–5] Sleep quality is largely dependent on two sleep phases in particular, which may be affected by these diseases: Rapid Eye Movement (REM) sleep, also known as the dream sleep, which is essential for processing of sensory impressions and recovery and deep sleep (N3), which is fundamental for memory consolidation and cognitive performance.[6,7]

Different parameters, such as increased body weight raising the risk for obstructive sleep apnea (OSAS), can negatively affect sleep quality.[8] In dermatologic diseases, itching has been discussed as one of the predominant factors leading to impaired sleep by causing difficulty falling and staying asleep or waking up too early.[9,10]

One aim was to study the sleep pattern in the two most common, both chronic and inflammatory, skin diseases, which are also most often associated with pruritus. Another aim was to assess possible influencing factors including

improvement under treatment. Patients with prior systemic treatment were excluded, and only topical treatment was allowed, in order to exclude any potential, central effect of systemic therapy such as steroids, including the as yet unmeasured effects of biologics.[11] As part of the treatment plan, patients received basic care and also anti-inflammatory topicals, including class II–III steroids, on a daily basis for 2 weeks.

Poor sleep has far-reaching health consequences, the extent of which physicians and researchers are slowly beginning to understand.[12] However, there is still a lack of valid sleep data to assess the extent of sleep disturbances and, based on this, possible influencing factors in patients with chronic inflammatory skin diseases. Patients are often asked about the impact on sleep; however, the question remains whether these patient-rated outcomes (PROs) correspond to quality of sleep.

METHODS

Pilot study on psoriasis (PSO) and atopic dermatitis (AD) patients from the Department of Dermatology, University Medical Center in Mainz, Germany. Outpatients, who were scheduled for day clinic treatment and who gave written informed consent to be observed over a period of 2 weeks under intensive topical treatment, were included in the study.

The following objective and subjective parameters were evaluated at both time points: Sleep assessment by polygraphy was carried out before therapy (V1) and 2 weeks after intensive topical therapy (V2) by means of a portable sleep device in the home environment. To avoid possible systemic effects, only topical treatment was used. This was done according to current guidelines and under observation in our day clinic. Patients with diseases or use of other oral treatments that could influence the results were not included.

Disease activity

Besides demographic data, disease activity was assessed by validated scores at V1 and V2: Eczema Area and Severity Index (EASI) in AD patients and Psoriasis Area and Severity Index (PASI) in PSO patients.

Patient-rated outcomes (PROs) were assessed using the Dermatologic Quality of life Index (DLQI), the Numeric Rating Scale (NRS) from 0–10 for pruritus intensity and to further depict the impact of pruritus, the Itchy Quality of Life (ItchyQoL) questionnaire was used. The ItchyQoL is a questionnaire used to measure the quality of life in patients with chronic pruritus. It is composed of 22 items regarding symptoms, functions, emotions, and self-perception, and is currently under copyright protection.[13] To assess sleep impairment the Epworth Sleepiness Scale (ESS) and Insomnia Severity Index (ISI) were chosen.

The Epworth Sleepiness Scale (ESS) asks patients about their daytime sleepiness on the basis of eight described everyday situations. Depending on the answer, zero to three points are awarded per question. A total of 24 points can be scored. A score of zero to nine is considered normal. From a score of 10 to 24, medical clarification is advisable in order to explore the causes of daytime sleepiness.[14]

The ISI is a validated 7-item questionnaire asking patients to rate their current quality of sleep, in order to assess the extent of insomnia. The maximum score is 28 points. A score of 22 to 28 points indicates severe insomnia, a score of 15 to 21 indicates moderate insomnia, a score of 8 to 14 indicates subclinical insomnia, and a score of 0 to 7 indicates no significant clinical insomnia.[15]

Sleep architecture

Polysomnography is a diagnostic tool to record multiple parameters during sleep. With sensors for electroencephalogram (EEG) and electrooculogram (EOG), for detection of eye movement during REM sleep, the sleep architecture can be recorded. Additional parameters can include respiratory monitoring, with sensors to chest and abdomen (also used to determine the body position) and nasal canula, and pulse oximeter for oxygen saturation. The sleep cycle can be measured with electroencephalography (EEG).[16]

