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1.Einleitung

1.1 Entzündliche Hauterkrankungen als Systemerkrankungen

Chronisch entzündliche Hauterkrankungen sind eine bedeutende Gruppe von dermatologischen Erkrankungen. Sie sind durch anhaltende Entzündungsprozesse der Haut sowie systemische Entzündung gekennzeichnet(1-3). Die Erkrankungen können sich sowohl im Kindesalter, als auch im Erwachsenenalter erstmanifestieren und treten familiär gehäuft auf.

Zu den häufigsten chronisch entzündlichen Hauterkrankungen zählen Psoriasis vulgaris (Pso), atopische Dermatitis (AD), chronische Urtikaria (CU) und Acne inversa (AI)(2). Das Ausmaß der Symptome und die Beeinflussung der Lebensqualität (Krankheitslast) variieren je nach Erkrankung, umfassen jedoch bei allen: Pruritus und/oder Schmerzen. Ihnen ist weiterhin gemeinsam, dass sie in Schüben verlaufen können und mit erheblichen Einschränkungen der Lebensqualität einhergehen. Zu Komorbiditäten zählen unter anderem kardiovaskuläre Erkrankungen, Stoffwechselerkrankungen, psychische Erkrankungen, Autoimmunerkrankungen aber auch Schlafstörungen und Adipositas, sodass man auch von Systemerkrankungen spricht(1-3). Eine bidirektionale Beeinflussung wird immer wieder diskutiert.

Die Krankheitslast dieser Erkrankungen definiert sich als Kombination von Krankheitsaktivität und Lebensqualität. Komorbiditäten können die Krankheitslast zusätzlich verstärken.

Das fehlende Bewusstsein und Wissen über die mit der Erkrankung einhergehende Krankheitslast und Komorbidität führt häufig zur Verschlechterung von physischer und psychischer Gesundheit. Eine frühzeitige Behandlung der Erkrankung inkl. Komorbidität im ganzheitlichen Ansatz, sowohl durch topische und systemische Therapie, als auch durch Lebensstiländerung und psychologischer Unterstützung, sind in das Behandlungskonzept zu integrieren.

Ein wesentlicher Aspekt in der Behandlung von Patienten mit entzündlichen Hauterkrankungen ist die Berücksichtigung von Schlafstörungen, da diese nicht nur die Krankheitsaktivität beeinflussen, sondern auch das alltägliche Leben der Patienten erheblich beeinträchtigen. Schlafstörungen tragen somit maßgeblich zur

Krankheitslast bei. Zum besseren Verständnis und zur Ermittlung der Krankheitslast können sowohl epidemiologische Daten („real-world Daten“) von Bedeutung sein, als auch validierte Fragebögen. Diese Fragebögen u.a. zu Schlafstörungen inkl. Patient-rated outcomes (PROs) werden durch objektive diagnostische Messinstrumente wie die Polygraphie ergänzt. Eine zentrale, in der Dermatologie jedoch häufig unterschätzte Komorbidität, sind Schlafstörungen. Sie können in vielerlei Hinsicht die Krankheitslast erhöhen und haben weitreichende Auswirkungen. Sie können sekundär durch z.B. Pruritus und Schmerz entstehen aber auch primär (z.B. obstruktive Schlafapnoe) vorhanden sein und den Krankheitsverlauf negativ beeinflussen. Darüber hinaus resultieren negative Konsequenzen für die mentale Gesundheit, das kardiovaskuläre System und das Immunsystem indem proinflammatorische Prozesse gefördert werden. Es entsteht ein Teufelskreis, der sich wiederum auf entzündliche Hauterkrankungen auswirken kann.

Durch die Erkenntnisse der letzten Jahre konnten die Pathomechanismen besser verstanden werden, Der Nachweis einer systemischen Entzündungslast bei entzündlichen Hauterkrankungen (Systemerkrankung), beeinflusst das Auftreten von Komorbiditäten. Untersuchungen zu „Cummulative Life Course Impairment“ bei der Modellerkrankung der Psoriasis zeigen deutlich auf, dass eine frühzeitige Behandlung der Symptomatik den Teufelskreis unterbrechen und eine Verselbständigung der Erkrankung verhindern kann(4, 5). Neueste Forschungsansätze bei chronisch entzündlichen Hauterkrankungen wollen durch die Bestimmung geeigneter Biomarker eine frühzeitige Beeinflussung der Krankheitsaktivität und der Komorbiditäten sowie das Bewusstsein für die Interaktionen vorantreiben(2). Das Verständnis der zugrunde liegenden Zusammenhänge verbessert die Behandlungsmöglichkeiten der Patienten und somit das Management dieser Erkrankungen.

2. Methodik

2.1. Fragebögen zur Krankheitsaktivität

Eine Möglichkeit zur Erfassung der Krankheitsaktivität stellen vom behandelnden Arzt erfasste validierte spezifische Krankheits-Scores dar. In unseren Untersuchungen verwendet wurden der Eczema Area and Severity Index (EASI) für die AD, Psoriasis Aktivitätsindex (PASI) für die Pso und Hurley Grad I-III für die AI. Ab einem EASI von 7,1, einem PASI von 10 und einem Hurley Grad II liegt eine mittelschwere Krankheitsaktivität vor (6-9).

Eine Übersicht über die verwendeten Fragebögen inklusive deren Interpretation gibt Tabelle 1. Deren Einordnung (Krankheitsaktivität bzw. Lebensqualität) Abbildung 1.

Beim Urtikaria Kontroll-Test (UCT) und Urtikaria Aktivitätsscore (UAS) für die CU, handelt es sich um Patient-reported outcomes (PRO), die Krankheitsaktivität bzw. der Therapieerfolg wird somit vom Patienten erfasst. Ab einem UCT von weniger als 12 spricht man von einer unkontrollierten Urtikaria, beim UAS7 werden Quaddeln und Pruritus der letzten 7 Tage addiert, hier liegt ab einem Punktwert von 16 eine unkontrollierte Urtikaria vor (10, 11).

Um den Schweregrad des Pruritus bei diesen Erkrankungen zu erfassen eignet sich einerseits der Pruritus Numerische Rating Skala (NRS), der den durchschnittlichen Pruritus auf einer Skala von 0-10 täglich erfasst. Ab einem Wert von ≥ 4 sprichts man von klinisch relevantem Pruritus. Die „minimal Clinically important difference“ (MCID) liegt bei -3 Punkte Pruritus-Verbesserung. (12-14).

2.2. Fragebögen zu Komorbidität/Lebensqualität

Weitere PROs können dabei helfen Komorbiditäten frühzeitig zu erkennen oder sogar zu verhindern (s. auch Tabelle 1).

Zur Beurteilung ob Depressionen und/oder Angststörungen als Komorbidität vorliegen eignet sich der 14-Item Hospital Anxiety and Depression Scale (HADS) (Score 0-42), der Angststörung und Depression abfragt. Ein Wert ab 10 wird als auffällig eingestuft (15).

Die Lebensqualität wird bei dermatologischen Erkrankungen grundsätzlich mittels 10 Fragen durch den Dermatologischen Lebensqualitäts Index (DLQI) ermittelt (Score 0-30). Er befasst sich mit den Domänen: Symptome und Gefühle; tägliche Aktivitäten; Freizeit; Arbeit und Schule; persönliche Beziehungen; und Behandlung. Ab einem Wert von 10 spricht man von einem relevanten Einfluss auf die Lebensqualität (16, 17).

Beim Pruritus Quality of Life (ItchyQol) Fragebogen, bewertet der Patient speziell den Einfluss des Pruritus auf die Lebensqualität (Score 0-110). Er umfasst die Domänen Symptome, Funktion und Emotionen. Unter anderem wird hier auch nach der Beeinflussung des Schlafes durch Pruritus gefragt. Ab 31 Punkten ist von einer milden Beeinflussung auszugehen(18).

Ein weiterer Fragebogen, der zum Therapiemanagement bei entzündlichen Hauterkrankungen Verwendung finden kann, ist der Health Education Impact Questionnaire (heiQ). Er besteht aus 40 Fragen in 8 Domänen, die es ermöglichen, die Selbstmanagementkompetenz der Patienten in Bezug auf den Umgang mit ihrer Erkrankung zu erfassen. Je höher der Score, desto besser die Fähigkeit mit der Erkrankung umzugehen. Eine Ausnahme bildet emotionaler Stress, dieser wird negativ gerankt. Die Domänen umfassen: soziale Integration, positive und aktive Teilnahme am Leben, Erlangen von Fähigkeiten und Techniken, konstruktive Einstellung und Herangehensweise, Selbst-Monitoring und Erkenntnis, Gesundheits-bezogene Aktivitäten, Navigation im Gesundheitssystem (Kommunikation mit dem Behandler) und emotionales Wohlergehen (19).