The mobile polygraphy device used in this study allows recording of these parameters in a home environment. The recorded parameters include N3 percentage, REM percentage, Apnea-Hypopnea Index (AHI) through respiratory monitoring, sleep efficiency (Time in Bed [TIB]/Total Sleep Time [TST]) and sleep latency (time to fall asleep), helping to achieve valid test results.[17,18]

Physiologically, REM and deep sleep each account for approximately 20%–25% of total sleep.[19]

In order to assure correct handling, patients were trained in the installation of the device prior to both recordings.

Statistics

For statistical analysis SPSS Version 27 was used. All variables were tested for their distribution (Shapiro-Wilk) and either a t-test (in case of parametric distribution) or Wilcoxon test (in case of non-parametric distribution) was performed to test for significance. Statistics were corrected for multiple testing. The significance level was set to $p < 0.05$. Cohen's d was used to assess the effect size. According to Cohen, a value of $r = 0.10$ can be assumed to be a weak effect, $r = 0.30$ a medium effect, and $r = 0.50$ a strong effect.[20]

The study was performed after obtaining patient consent in accordance with the Ethics Committee of Rhineland-Palatinate (reference number 2020–14835).

RESULTS

Descriptive statistics

Twenty-five patients, eleven patients with AD and 14 patients with PSO were included in the study. At the time of study inclusion seven of the 14 patients with PSO (50.00%) and seven of the eleven patients with AD (63.63%) showed a BMI > 25, by a mean of 29.68 kg/m^2 in PSO patients and 26.6 kg/m^2 in the AD group (Tables 1, 2).

At V1, the mean EASI in AD patients was 13.95 ± 5.87. This value was significantly reduced to 7.39 ± 4.76 at V2 ($p < 0.001$, Cohen's d r = 1.66).

There was a significant reduction of the mean PASI in PSO patients from 10.46 (SD ± 1.30) at the beginning of treatment to 5.65 (SD ± 0.91) at V2. Wilcoxon test performed yielded z = −3.296 with $p < 0.001$ at n = 14 and a 95% confidence interval (CI) of −6.2 to −3.0. The effect size was r = −0.88. According to Cohen, a strong effect can be assumed. Before initial therapy, a correlation between the PASI and REM sleep became apparent ($p < 0.05$) (data not shown).

In AD the mean DLQI improved from 10.27 (SD ± 7.27) to 6.64 (SD ± 8.29) (p = 0.07, Cohen's d r = 0.612). In PSO patients, the DLQI improved from 11.5 (SD ± 8.07) to 7.07 (SD ± 6.4) (p = 0.026, Cohen's d r = 0.67) (Table 1, Figure 1) The IQR changed from 16.5 to 7.75.

In AD patients, the ItchyQol decreased in 2 weeks from 71.36 ± 18.81 to 49.82 ± 24.75 (p = 0.005). According to Cohen a strong effect was present (d = 1.07), in contrast, in PSO patients only a slight reduction from 58.34 (SD ± 19.02) to 57.21 (SD ± 23.98) was noted (p = 0.479, d = 0.203). An increase of IQR = 34 to IQR = 42 was seen.

In AD patients, a reduction of the mean NRS from 6.09 (SD ± 2.66) to 2.27 (SD ± 2.90) was observed (p = 0.001, Cohen's d = 2.68). A change in the IQR from 17 to IQR = 8 was seen.

In PSO an improvement of the mean value from 4.79 (SD± 2.83) to 2.57 (SD ± 2.47) was observed ($p < 0.05$, Cohen's d = 2.64). The IQR changed from 14.75 to IQR = 11.5.

The mean value of the ESS in AD patients was 8.18 (SD ± 2.93) before and was reduced to 7.18 (SD ± 4.38) after 2 weeks of topical therapy (p = 0.128). At Cohen's d = 0.5, the effect was strong.

In PSO patients, the ESS showed a decrease of the mean value from 10.71 (SD ± 3.67) to 8.93 (SD ± 4.83). No significant change could be seen (p = 0.96). The box plot shows an increase of the IQR from 4 to IQR = 10 (Figure 1).

The Insomnia Severity Index (ISI) questionnaire in AD patients showed a significant reduction of the mean values from 14.55 (SD ± 7.63) to 9.82 (SD ± 8.81; p = 0.001). According to Cohen's d, there was a strong effect size (r = 1.41). The IQR remained unchanged with a value of 14. To distinguish the total scores obtained in the evaluation of the ISI, 8 was set as the cut-off score.[15] From before to after topical treatment, the number of patients affected by subthreshold or clinically relevant insomnia decreased from 9 (81.81%) to 5 (45.45%).

In PSO patients the score changed from 13.64 (SD ± 6.72) to 11.64 (SD ± 7.48). IQR remained almost the same with 11.5 and 12. The difference was significant p = 0.043. The effect size according to Cohen's d = 0.601 strong.

Polygraphy

Deep sleep

The percentage of deep sleep in AD patients increased from 5.98% to 16.83% (p = 0.003, Cohen's d = 0.88) between the two investigated time points. The box plot shows an increase from IQR = 9.3 to IQR = 16.26. In PSO patients the mean value increased from 6.1% to 12.33% (p = 0.016, Cohen's d = 0.65).

REM

In AD patients the REM sleep increased from 5.68% before therapy to 11.98 (SD ± 9.66). According to Cohen, the effect was strong (p = 0.016; Cohen's d = 0.73). The IQR changed from 13.2 to 16.44 (Figure 1).

At the start of the investigation, the REM sleep of psoriasis patients was 5.19% and increased to 13.36% after the topical treatment period of 2 weeks (p = 0.014, Cohen's d = −0.76). The IQR changed from 8.94 to 10.91.

Apnea-Hypnea Index

An AHI score of 5 or higher is seen as potentially pathological.[21] Although not significant (p = 0.273), a decrease of the AHI in AD patients from 15.15 to 12.4 was seen, which is still pathological. The IQR decreased from 11.8 to 9.6.

In PSO patients the AHI decreased from 20.16 at baseline to 18.27 (p = 0.221). The effect was moderate (Cohen's d = −0.33). A decrease from IQR = 25.15 to IQR = 15.65 was notable.

In the boxplot, an outlier for the calculated first value of the AHI can be seen. In the second measurement, the majority of the values were at a lower level, although they had increased overall. Two outliers are identifiable.

Sleep efficacy (TST/TIB)

In AD patients sleep efficacy increased from 54.11% to 69.55% (p = 0.13; Cohen's d = −0.49) and a decrease from IQR = 41.2 to IQR = 18.9 was noted.

TABLE 1 Demographic data and results of the examination before and after therapy of atopic dermatitis and psoriasis.

Variable	Before therapy	After therapy	Effect strength	Crude beta (95% CI)	p value	Before therapy	After therapy	Effect strength	Crude beta (95% CI)	p value
	Atopic Dermatitis (AD), n = 11					***Psoriasis (PSO), n = 14***				
Gender n (%)										
Female	4 (36.4)					6 (42.9)				
Male	7 (63.6)					8 (57.1)				
Age in years mean ± SD (range)	49.09 ± 22.28 (19–83)					48.93 ± 16.64 (19–72)				
BMI mean ± SD (range)	26.6 ± 3.53 (20.45–33.20)					29.68 ± 7 (22.41–47.13)				
EASI mean ± SD (range)	13.95 ± 5.87 (8–26)	7.39 ± 4.76 (3–18)	1.66	3.91–9.22	0.001*					
PASI mean ± SD (range)						10.46 ± 4.87 (6–21)	5.58 ± 3.40 (1–14)	−3.30	−6.2–3.0	0.001*
PASI n ≥ 10 (%)						7 (50)	2 (14.29)			
NRS-P mean ± SD (range)	6.09 ± 2.66 (2–10)	2.27± 2.90 (0–10)	2.68	2.02–5.62	0.001*	4.79 ± 2.83 (0–10)	2.57 ± 2.47 (0–8)	2.46	0.69–3.74	0.008*
DLQI mean ± SD (range)	10.27 ± 7.27 (2–27)	6.64 ± 8.30 (0–30)	0.61	−0.35–7.63	0.07	11.5 ± 8.07 (1–24)	7.07 ± 6.42 (0–22)	2.52	0.63–8.23	0.026*
ESS mean ± SD (range)	8.18 ± 2.93 (3–13)	7.18 ± 2.93 (2 –13)	0.5	−0.34–2.34	0.128	10.71 ± 3.67 (5–17)	8.93 ± 4.83 (1–18)	1.79	−0.37–3.94	0.96
ISI mean ± SD (range)	14.55 ± 7.63 (5–27)	9.82 ± 8.81 (1–26)	1.41	2.48–6.98	0.001*	13.64 ± 6.27 (4–24)	11.64 ± 7.48 (0–25)	2.25	0.08–3.92	0.043*