Um die mögliche Krankheitslast des Schlafes zu messen werden Fragebögen wie der Insomnie Schweregrad Index (ISI) eingesetzt, ein Fragebogen, der die Schlafqualität während der letzten zwei Wochen abfragt und dabei zwischen Einschlaf-, Durchschlafstörungen und zu frühem Erwachen unterscheidet und gezielte Fragen über die Schlafzufriedenheit und die Beeinflussung des alltäglichen Lebens stellt. Er eignet sich ebenfalls zur Verlaufskontrolle unter Therapie (Score 0-28). Ein Wert ab 8 zeigt bereits eine subklinische Insomnie an (20).

Um die Auswirkungen von Schlafstörungen auf die Tagesmüdigkeit weiter zu erfassen, eignet sich der Epworth Schläfrigkeits-Skala (ESS). Dieser erfasst die Wahrscheinlichkeit in verschiedenen Alltagssituationen einzuschlafen. Er wird einerseits als Screening Methode für eine bereits bestehende Tagesmüdigkeit eingesetzt sowie um die zentralnervöse Wirkung eines Medikaments einzuschätzen. Möglich ist auch die Messung von Therapieerfolgen (Score 0-24). Ein Score von ≥ 10, gilt als auffälliger Befund (21).

Zusammenfassung:

- Übersicht über die verwendeten Fragebögen zur Krankheitsaktivität
- (EASI für AD, PASI für Pso und Hurley Grad für AI),
- Patient Reported Outcomes:
- Urtikaria: UCT und UAS7
- Pruritus: Itchyqol und Pruritus NRS
- Insomnie, Tagesmüdigkeit: ISI und ESS
- Dermatologische Lebensqualität: DLQI

Tabelle 1: Übersicht über die verwendeten Fragebögen (PRO) und deren Interpretation (nach (11-14, 16-18, 20, 22-24) erstellt durch C.Mann)

Fragebogen	Fragen-anzahl	Skala	Zeitraum*	Min./Max.	Beurteilung
Urticaria Control Test (UCT)	4	0-4	4 Wochen	0-16	16=vollständig kontrolliert 12-15=gut kontrolliert < 12=unkontrolliert

Urtikaria Aktivitäts-Score	14	0-3	7 Tage	0-42	0 =kein Pruritus oder Quaddeln 1–6=gut-kontrolliert 7–15=milde Aktivität 16–27=mittel-schwere Aktivität 28–42=schwere Aktivität
Pruritus Numerische Rating Skala (NRS)	1	0-10	aktuell	0-10	0-2,9=kein - milder Pruritus 3–6.9=mittel-schwer 7–10=schwer
Insomnie Schweregrad Index (ISI)	7	0-28	2 Wochen	0-28	0-7=keine signifikante klinische Insomnie 8-14=subklinisch 15-21=mittelgradig 22-28=schwer
Epworth Sleepiness Scale (ESS)	8	0-3	letzte Wochen	0-24	0-7=normale Tagesmüdigkeit 8-9= durchschnittliche Tagesmüdigkeit 10-14=erhöht Ab 15=sehr hoch
Hospital Anxiety and Depression Scale (HADS)	14	0-3	7 Tage	0-21	0-7=normal 8-10=grenzwertig abnormal 11-21=abnormal
Dermatologischere Lebensqualitäts-Index (DLQI)	10	0-3	7 Tage	0-30	0-1=Haut-erkrankung hat keinen Einfluss auf die Lebensqualität 2-5=kleiner Einfluss

					6-10=mittelschwerer Einfluss 11-20=starker Einfluss Ab 21=sehr starker Einfluss
Pruritus Lebensqualitäts Fragebogen (ItchyQol)	22	1-5	7 Tage	0-110	0-30=geringe Beschwerden 31-50=milde Beschwerden 51-80=mittel-schwer 81-110=schwer
Health Education Impact Questionnaire	40	1-4	aktuell	40-160	Je höher der Wert, desto höher die Kompetenz mit der Erkrankung umzugehen Beurteilung mittels Effektstärke (Cohens' d): >0,5 mittlerer Effekt >0,8 starker Effekt

*Der Zeitraum kann je nach Forschungsfrage angepasst werden, dies sollte jedoch entsprechend erwähnt werden

Abbildung 1: Krankheitslast als Folge von Krankheitsaktivität und eingeschränkter Lebensqualität. Verwendete Scores zur Beurteilung der Krankheitsaktivität und Lebensqualität um die Krankheitslast zu erhalten (erstellt durch C.Mann).

2.2. Objektive Methoden Krankheitslast zu erfassen

Neben der vom Behandler beurteilten Krankheitsaktivität anhand von Scores, gibt es die Möglichkeit mittels objektiver Messmethoden, zumindest indirekt, die Lebensqualität und damit auch die Krankheitslast zu objektivieren. Hier sind Untersuchungen des Schlafes mittels Polygraphie eine adäquate Methode. Polygraphie mittels Screening-Geräten bietet die Möglichkeit im häuslichen Umfeld, die Schlafarchitektur mittels u.a. EEG, EMG, Sauerstoffsättigung, Atembewegungen, Lagesensor und Mikrofon (Schnarchen) darzustellen und somit unterschiedliche Formen der Schlafstörungen (insbesondere auch Insomnie und Schlafapnoe) darzustellen.

Dies lässt Aussagen über die Schlafqualität zu, indem unter anderem Apnoen, Hypopnoen (Apnoe/Hypopnoe Index (AHI)) über die Bauchatmung und Thorax Atmung und Sauerstoffmessung erfolgt. Mittels EEG lassen sich anhand der spezifischen Gehirnwellen die Einschlaflatenz in Minuten, die Schlafeffizienz (totale Schlafenszeit („total sleep time“ (TST)) im Verhältnis zur Zeit, die im Bett verbracht wurde („time in bed“ (TIB)) sowie die Schlafstadien bestimmen. Diese sind Wach (W), leichter Schlaf (N1, N2) Tiefschlaf (N3) und Traumschlaf (REM). Weniger als 15 % Tief- oder weniger als 20 % REM-Schlaf, werden als pathologisch bewertet (25).

Abbildung 2 zeigt eine beispielhafte polygraphische Auswertung mit Hypnogramm und relevante Schlafparameter mit Normwerten.

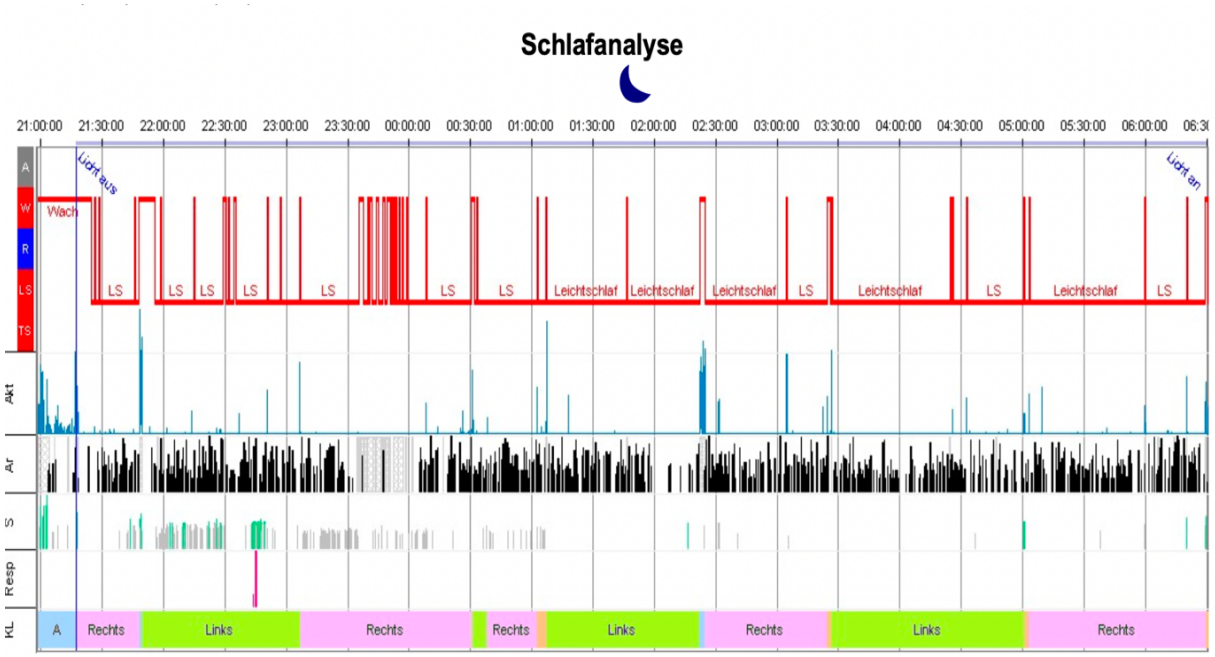
Die Polygraphie-Daten wurde an ambulanten Patienten der Hautklinik in Mainz mit AD, Pso und CU erhoben und zur Krankheitsaktivität korreliert. Dabei konnten verschiedene Schlafphasen beurteilt werden: der Hauptfokus lag hierbei auf dem REM-Schlaf (u.a. essenziell für die Bearbeitung von emotionalen Erlebnissen) und dem Tiefschlaf (N3) (Verinnerlichung von Gelerntem) (26, 27).