(Continues)

TABLE 1 (Continued)

Variable	Before therapy	After therapy	Effect strength	Crude beta (95% CI)	p value	Before therapy	After therapy	Effect strength	Crude beta (95% CI)	p value
	Atopic Dermatitis (AD), n = 11					***Psoriasis (PSO), n = 14***				
ISI ≥ 8 (%)	9 (81.81)	5 (45.45)				10 (71.43)	10 (71.43)			
ItchyQoL mean ± SD (range)	71.36 ± 18.81 (46–97)	49.82 ± 24.75 (23–98)	1.07	7.99–35.1	0.005*	58.54 ± 19.02 (28–105)	57.8 ± 23.98 (22–101)	0.73	−6.41–12.87	0.479
N3 in % mean ± SD (range)	5.976 ± 5.87 (0–16.9)	16.83 ± 8.28 (5.65–30.06)	0.88	5.92–16.15	0.003*	6.09 ± 5.51 (0–22.49)	12.33 ± 7.30 (0.34–25.71)	2.42	2.417	0.016*
REM in % mean ± SD (range)	5.68 ± 6.07 (0–15)	11.98 ± 9.66 (0.14–29.54)	0.73	1.40–13.45	0.016*	5.19 ± 4.96 (0–14)	13.36 ± 9.86 (1.61–40)	−2.85	−14.36 to −1.99	0.014*
Sleep efficacy in % mean ± SD (range)	54.11 ± 24.08 (13.9–96.4)	69.55 ± 18.88 (24.7–94.6)	−0.50	−36.26–5.39	0.13	69.06 ± 23.96 (27.9–99.9)	70.36 ± 21.35 (23.4–95.8)	−0.2	−15.354–12.754	0.845
AHI mean ± SD (range)	15.15 ± 12.68 (1.1–35.8)	12.4 ± 11.1 (1–39)	0.35	−2.52–8.01	0.273	20.16 ± 24.53 (2.1–86.5)	18.27 ± 24.62 (0–85)	−1.22	−8.65–0.85	0.221
AHI n ≥ 5 (%)	7 (63,63)	8 (72,72)				10 (71.14)	8 (61.53)			
Sleep onset latency in min mean ± SD (range)	43.36 ± 59.96 (0.5–187.5)	19.55 ± 30.29 (0.5–94.5)	−0.2322	−83.5–28.5	0.44	30.07 ± 60.93 (0.5–223)	31 ± 46.16 (0.5–129.5)	0.04	−10.75–16	0.969

*Two-sided significance at $p < 0.05$

Abbr.: BMI, Body Mass Index; EASI, Eczema Area and Severtiy Index; PASI, Psoriasis Area and Severity Index; NRS-P, Numeric Rating Scale-Pruritus; DLQI, Dermatology Life Quality Index; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; ItchyQol, Itch Quality of Life; N3, deep sleep; REM, Rapid-Eye-Movement sleep; AHI, Apnea-Hypopnea Index