Bei Patienten mit unkontrollierter AD, als auch CU und Psoriasis konnte mittels Polygraphie und PRO eine signifikante Einschränkung der Lebensqualität (DLQI), sowie auch des Tief- und REM-Schlafes gezeigt werden(28).

Die Polygraphie ermöglicht es somit die Beeinflussung der Lebensqualität ergänzend zu objektivieren. Diese Daten zeigten auch, dass die subjektiv wahrgenommene Schlafqualität von der objektiven abweicht. Der Schlaf wird nach erfolgter Therapie zwar signifikant besser eingeschätzt, jedoch tendenziell immer noch schlechter, als objektiv gemessen(28).

Zusammenfassung:

- Pruritus als wesentliche Komorbidität und Ursache für gestörte Lebensqualität/Schlaf bei AD, Pso und CU Patienten.
- Pruritus zeigt Einfluss vor allem auf den in der Polygraphie gemessenen Tiefschlaf (N3).
- Positive Beeinflussung des Pruritus durch topische Therapie bei AD und Pso und hochdosierte Anthistaminika bei CU



Relevante Schlaf-Parameter	Schlafstadium N1 und N2 (Leichtschlaf)	Schlafstadium N3 (Tiefschlaf)	Schlafstadium REM (Traumschlaf)	Apnoe-Hypopnoe Index (AHI) pro Stunde (h)	Schlafeffizienz (TST/TIB)
Normwerte	N1: ca. 5% Anteil am Schlaf N2: ca. 45% Anteil am Schlaf	>15 % Anteil am Schlaf	> 20 % Anteil am Schlaf	Gesund: AHI < 5 /h Leichtgradig: AHI von 5 bis 14/h. Mittelgradig: AHI von 15 bis 30/h Schwergradig: ab einem AHI > 30/h.	>80-85 %

Abbildung 2: Beispielhafte Auswertung einer Schlafanalyse (Hypnogramm) mit Darstellung von oben nach unten: Uhrzeit, Schlafphasen: Wach, Leichtschlaf (LS; N1 und N2), Tiefschlaf (TS), REM (R); Bewegung (Akt), Arousal (Ar), Schnarchen (S), Atmung (Resp), Körperlage (KL) (Tabelle nach (25) (29-31).(Bildquelle: Schlafanalyse eines Patienten mit dem Home-Sleep Test einem Polygraphiegerät der Firma Somnomedics©)

3. Ergebnisse und Schlussfolgerungen

3.1. Prävalenz von Komorbiditäten bei entzündlichen Hauterkrankungen

Komorbidität bei Patienten mit chronischen entzündlichen Hauterkrankungen wie z.B. der CU, sind im klinischen Alltag nicht selten. Bei der CU kommen Komorbiditäten aus dem atopischen Formenkreis besonders häufig vor , aber auch kardiovaskuläre, Autoimmunerkrankungen, maligne Erkrankungen, Schlafstörungen und psychische Erkrankungen (Tabelle 2 aus der Publikation)(32). Von n=212 retrospektive analysierten Patienten aus unserer CU-Sprechstunde hatten n=59 eine zusätzliche Komorbidität. 62 % hatten spontane CU, 35,2 % zusätzlich induzierbare Formen. Schilddrüsenerkrankungen z.B. werden als häufige Ursache der Urtikaria angesehen. In der hier untersuchten Kohorte ergab sich eine hohe Prävalenz von Hypothyreose (46,3%), was diese Annahme bestätigen würde. Auch die art. Hypertonie (43,5%) ist eine häufige bei der Urtikaria vorkommende Komorbidität. Darüber hinaus trat bei 14,8 % eine therapiepflichtiger Depression auf, bei 13 % eine medikamentös behandelte Schlafstörung, bzw. 2,8 % Schlafapnoe. Unter den Autoimmunerkrankungen (11,1%) war auch Psoriasis mit 2,8 % vertreten (Tabelle 2 aus der Publikation)(32).

Schlafstörungen, insbesondere die Insomnie, tritt nicht nur bei der CU als Komorbidität auf, auch bei anderen entzündlichen Hauterkrankungen wie der AD, Pso und der AI kommen sie vor. Eine weitere gemeinsame Komorbidität ist der Pruritus, dessen Relevanz für Patienten mit Psoriasis häufig unterschätzt wird. Pruritus spielt wiederum auch bei Schlafstörungen eine entscheidende Rolle (28, 33).

Weitere Komorbiditäten, die insbesondere bei der AI und Pso beschrieben sind, jedoch auch bei CU eine Rolle zu spielen scheinen, sind Adipositas und kardiovaskuläre Probleme (metabolisches Syndrom). So waren in einer weiteren Erhebung von insgesamt 61 Patienten mit AD und CU etwa die Hälfte der Patienten mit einem BMI von >24,9 kg/m^2 übergewichtig (33). Bei 258 Patienten mit AI lag der BMI im Mittel bei 32,5 kg/m^2 (34). Bei diesen AI-Patienten, zeigte sich jedoch in der Untersuchung, dass weder Adipositas noch Nikotinabusus (mit ca 70% Rauchern oder Ex-Rauchern) mit einem erhöhten Risiko für Krankheitsaktivität (inkl. Schmerzen),

Depression/Angststörungen, Insomnie oder Lebensqualitätseinschränkung assoziiert sind. Bei einer weiteren von uns nicht vorselektierten Kohorten, zeigt sich bei 25 Patienten (11 AD und 14 Pso) eine deutlich höhere Prävalenz von Übergewicht bei AD im Vergleich zu Pso (28).

Zusammenfassung:

- Hohe Prävalenz von Komorbiditäten bei Patienten mit chronisch entzündlichen Hauterkrankungen
- Pruritus als Komorbidität von chronisch entzündlichen Hauterkrankungen
- Adipositas als häufigste Komorbidität bei allen Hauterkrankungen

3.2. Komorbiditäten inkl. Komedikation und deren Management

Ziel ist es in der Behandlung der entzündlichen Hauterkrankung eine Symptomkontrolle zu erreichen. Eine Herausforderung stellen dabei bereits bestehende oder assoziierte Komorbiditäten dar. Dies gilt insbesondere dann, wenn mehrere Medikamente miteinander kombiniert werden müssen. In unserer Untersuchung von 212 Patienten mit CU hatten 108 (50,9%) Patienten eine Komedikation. Unter den häufigsten Begleitmedikationen waren vorwiegend das Schilddrüsenhormon Levothyroxin (41,7 %), Beta-Blocker (18,5%), AT-1 Rezeptor Antagonisten (13.9%), Thrombozytenaggregationshemmer (10,2 %), Statine (7,4 %) sowie Serotonin-Wiederaufnahme-Hemmer (5,6 %)(32).

Im Fall der CU empfiehlt die aktuelle internationale Leitlinie eine Therapie mit einem bis zu 4-fach dosiertem Antihistaminikum und, im Falle fehlender Symptomkontrolle, bei CSU die zusätzliche Gabe z.B. des anti-IgE Antikörpers Omalizumab. Da in der Behandlung die vollständige Symptomkontrolle angestrebt wird, werden in seltenen, Therapie-resistenten Fällen der CU, noch weitere Medikamente wie Dapson oder Ciclosporin eingesetzt, bei Bedarf auch in Kombination. Die mittlere Behandlungsdauer in der zweifachen Kombination (Antihistaminikum plus weitere Systemtherapie) war in unserer Untersuchung 24,6 Monate (SD ± 21.3) und die dreifache Kombination mit einer weiteren Systemtherapie 4,9 Monate (SD ± 3,2).

Zusätzlich sind nicht selten bei der CU weitere Komorbiditäten und demnach die Kombination mehrerer Medikamente üblich (Polymedikation).
Zum Beispiel wurde in unserer Kohorte die Therapie der CU, bei bestehender oder neu-aufgetretener maligner Grunderkrankung oder Autoimmunerkrankung, nicht beendet (32). Die Patienten berichteten über geringe Nebenwirkungen wie Gewichtszunahme und Fatigue (18,5%) aber keine schwerwiegenden Ereignisse.
Die Leitlinien-gerechte Therapie der CU ist nach diesen Untersuchungen als sicher und durchführbar einzustufen (Supplement Fig.1 aus der Publikation)(32).
Zudem lässt sich sagen, dass die Therapie der CU trotz Komorbidität zu keiner negativen Beeinflussung der jeweiligen Erkrankung führt. Komedikation ist möglich.