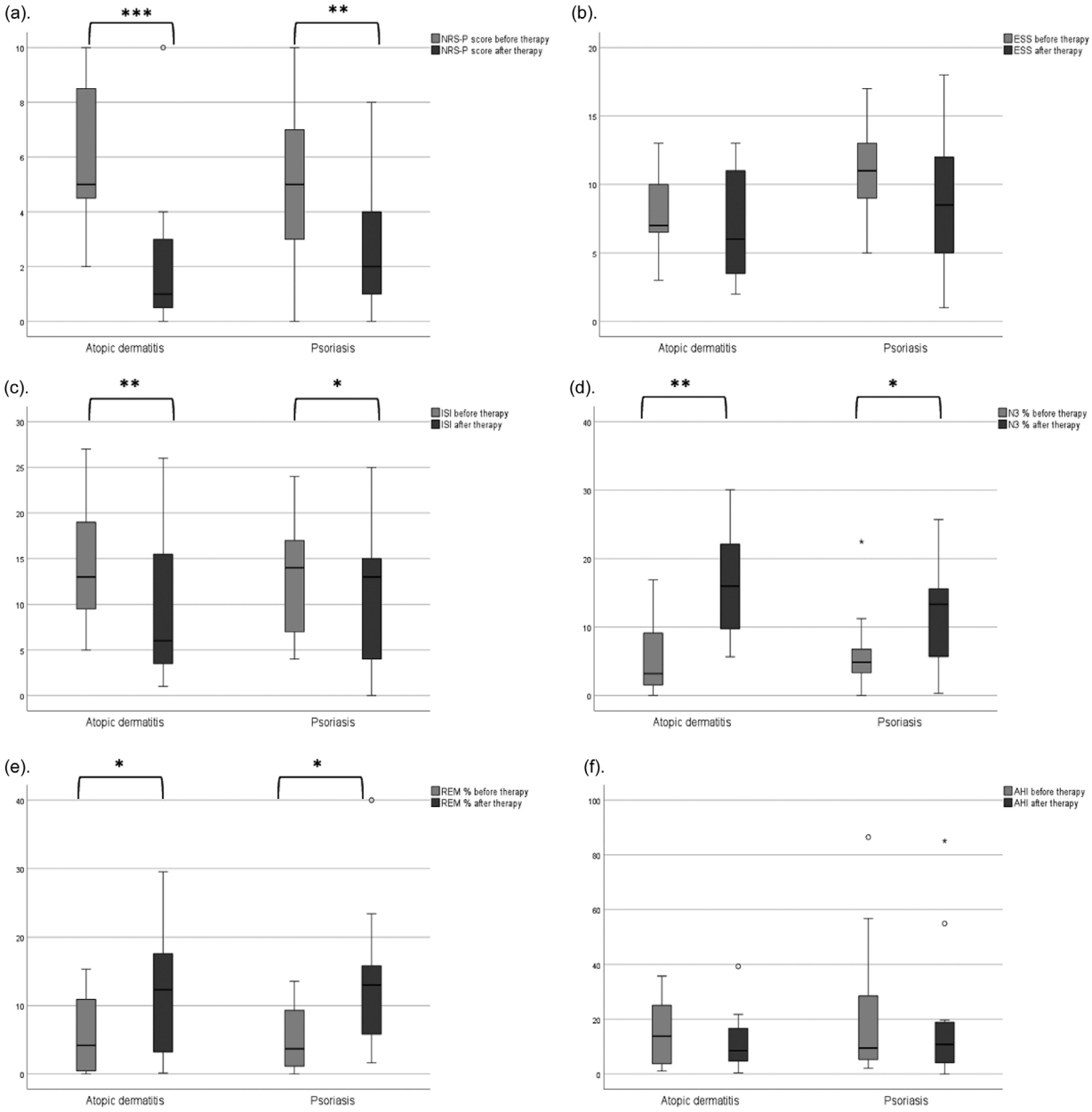

FIGURE 1 Boxplots showing changes before and after therapy. x-axis: Atopic Dermatitis (left) and psoriasis (right) patients y-axis: Scores of patient-rated outcomes (a–c) and polygraphy data (d–f) *p < 0.05, **p < 0.01, ***p < 0.0001 *Abbr.*: NRS-P, Numeric Rating Scale Pruritus; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; N3, deep sleep; REM, rapid eye movement sleep; AHI, Apnea-Hypopnea Index

In PSO patients only a slight increase of the mean value from 69% to 70.36% was observed with no significance or effect ($p = 0.845$, $r = -0.05$).