Zusammenfassung:

- Sicheres Therapieren von chronisch entzündlichen Hauterkrankungen wie CSU trotz Komorbidität und Ko-Medikation ist möglich
- Geringes Nebenwirkungsprofil von CU-Medikation auch als Kombinationstherapie

3.2. Ermittlung der Krankheitslast mittels Fragebögen

3.2.1. Insomnie Schweregrad-Index

Eine Übersicht über die verwendeten Fragebögen inklusive deren Beurteilung gibt Tabelle 1.

Neben dem DLQI zur Erfassung der Lebensqualität, erweist sich zusätzlich der ISI-Fragebogen als geeignet, die Lebensqualitätseinschränkung wiederzugeben und andererseits die Insomnie, die häufigste aller Schlafstörungen, einzuschätzen. Schlafstörungen sind bei Patienten mit chronisch entzündlichen Hauterkrankungen häufig und werden jedoch in ihrer Relevanz unterschätzt. Die Insomnie zeigt eine erhöhte Prävalenz bei AD, Pso, CU und auch AI.

Eine Möglichkeit Insomnie zu messen stellt der validierte Fragebogen „Insomnie Schweregrad Index (ISI)“ da. Auch zum Messen des Therapieerfolgs kann dieser Fragebogen zum Einsatz kommen. Im Falle von CU und AD zeigt sich ein direkter

Zusammenhang zwischen einem Erkrankungsschub und dem Anstieg der Insomnie Schweregrads. Es kam zu einer mehr als Verdopplung der Insomnie im Schub bei beiden Erkrankungen: ISI-Mittelwert vor einem Krankheitsschub: 8,7 (SD ± 5.6) bei AD und 6,8 (SD ± 4,9) in CU, während eines Schubes: 16 (SD ± 6,4) bei AD und 14,9 (SD ± 6,0) bei CU. Somit ergab sich eine klinisch relevante Insomnie (Tabelle 1 der Publikation)(33). Bei der Auswertung der Einzelfragen des ISI ergab sich bei CU Patienten, mit hoher Krankheitsaktivität und schwerem Pruritus, eine relevante Unzufriedenheit mit der Schlafqualität, gewertet an der Einzelfrage über die „Zufriedenheit mit dem eigenen Schlaf“ (33). Die Krankheitsaktivität bei AD, gemessen am EASI, zeigte ebenfalls einen signifikanten Zusammenhang mit dem ISI.
Bei 14 Patienten mit unbehandelter Psoriasis, zeigte sich ein ISI von 13,58 (SD ± 6,27)(28). Obwohl sich die AI-Patienten bereits in Behandlung befanden, lag der erfragte mittlere ISI-Score bei 179 Patienten immer noch bei 9,58 (SD ± 5,76) und somit bei einer „unterschwelligen Insomnie“(34). Dass die Lebensqualität durch die Insomnie beeinflusst wird, zeigte sich in einer signifikanten Korrelation bei beiden Erkrankungen (33). Patienten mit AD schienen größere Probleme mit Einschlafstörungen zu haben, während CU-Patienten eher unter zu frühem Erwachen, mit direktem Einfluss auf den DLQI, litten (33). Ein erhöhter DLQI korrelierte ebenfalls mit der ISI-Einzelfragen über die Zufriedenheit des Schlafprofils. Patienten mit hohem DLQI waren weniger zufrieden mit ihrem Schlaf. Somit lässt sich zusammenfassen, dass die Lebensqualität der Patienten wesentlich durch die Schlafqualität bestimmt wird. Ein erhöhter BMI zeigte sich zwar unabhängig vom ISI-Score, jedoch korrelierter dieser bei CU signifikant mit der Lebensqualität.

3.2.2. Beurteilung der Lebensqualität mit dem DLQI

Der DLQI eignet sich zur Beurteilung der Lebensqualitätseinschränkung während eines Krankheitsschubes. Im Falle von 25 AD und 36 CU Patienten zeigte sich ein mittlere DLQI-Wert mit 14,0 (SD ± 8,7) bei AD und respektive 9,6 (SD ± 8,0) bei CU. Dies spiegelt damit ein relevante Lebensqualitätseinschränkung vor allem der Patienten mit AD wider (33).
Der Verlauf des DLQI zur Beurteilung des therapeutischen Ansprechens zeigte, dass sich innerhalb von 2 Wochen der Mittelwert bei 14 Patienten mit Pso von 11,5 (SD ± 8,07) vor Therapie auf 7,07 (SD ± 6,42) unter Therapie reduzierte. Bei 11 AD Patienten ergab sich unter Therapie innerhalb von 2 Wochen ebenfalls eine Verbesserung von

10,27 (SD ± 7,27) auf 6,64 (SD ± 8,30). Bei unserer Pilotstudie mit 10 CU Patienten zeigte sich unter leitliniengerechte „Up-dosing“ mit Anthistaminika der 2. Generation eine signifikante Verbesserung des DLQI von 15,0 auf 6,0 nach nur 5 Tagen (35). In unserer Kohorte mit 194 AI Patienten, die sich bereits in systemischer und topischer medikamentöser Vorbehandlung befanden, ergab eine Querschnittserhebung des DLQI einen mit 11,40 Punkten (SD ± 7,79) nach wie vor erhöhten Wert (34).

3.2.3. Pruritus

Es ist evident, dass Pruritus die Lebensqualität der betroffenen Patienten mit chronischen Hauterkrankungen signifikant beeinflusst. Bei AD und CU Patienten, die sich im akuten Krankheitsschub befanden, ergab sich eine signifikante Korrelation des Pruritus NRS mit dem DLQI ($p<0,05$)(33). Der Einfluss des Pruritus auf die Lebensqualität war auch bei einer weiteren Untersuchung bei Patienten mit AD uns Pso nachweisbar. Hier zeigte der ItchyQol insbesondere bei der AD eine hohe Belastung mit 71,36 Punkten (SD ± 18,81) an. Aber auch bei der Pso stellte sich eine moderate Beeinflussung der Lebensqualität durch Pruritus mit 58,54 Punkten (SD ± 19,02) dar. Die durchgeführte Regressionsanalyse bildete eine signifikante Beeinflussung des Tiefschlafes (N3) in der Polygraphie von 25 Patienten (11 AD und 14 Pso) ab. Dieser negative Einfluss verschwand nach zweiwöchiger Therapie (Tabelle Suppl. 1 aus der Publikation)(28). Dies machte auch deutlich, inwieweit bereits topische Therapien den Pruritus positiv beeinflussen können. Bei Patienten mit AD reduzierte sich unter topischer Therapie der Pruritus innerhalb von 2 Wochen, was mittels der signifikanten Reduktion des Pruritus
NRS ($p=0,001$) im Verlauf gemessen wurde.
Auch der ItchyQol wies eine signifikante Verbesserung nach erfolgter Therapie bei AD auf ($p=0,005$). Pso-Patienten berichteten ebenfalls über eine signifikante Verbesserung des Pruritus unter alleiniger topischer Therapie ($p=0,008$) (28). Die Therapie zur Pruritus-Kontrolle bei CU ist leitliniengerecht durch hochdosierte Antihistaminika der 2. Generation empfohlen. Hier kommt es innerhalb der therapierten 5 Tage zur signifikanten Verbesserung des subjektiven Pruritus (NRS) während des Tages ($p=0,0120$)(35).

Fehlende Korrelationen des Pruritus NRS mit dem ISI-Score, sowie eine fehlende signifikante Verbesserung des subjektiv empfundenen nächtlichen Pruritus unter hochdosierten Antihistaminika der 2. Generation, lassen vermuten, dass neben dem Pruritus weitere Faktoren zu Schlafstörungen beitragen. Alternativ muss diskutiert werden ob eine subjektive Einschätzung des nächtlichen Pruritus, anders als dem tagsüber, nur ungenau möglich ist (28, 35).

AI ist eine chronische Hauterkrankung, bei der zwar auch Pruritus, jedoch vorwiegend der Schmerz als Symptom im Vordergrund steht. Dies zeigt sich um so mehr, wenn emotionaler Stress konstatiert wird (34). Daher spielt auch die Therapie von Schmerzen eine zentrale Rolle in der Krankheitskontrolle und Verbesserung der Lebensqualität.

4. Behandlungsansätze

4.1. Durch Symptomkontrolle Verbesserung der subjektiven und objektiven Schlafqualität

Mittels Polygraphie lassen sich direkte Einflüsse der Krankheitsaktivität auf den Schlaf darstellen und somit die Einschränkung der Lebensqualität objektiv beurteilen (Abbildung 2). Weiterhin lässt sich die Polygraphie nutzen um Einflüsse, u.a. einer medikamentösen Therapie, auf den Schlaf darzustellen und somit indirekt auch Auswirkungen auf die Lebensqualität. Dies lässt sich am Beispiel der CU zeigen. Zur Symptomkontrolle der CU spielen Antihistaminika der 2. Generation eine wichtige Rolle. Unter nur 5 Tagen der Hochdosistherapie kam es nicht nur zur signifikanten Verbesserung der Krankheitskontrolle (UCT p=0.0007), sondern auch zur signifikanten Erhöhung des REM-Schlafanteils von 3,9 % auf 14,3 % und zur Verbesserung des Tiefschlafes von 8,7% auf 12,3%. Auch Einschlafstörungen wurden verbessert, dies zeigte sich an einer signifikant verkürzten Einschlaflatenz von 10,7 auf 5,4 min in der Polygraphie (Abbildung 2 der Publikation)(28). Darüber hinaus stellte der ISI als PRO ergänzend eine signifikante Verbesserung des Schlafes dar (p=0,0349).

Bei der CU stellt sich durch die Hochdosierung der Antihistaminika der 2. Generation immer wieder die Frage, in wieweit dies zur vermehrten Tagesmüdigkeit von Patienten führen kann. Unsere Ergebnisse zeigten keine erhöhte Tagesmüdigkeit (Score des ESS-Fragebogens), im Gegenteil, die systemische Therapie mit den hochdosierten Antihistaminika führte innerhalb von 5 Tagen zu einer geringen Reduktion des ESS. Dies lässt sich ggf. durch eine bessere Krankheitskontrolle erklären.

Eine zweiwöchige adäquate topische Therapie resultierte in Reduktion des EASI und PASI sowie einer signifikanten Reduktion des Pruritus konnte bei AD und Pso Bei diesen Patienten konnte ebenfalls eine Reduktion der Tagesmüdigkeit erreicht werden und die Lebensqualität dieser Patienten verbesserte sich signifikant ($p<0,0001$) (Abbildung 1 der Publikation)(28).

Im Hinblick auf die objektive Schlafqualität zeigte sich eine signifikante Verbesserung von REM- und Tiefschlaf. Der Tiefschlaf bei AD Patienten erhöhte sich von 5.98 % to 16.83% ($p=0.003$). In Pso von 6.1% to 12.33% ($p= 0.016$).
Durch die Behandlung von Patienten mit topischen Therapien verlängerte sich der REM Schlaf von 5.68% auf 11.98 % ($p=0.016$) bei AD, von 5.19% auf 13.36% ($p=0.014$) bei Pso. Auch eine Steigerung der Schlafeffizienz, vor allem bei AD von ca 54 % auf 70 % war zu beobachten (Tabelle 1 und Abbildung 1 der Publikation)(28). Der Schlaf war insgesamt eingeschränkter bei AD als bei Pso Patienten und konnte bei AD schneller durch topische Therapie positiv beeinflusst werden (28).

Es zeigte sich zudem eine tendenzielle Reduktion des Apnoe-Hypnoe-Index (AHI Index aus: zentralen und obstruktiven Apnoen, sowie Hypopnoen) bei Pso und AD Patienten unter topisch antientzündlicher Therapie in einem Zeitraum von nur 2 Wochen. Grundsätzlich unterscheidet man zwischen zwei Formen der Apnoe, der häufigeren obstruktiven, bei der es zu einer Erschlaffung der Rachenmuskulatur und damit zu einer Behinderung des Atemflusses kommt, und der zentralen Form, bei der der zentrale Atemantrieb vermindert ist sowie der Hypopnoe, einem verminderten Atemfluss (36). Alle Formen der Atmungsstörungen konnten in der zuletzt beschriebenen Kohorte nachgewiesen werden. Ein AHI größer 5 ist leichtgradig erhöht und ab 15 oder mehr ist als klinisch relevant anzusehen (Abbildung 2)(29). Der

mittlere AHI bei AD- und Pso-Patienten lag bei 15,1 und 20,2 vor Therapie und verringerte sich auf 12,4 respektive 18,3 unter zweiwöchiger topischer Therapie. Die fehlende Signifikanz könnte teilweise durch das Vorhandensein von statistischen Ausreißern von Patienten mit schwerem OSAS aufgrund von Adipositas erklärt werden. In der Literatur wird ein MCID von -5 Apnoe/Hypnoe-Ereignissen pro Stunde bei Patienten mit OSAS beschrieben, spezifische Daten für Hauterkrankungen fehlen (37, 38). Nach diesen Kriterien konnte eine solche Abnahme bei 5 von 11 AD-Patienten und bei 2 von 14 Pso-Patienten beobachtet werden. Außerdem lag bei Pso-Patienten ein AHI-Wert >5 bei 10 und nur bei 5 nach zwei Wochen intensiver topischer Therapie vor (28). Eine Schlafapnoe war bei diesen Patienten nicht als Komorbidität vorbekannt. Die Patienten mit auffälligen AHI-Scores wurden zur weiteren Behandlung und Sauerstoff-Maskenanpassung in spezialisierte Schlaflabore geschickt.
Der BMI hatte in allen polygraphischen Untersuchungen keinen Einfluss auf die objektive Schlafqualität, weder bei Patienten mit CU noch bei AD oder Pso. Auch der ESS zeigte keine Korrelation mit dem BMI der Patienten.

Zusammenfassung:

- Prozentuale Erhöhung von Tief- und REM-Schlaf, Einschlaflatenz und Tagesmüdigkeit unter topischer Therapie bei AD und Pso und unter hochdosierten Antihistaminika bei CU
- Reduktion des Tagesmüdigkeit (ESS)
- Verbesserung der Krankheitsaktivität und Lebensqualität
- Reduktion des AHI-Scores unter topischer Therapie bei AD und Pso

4.3. „Selbst-Management“ als therapeutischer Ansatz

Die Edukation von Patienten kann, ähnlich wie bei der kognitiven Verhaltenstherapie bei der Insomnie, als eine Möglichkeit zur unterstützenden Therapie betrachtet werden. Die Selbst-Edukation des Patienten zielt einerseits darauf ab, dass er zum Experten seiner eigenen Erkrankung wird, andererseits, dass er befähigt wird, selbstständig in bestimmten Krankheitsphasen frühzeitig zu intervenieren. Die Identifikation potenzieller Ansatzpunkte für die Erhöhung der Selbstmanagement-Kompetenz kann mittels des HeiQ-Fragebogens, der verschiedene Kompetenz-Bereiche im Alltag des Patienten abdeckt, erfolgen. In einer Untersuchung mit 194 AI-Patienten konnten wir zeigen, dass insbesondere die Patienten, die weniger soziale Kompetenz (soziale

Integration) aufweisen und nicht aktiv am Leben teilnahmen, ein höheres Risiko für Schmerzen, Depressionen, Schlafstörungen und eine eingeschränkte Lebensqualität aufweisen (34). Der stärkste negative Einfluss auf die Krankheitsaktivität zeigt sich durch fehlendes emotionales Wohlbefinden und eine fehlende konstruktive Einstellung und Herangehensweise. Auffällig war ein hohes Risiko für psychische Probleme (HADS), wenn keine aktive Teilnahme am Leben stattfand (OR=32,727). Einen negativen Einfluss hatten: fehlende konstruktive Einstellung und Herangehensweise (OR=46,600), fehlende soziale Integration (OR=29,597) und fehlendes emotionales Wohlbefinden. Insomnie wurde ebenfalls am stärksten durch fehlende aktive Teilnahme am Leben (OR=4,714) und fehlende soziale Integration (OR=7,453) begünstigt. Ein höheres Risiko für eine verminderte Lebensqualität barg fehlendes emotionales Wohlbefinden, eine fehlende konstruktive Einstellung/Herangehensweise und fehlende soziale Integration (34). Die Daten zeigen, dass ein positiver Effekt sowohl auf die psychische Gesundheit als auch auf den Schlaf und die Lebensqualität durch gesteigerte soziale Integration sowie durch gesteigerte physikalische Aktivität zu erwarten ist. Diesbezüglich sei auf Tabelle 3 der Publikation verwiesen, welche die Ergebnisse der AI-Studie darstellt (34). In Abhängigkeit von der führenden Problematik lassen sich entsprechend den einzelnen Domänen des heiQ weitere Interventionsmöglichkeiten und Hilfestellungen für den Patienten ableiten. Zum Beispiel stellt die optimierte Kommunikation zwischen den behandelnden Ärzten und dem Patienten einen wesentlichen Faktor zur Verbesserung des Verständnisses der Erkrankung dar. Selbsthilfegruppen können unter anderem zu emotionalem Wohlergehen und sozialer Integration beitragen.