A change of the IQR from 41.3 to 32.58 was seen.

Sleep onset latency

In AD patients sleep onset improved from 43.36 min (SD ± 49.96 min) to 19.55 min (SD ± 30.29 min) ($p = 0.44$, $r = -0.23$). The IQR changed from 85 to 22.5. One outliner was seen before therapy and two after therapy. These measured values were more than 1.5 times outside IQR. In PSO patients the mean value changed only insignificantly from 30 min (SD ± 60.93 min) to 31 min (SD ± 4.16 min) ($p = 0.969$, Cohen's $d = 0.01$). The IQR changed from 18.25 to 58.38.

Regression models for AD and PSO

To evaluate the influence of pruritus on sleep, a linear regression model was used, which showed a significant influence on deep sleep before therapy ($p < 0.05$), which was no longer seen after therapy. A significant correlation

is also seen between the itch and the ISI after therapy ($p < 0.05$) (online supplementary Table S1).

The influence of the BMI was of particular interest, because of its known influence on sleep. The regression model showed a significant influence on both the ISI ($p < 0.05$) and the AHI ($p < 0.001$); however, this influence was no longer present after 2 weeks of topical therapy. No effect on N3 or REM was seen (online supplementary Table S2).

DISCUSSION

Sleep disturbances in patients with AD and psoriasis are a relevant comorbidity as determined in this real-world clinical cohort. All patients suffered from impaired sleep, which was shown by reduced REM and/or deep sleep.

Before starting the investigation, both patient groups suffered from moderate to severe disease activity, according to the EASI and PASI score.[22] The response of intensive topical therapy significant improved sleep quality in both groups. Sleep was more impaired in patients with AD than with PSO, but it could be improved more rapidly.

This was reflected by a significant improvement in data such as sleep latency and sleep efficacy, with a moderate effect size, as well as a more pronounced increase in deep sleep and REM sleep. According to Cohen's d, a strong effect was seen in both disease states for both subjective (ISI) and objective (REM, N3) parameters. Based on the established criteria of the minimal clinically significant differences (MCID), an increase in deep sleep length of 30% has been discussed in the literature.[23,24] Such an increase was observed in nine of eleven patients (81%) in AD and (57%) in PSO. It is known that about 10% of the worldwide population is affected by permanent insomnia. An occasional occurrence has been reported for 20% of people.[25] Similar to our findings, the overall reported prevalence of sleep disturbances in patients with chronic inflammatory skin diseases is strikingly higher with 33%–90% in AD and 6%–35% in PSO.[1] Silverberg et al. saw an increased risk for poorer overall health status in eczema patients with sleep disturbances, which underlines the relevance of screening to enable early intervention.[4]

In accordance with our findings, Kaaz et al. also found more pronounced sleep disturbances in patients with AD than with psoriasis; however, objectifiable data are missing.[26]

Daytime sleepiness according to the ESS was more pronounced in PSO patients, as was the recorded time spent in bed. A clinically relevant reduction (MCID) was found in four patients (36%) with AD and six (42%) with psoriasis.[27]

Influence of itch

Itch is likely to be perceived differently in the two diseases (stinging or burning), but it plays a role in both.[28,29] Although in AD it is a well-known symptom, in psoriasis it has long been an underestimated burden. Psoriasis patients rated their itch severity on NRS as less severe than patients with AD. Accordingly, the ItchyQol also shows greater impairment in AD than in psoriasis.

A significant reduction in itch NRS was seen in both patient groups. However, the ItchyQol only showed significant improvement in AD. Furthermore, a significant correlation between daytime sleepiness and itch could confirm these results and was only seen in AD patients.