Etwa 84% der AI-Patienten aus unserer Kohorte, zeigten eine erhöhte Krankheitsaktivität mit einem Hurley Grad von II-III. Bei der AI ergeben sich aufgrund der dort im Vordergrund stehenden Abszesse und Wunden sowie Narben vor allem in diesem Bereich Aufklärungswünsche, die Patienten in Form einer digitalen Applikation erhalten könnten. Demnach wünschen sich die Patienten in einer potentiellen digitalen Applikation am meisten Pflegetipps, Aufklärung über die Krankheit sowie Wissen über potentielle Trigger- und Risikofaktoren (Tabelle 4 der Publikation).

Zusammenfassung:

- Ziel ist es Patienten zum Experten seiner eigenen Erkrankung zu machen.
- Erhöhtes Risiko für Schmerzen, eingeschränkte Lebensqualität, Insomnie, Depression/Angststörungen durch fehlerhaften Umgang und Leben mit der Erkrankung (am Beispiel der AI).
- Durch Selbstmanagement Krankheitslast reduzieren.
- Ansätze für die Entwicklung einer Gesundheits-App.

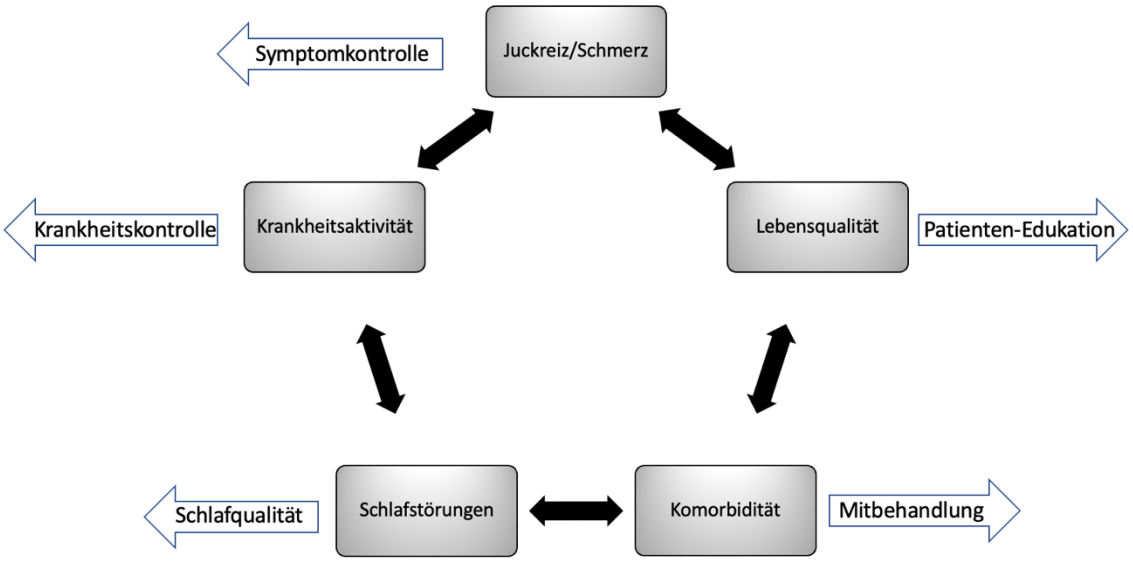


Abbildung 3: Teufelskreis der Krankheitslast und mögliche Auswege

5. Diskussion

Zur ganzheitlichen optimierten Versorgung von Patienten mit chronisch entzündlichen Hauterkrankungen und damit verbundener Reduktion der Krankheitslast gehört nicht nur die adäquate Therapie der Krankheitsaktivität, sondern auch die Therapie der Komorbiditäten und die damit verbundene Steigerung der Lebensqualität.
Die Prävalenz von Komorbiditäten bei chronisch entzündlichen Hauterkrankungen ist Thema vieler epidemiologischer Studien.
Selbst bei Kindern mit Urtikaria zeigen Studien bereits eine hohe Prävalenz von Komorbiditäten (39). Die Tatsache, dass diese sich bereits im Kindesalter manifestieren, deutet auf einen möglichen kausalen Zusammenhang hin und lässt die Notwendigkeit von präventiven bzw. frühzeitigen Interventionen deutlich werden. Die Erhebung weiterer epidemiologischer Daten zur Identifizierung von Biomarkern, könnte das Management dieser Erkrankungen verbessern.

5.1. Chronisch entzündliche Hauterkrankungen und Komorbidität

In der Literatur werden Assoziationen bei CU mit unterschiedlichen Erkrankungen beschrieben u.a. aus dem atopischen Formenkreis, Autoimmunerkrankungen, Stoffwechselerkrankungen und kardiovaskuläre Erkrankungen, aber auch psychische Komorbidität (40, 41). Es ist bekannt, dass Zöliakie (Transglutaminase Antikörper), aber auch Schilddrüsen-Antikörper (IgG-Anti-TPO) Ursache einer autoimmunen-CU sein können. Diese Form der CU spricht häufig nicht oder nur langsam auf eine Therapie mit Omalizumab an. Als Biomarker können sie daher dabei helfen, die richtige CU-Therapie auszuwählen oder als Prädiktor auf die Schnelligkeit des Ansprechens hinweisen (42, 43). Auch unsere Daten zeigten Zöliakie und Schilddrüsenerkrankungen als Komorbidität der CU-Patienten. Die Therapie der Urtikaria ist unabhängig von bestehenden Komorbiditäten dennoch erfolgreich möglich (32).

Bei Patienten mit Psoriasis zeigen sich neben vielen Komorbiditäten (z.B metabolisches Syndrom, chronisch entzündlichen Darmerkrankungen, AI) vermehrt kardiovaskuläre Komorbiditäten(44). Weiterhin leiden Patienten mit entzündlichen Hauterkrankungen vermehrt an Depressionen, was auch der erhöhte HADS bei den befragten AI-Patienten verdeutlicht (34). Es wird diskutiert, ob psychischer Stress und

Depression die Ursache von chronisch entzündlichen Hauterkrankungen sind. In diesem Zusammenhang wird auch die Rolle von IL-17 in der Entstehung einer Depression diskutiert, oder eine bereits bestehende psychische Komorbidität die Hauterkrankungen verschlechtern kann (45).
In jedem Fall scheint der Schweregrad der Hauterkrankung mit einem höherem Grad and Depression, Stress und eingeschränkter Schlafqualität assoziiert zu sein (46).
Eine gestörte nächtliche Ruhephase wirkt sich negativ auf das allgemeine Wohlbefinden und die kognitive Leistungsfähigkeit aus, was wiederum die Ursache für diverse psychische Probleme sein kann. Schlafstörungen sind Hauptsymptom einer Depression und können umgekehrt diese auch auslösen/verstärken (47). Chronisch entzündliche Hauterkrankungen sind wiederum dafür bekannt, dass sie mit einer erhöhten Rate an psychischen Problemen wie Depressionen einhergehen (48). Dies bestätigten unsere Untersuchungen (32).
Sowohl Schlafstörungen als auch Hauterkrankungen ist gemeinsam, dass sie psychosoziale Konsequenzen haben, aber auch mit kardiovaskulären und immunologischen Erkrankungen assoziiert sind. In wie weit eventuell sogar Schlafstörungen bei entzündlichen Hauterkrankungen die treibende Kraft in diesem Teufelskreis sind, gilt es zu diskutieren.

5.2. Lebensqualität (PRO)

Zur Ermittlung der Lebensqualitäts-Einschränkung bei Patienten mit chronisch entzündlichen Hauterkrankungen haben sich PRO bewährt. Der bei vielen Hauterkrankungen verwendete DLQI ist jedoch nicht krankheitsspezifisch.

Anders als der DLQI, der die Lebensqualität über die letzten 2 Wochen bei Erwachsenen ermittelt, erfragt der Kinder-Lebensqualitätsfragebogen (C-DLQI) Schlafstörungen der vergangenen Woche: „Wie sehr war der Schlaf durch die Hauterkrankung beeinflusst“(49). Auch unsere Untersuchungen zeigten eine Erhöhung der Lebensqualität im DLQI unter Therapie innerhalb kürzester Zeit.
Weiere PROs wie der ItchyQol, der sich mit der Beeinflussung der Lebensqualität durch Pruritus befasst, erfragt den Einfluss auf den Schlaf „mein Juckreiz beeinflusst wie gut ich schlafe“(18). Der SCORAD erfragt die Schlafqualität der letzten 3 Tage auf einer visuellen Analogskala von 0-10. Auch die ergänzenden Fragen zum Schlaf in der Validierung des Deutschen Pruritus-Fragebogens, spiegeln die Relevanz der

Erfassung wider (50). Dass Lebensqualität und Schlafstörungen assoziiert sind und dies durch die verwendeten Fragebögen valide widergespiegelt werden kann, zeigt die signifikante Korrelation des DLQI mit dem ISI-Score.
Ein Indiz, dass der DLQI die tatsächliche Einschränkung der Lebensqualität nicht bei jeder Hauterkrankung vollumfänglich darstellt, ist die Tatsache, dass die 36 untersuchten CU-Patienten während eines Krankheitsschubes nur einen mittleren DLQI von 9,6 hatten und damit deutlich weniger als bei Patienten mit AD und Pso (33). Zur genaueren Darstellung der Lebensqualitätseinschränkung hat sich daher bei Patienten mit CU der „Chronic Urticaria Quality of Life“ (CU-QoL) bewährt, der auch nach Schlafstörungen fragt und daher in zukünftigen Untersuchungen bei CU zur Ermittlung der krankheitsspezifischen Lebensqualität zum Einsatz kommen sollte (51).

5.3. Chronisch entzündliche Hauterkrankungen und Schlafstörungen

Gerade bei chronisch entzündlichen Hauterkrankungen mit Pruritus und/oder Schmerzen stellen Schlafstörungen ein bisher zwar erkanntes, jedoch nach wie vor nicht ausreichend untersuchtes Teilgebiet in der Dermatologie dar. Dabei haben sie einen wesentlichen Anteil an der Lebensqualität. In der Gesamtbevölkerung zeigt sich bei mindestens 20% der Bevölkerung zumindest zeitweise eine Insomnie (52). In Übereinstimmung mit unseren Ergebnissen zeigen die in der Literatur zusammengefassten Daten mit 33-90% in AD und 6-35% in Pso eine wesentlich höhere Prävalenz bei Patieten mit chronisch entzündlichen Hauterkrankungen (53).
Als erstes gilt es, Schlafstörungen zu erkennen und ihren Schweregrad zu erfassen. Dazu dienen validierte Fragebögen und zur Objektivierung die Polygraphie. Weiterhin ist es relevant zu ermitteln, inwiefern die Einschätzung des Patienten zur möglichen Schlafstörung die Qualität des Schlafes mittels objektiver Erhebung der Schlafqualität übereinstimmt. Umsomehr wenn wir den Juckreiz als bislang vermuteten Hauptparameter der Schlafqualitätsbeeinflussung heranziehen.

Die erhobenen Daten zeigen einen deutlichen Zusammenhang zwischen der Krankheitsaktivität und Schlafstörungen (Korrelation mit dem EASI und PASI Score).

Dies wurde in einer kürzlich publizierten Studie aus Italien, die zeigte, dass sich Schichtarbeit negativ auf die Krankheitsaktivität von Patienten mit Psoriasis auswirkt (54) bestätigt.

Die Ergebnisse unserer retrospektiven Datenanalyse mit CU Patienten lassen vermuten, dass CU-Patienten im Vergleich zu anderen dermatologischen Patientengruppen relativ selten von Schlafproblemen berichten (6,6 %)(32). Allerdings zeigte unsere gezielte Analyse der Insomnie sowohl mittels Fragebogen, als auch Polygraphie, eine deutlich höhere Prävalenz, was darauf hinweist, dass die gezielte Nachfrage nach Schlafstörungen ein wichtiger Faktor bei der Erfassung von Patientenbeschwerden ist (32, 33).

Die bislang gewonnenen Erkenntnisse legen nahe, dass eine Reduktion der REM-Schlafdauer die Verarbeitung von Traumata beeinträchtigt und auf diese Weise zu psychischen Belastungen führen kann (55). Zu wenig Tiefschlaf wiederum führt dazu, dass gelerntes Wissen nicht verinnerlicht werden kann(56). Dies unterstreicht die Notwendigkeit von optimalen Behandlungsmaßnahmen zur Erhöhung von REM- und Tiefschlaf auch bei entzündlichen Hauterkrankungen. Dies gelang uns beispielsweise durch topische Therapie bei AD und Pso und systemische Therapie mit Antihistaminika der 2. Generation bei CU. Untersuchungen haben gezeigt, dass im Gegensatz zur 2. Generation, Antihistaminika der 1. Generation, ~~Im~~ (z.B. Dimetinden) aufgrund ihrer zentralen Wirkung zur REM-Schlaf Suppression und verstärkten Müdigkeit führen können(57, 58). Sie werden daher in der Praxis häufig als Einschlafhilfe bei Patienten mit Pruritus eingesetzt. Dies führt jedoch langfristig zu einem gestörtem Schlafprofil und bringt die damit bereits erwähnten Nebenwirkungen mit sich (Tagesmüdigkeit, fehlende emotionale Verarbeitung von Stress etc.). Eine Einnahme sollte deswegen nicht über einen längeren Zeitraum erfolgen.

Ergänzend wurde in prospektiven Studien postuliert, dass eine verminderte Schlafeffizienz (Effizienz <85 %) mit einer erhöhten Mortalität assoziiert ist (30, 59). In einer Studie von Silverberg et al. wurde bei 34.613 Patienten mit AD mittels PRO eine verminderte Schlafeffizienz beobachtet. Zudem konnte eine Assoziation von AD in

Kombination mit Schlafstörungen mit einem selbst-evaluierten beeinträchtigten Gesundheitsstatus nachgewiesen werden(60).
Die Ergebnisse unserer Untersuchung legen nahe, dass sich die Schlafeffizienz sowohl bei Patienten mit AD als auch bei solchen mit Psoriasis nach einer zweiwöchigen topischen Therapie erhöhen lässt. Der erzielte polygraphisch gemessene Mittelwert der Schlafeffizienz (TST/TIB) von ca. 70 % bei beiden Erkrankungen lag damit jedoch immer noch 15 % unter dem empfohlenen Mindestwert. Dies könnte unter anderem auf einen noch nicht vollständig therapierten Hautbefund (mittlerer EASI nach zweiwöchiger Therapie bei 7,39 und PASI bei 5,58) sowie auf einen weiterhin bestehenden Pruritus zurückzuführen sein (Tabelle 1 der Publikation)(28). Studien zu Schlafeffizienz unter Therapie über einen längeren Therapiezyklus fehlen bislang.

5.4. Hauterkrankungen als Systemerkrankung: Schlafapnoe und systemische Entzündung

Der Schlaf hat auch wesentliche Einflüsse auf das Immunsystem. Durch gestörten Schlaf kann es zur Ausschüttung proinflammatorischer Zytokine, z.B. TNFalpha, IL1-beta und IL-6 kommen(61, 62). Zudem kommt es zur Entstehung reaktiver, proinflammatorischer Sauerstoffspezies (63). Diese proinflammatorischen Signale spielen bei entzündlichen Hauterkrankungen eine Rolle und deuten auf einen möglichen Zusammenhang hin. Eine prospektive Studie ein erhöhtes Risiko innerhalb von 5,5 Jahren nach Erstdiagnose einer Schlafapnoe, eine AD zu entwickeln (64).
Der in unseren Untersuchungen objektiv gemessene, erhöhte AHI-Score, lässt eine hohe Dunkelziffer von Schlafapnoe bei Patientin mit AD und Pso vermuten. Obwohl Schlafapnoe häufig mit Adipositas assoziiert ist, war der AHI-Wert in den untersuchten Kohorten unabhängig vom BMI. Andere Arbeitsgruppen zeigten eine erhöhte Prävalenz von Schlafapnoe bei chronisch entzündlichen Hauterkrankungen. Dies lässt mögliche Zusammenhänge, z.B. aufgrund systemischer Inflammation, vermuten (65). In jedem Fall sollte das Screening solcher Patienten verstärkt werden und ggf eine Interdisziplinäre Zusammenarbeit angestrebt werden, um Langzeitfolgen der Schlafapnoe zu verhindern.
Die höhere Inzidenz von Adipositas bei AD-Patienten im Vergleich zu Pso-Patienten in unserer untersuchten Kohorte steht im Gegensatz zu der in der Literatur erwähnten

Prävalenz, die Pso-Patienten eine höhere Wahrscheinlichkeit von Adipositas und auch eine höhere Inzidenz von OSAS zuschreibt (66). Dies unterstreicht die Notwendigkeit, nicht nur bei Psoriasis, sondern auch bei anderen chronisch entzündlichen Hauterkrankungen wie der AD oder AI, Schlafapnoe auszuschließen.

Die Tatsache, dass chronisch entzündliche Hauterkrankungen als „Systemerkrankungen“ und dies nicht nur aufgrund der Komorbiditäten gelten, macht einen Zusammenhang zwischen dem entzündlichen Geschehen der Haut und des Schlafes wahrscheinlich.