Interestingly, in the overall cohort, a significant correlation with deep sleep and itch could be seen in V1, but no longer at V2 after therapy completion. The fact that REM sleep was not affected by itching may be explained by the muscular atonia that is physiologically present in this stage of sleep. However, an increase in both deep sleep and REM sleep as well as sleep efficacy in both groups of patients indicates that more sleep cycles could be completed without interruption, which could be explained by the improvement in pruritus within only 2 weeks of topical treatment.

Sleep apnea/AHI

There are two broad forms of apnea: the more common obstructive form, in which the muscles of the pharynx relax and obstruct the flow of air, and the central form, in which the central respiratory drive is decreased.[30] Both forms of apnea could be detected in this cohort.

Apnea, in turn, leads to an increase in oxidative stress and the release of proinflammatory cytokines such as TNF-alpha, IL-2,4 and 6.[31] This makes an effect on chronic inflammatory skin diseases likely and the analysis of biomarkers for skin inflammation noteworthy.[1] An AHI greater than or equal to 15 is suggestive of OSAS.[32] The mean AHI in AD and PSO patients was 15.1 and 20.2. In the literature, an MCID of −5 A/H events per hour is discussed.[33,34] According to these criteria, such a decrease could be observed in 5 of 11 (45%) patients in AD, and in 2 of 14 (14%) in PSO patients. Furthermore, in PSO patients, ten (71.14%) had an AHI > 5 before and only five (35%) after 2 weeks of intensive topical therapy. One possible risk factor for OSAS is obesity. However, there was a higher incidence of overweight or obesity in patients with AD (82%), than in PSO (50%), despite the higher AHI score in PSO patients. A higher incidence of obesity in AD patients compared to PSO patients is in contrast to the prevalence reported in the literature, where PSO patients are more likely to be obese and also have a higher incidence of OSAS.[35] This emphasizes the need to screen for OSAS not only in psoriasis, but also in other inflammatory skin disease such as AD.

To further clarify a possible correlation, a linear regression analysis was performed, which showed a correlation between AHI and BMI in the first analysis, but not in the second analysis, although the BMI had not changed or

had changed only slightly. However, a reduction in AHI to 12.4 and 18.3, respectively, was observed. The lack of significance may be partially explained by the presence of statistical outliers with severe OSAS due to obesity.

Furthermore, when looking at the influence of BMI on other sleep parameters, there was a significant influence on insomnia severity only before therapy. The BMI did not have an effect on deep sleep or REM and no significant correlation between the BMI and the ESS was seen, although the questionnaire is commonly used to screen for OSAS.[27] These results show that the BMI does contribute to sleep quality, albeit with limited effect.

The possible relationship between chronic systemic inflammation and increase in AHI score has been discussed earlier in other diseases.[8,36] This leads to the assumption that by reducing inflammation, possibly through intensive topical therapy alone, a possible improvement in AHI could be expected.

Limitations

The patient group was not age- or gender-matched, and there were different stages of disease severity. The main limitation is the small sample size.

CONCLUSIONS

Although both atopic dermatitis and psoriasis are chronic inflammatory skin diseases, there are significant clinical differences that also appear to affect sleep. After only 2 weeks of intensive topical therapy, there was a significant improvement in deep sleep and REM sleep in both patient groups, more so in AD patients than in PSO patients.

One possible explanation for this difference could be the intensity and subsequent reduction in itching, which was more pronounced in AD than in PSO. However, the results provide insight into the relevance of itch in PSO patients and raise questions about other possible factors. Itch appears to have a significant effect on deep sleep and therapeutic intervention with topicals may explain the rapid improvement. However, reducing skin inflammation also seems to have a significant impact on sleep, as shown in this pilot study.

ACKNOWLEDGMENT

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

None.

ORCID

Caroline Mann https://orcid.org/0000-0001-7044-2216

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How to cite this article: Mann C, Dreher M, Rothschmidt J-N, Staubach P. Burden of impaired sleep and its improvement through topical treatment in psoriasis and atopic dermatitis. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*. 2024;22:655–663.
https://doi.org/10.1111/ddg.15373