Generell wird ein Zusammenhang zwischen AHI und systemischer Entzündung bei anderen Erkrankungen diskutiert (67, 68). Bei Patienten mit Pso und AD zeigte sich eine Verbesserung des AHI-Scores nach zweiwöchiger topischer, antientzündlicher Behandlung. Um die Ergebnisse der sehr kleinen Kohorte zu bestätigen und Rückschlüsse über den Zusammenhang von Schlafapnoe und systemischer Entzündung bei Hauterkrankungen zu gewinnen, sind weitere Untersuchungen notwendig.

In diesem Zusammenhang ist zu diskutieren, ob eine rechtzeitige Behandlung der Hauterkrankungen, ähnlich wie es bei der Psoriasis und kardiovaskulärer Komorbidität gezeigt wurde, zu einer geringeren Inzidenz von Schlafapnoe führen könnte (5). Alternativ könnte bei bereits bestehender Schlafapnoe, wie es in einem Review aus dem Jahr 2020 diskutiert wird, die Behandlung eben jener zur Verbesserung der Hauterkrankung beitragen (65).

5.5. Erhöhung der Selbstmanagement Kompetenz

Neben der Behandlung von Komorbiditäten, zeigt die Erhöhung der Selbst-management Kompetenz auch bei anderen chronischen Erkrankungen wie z.B. COPD eine positive Auswirkung auf die gesundheitsbezogene Lebensqualität (69). Unsere Daten legen nahe, dass verbessertes Selbst-Management auch auf Hauterkrankungen eine positive Auswirkung hat. Diese Auswirkung verzeichnet sich insbesondere auf Schlaf (ISI), Depression/Angststörungen (HADS) und Lebensqualität (DLQI)(34). Weiterhin wird die Akzeptanz und der Umgang mit der Erkrankung erhöht. Interessanterweise zeigte sich in unserer AI-Kohorte, anders als häufig diskutiert, keine erhöhte Risikoassoziation von Nikotinabusus und Adipositas mit dem Ausmaß der Krankheitsaktivität. Zudem zeigte sich keine erhöhte Risikoassoziation von

Adipositas und Nikotinabusus mit der Lebensqualität, dem HADS und dem ISI Score (70). Im Rahmen der Befragung mittels heiQ Fragebogen wurde zur Bewertung des Umgangs mit der Erkrankung AI der Vergleich zu anderen chronischen Erkrankungen gezogen. Hier konnte insbesondere beim Vergleich mit den unterschiedlichen Domänen Parallelen zwischen AI-Patienten und Patienten mit onkologischen Erkrankungen festgestellt werden.

Wenn Pateinten ein besseres Verständnis über ihre Erkrankung erlangen und somit die Qualität einer optimalen Patientenversorgung erkennen, erhöht dies auch die Patienten-Autonomie und begünstigt das „shared-decision-making“ mit dem Behandler. Es werden dazu sogenannte Patientenschulungsprogramme entwickelt (71). Nicht nur AI-Patienten könnten von solchen unterstützenden Maßnahmen profitieren.
Eine finnische Studie zeigte nach zweiwöchiger Heliotherapie mit einer kleinen Kohorte von Patienten mit AD (n=13) und Pso (n=22) ein deutlicher Benefit durch Heliotherapie in Form von Selbsthilfegruppen sowie mentaler und physischen Übungen (72). Eine andere Studie zeigte einen positiven Einfluss auf die Krankheitsaktitvität bei Kindern mit AD (die meisten darunter <9 Jahre), deren Betreuer (n=134) Aufklärungen über Trigger und Risikofaktoren mittels digitaler App erhielten (73). Dieser Erfolg ließe sich bei Patienten mit AI erwarten, da in unseren Untersuchungen ein gesteigertes Informationsinteresse an möglichen Triggern und Risikofaktoren ermittelt wurde (34, 74).
Eine weitere Möglichkeit das Selbstmanagement zu erhöhen bildet neben Präsenzschulungsprogrammen die Implementierung von Gesundheits-Apps, wie sie bereits bei anderen Erkrankungen auch in der Dermatologie zum Einsatz kommen (z.B. Atopic APP mit z.B. Aufklärung über Trigger- und Risikofaktoren) und sogar ärztlich rezeptiert werden können (73, 75). Somit könnte man das Therapieziel einer personalisierten Medizin verbessern und die erheblichen Wartezeiten auf einen Termin bei in der dermatologischen Sprechstunde zu verringern. Diese Apps unterstützen die Erhebung, wichtiger epidemiologischer „real-world“ Daten.

5.6. Auswirkung von Pruritus auf Schlaf- und Lebensqualität

Pruritus ist ein bekanntes Symptom chronisch entzündlicher Hauterkrankungen, das zu Schlafstörungen und erheblicher Einschränkung der Lebensqualität führen kann (76). Auch unsere Daten zeigten einen Einfluss von Pruritus auf Schlaf und Lebensqualität und eine Verbesserung unter topischer und systemischer Therapie innerhalb weniger Wochen (28, 35). Unsere Ergebnisse zeigten einen Zusammenhang zwischen Pruritus und der objektiven Schlafqualität durch vermindertem Tiefschlaf (N3). Wir vermuten hier eine Verhinderung der Progression zum Stadium N3, das normalerweise nach Durchlaufen der Schlafstadien N1 und N2 auftritt. Diese Vermutung rührt daher, dass Kratzen, wie eine andere Studie aus den USA mittels Polysomnographie an 20 AD Patienten zeigte, vornehmlich während des Leichtschlafes (N1 und N2) auftritt. Die hieraus resultierenden Arousals und Erwachen des Patienten verhindern ein Fortschreiten in Stadium N3 (77).

Pruritus bei Patienten mit Pso wird nach wie vor häufig unterschätzt und demnach wenig Beachtung geschenkt. Fakt ist, dass ein Großteil der Patienten mit Pso an Juckreiz leiden (78). Auch unsere Daten zeigen, dass relevante Einflüsse von Pruritus auf die Schlafqualität bei Pso Patienten bestehen, wenn gleich auch der Pruritus bei AD und CU vergleichsweise stärker empfunden wurde (28, 33).

Unsere Ergebnisse legen nahe, dass neben der Pruritusintensität auch andere Einflüsse auf die Schlafqualität diskutiert werden müssen. So gaben einige Patienten mit geringem Pruritus Schlafprobleme an, während andere trotz fortbestehendem Pruritus über einen verbesserten Schlaf berichteten. Einschränkend muss man sagen, dass die Ermittlung des Pruritusstärke (NRS, ItchyQol) in diesen Studien nur mittels Fragebogen erhoben wurde und kein Pruritus (z.B. durch Videoaufnahmen) objektiviert werden konnte (33). Dass eine Objektivierung generell sinnvoll ist, belegen auch andere Studien, die eine Diskrepanz zwischen subjektiv wahrgenommener und objektiv gemessener Schlafqualität und nächtlichem Pruritus zeigten(79, 80).

Viele Bewegungen in der Nacht laufen im Unterbewusstsein ab. Das Gehirn erfährt kurze Wachepisoden (Arousals) ohne, dass diese zum Bewusstsein vordringen. Der Patient ist zwar am folgenden Tag erschöpft, kann sich jedoch nicht an die Ursache erinnern. Daher ist es wichtig objektive Messmethoden einzusetzen. Nichtsdestotrotz lässt eine Studie aus Israel ebenfalls Zweifel an der These aufkommen, dass Pruritus die einzige Ursache für gestörten Schlaf ist. In der Polysomnographie Untersuchung von 14 AD-Kindern (mittleres Alter 6 Jahre) wurde gezeigt, dass nur 15 % der Arousals

aufgrund von Kratzen auftraten und die restlichen zu gestörtem Schlaf führenden Arousals eine anderweitige, nicht bekannte Ursache haben (81).

5.7. Ausblick für zukünftige Forschung

Ein validierter Fragebogen, der sich gezielt mit unterschiedlichen Schlafstörungen bei dermatologischen Erkrankungen beschäftigt, existiert aktuell nicht. Eine Entwicklung wird angestrebt. Daher empfiehlt es sich zunächst auf bereits validierte Alternativen wie den ISI als nicht für dermatologische Erkrankungen spezialisierter und validierter Fragebogen zur Schlafqualität zurückzugreifen. Aufgrund seiner Kürze lässt er sich gut in die Patientenversorgung integrieren. Auch bei Studien zu anderen Erkrankungen z.B. Depression oder entzündlichen Darmerkrankungen, kommt er zum Einsatz (82, 83).

Um den Pruritus während der Nacht zu objektivieren bietet sich z.B. die Videoaufnahme im Schlaflabor an. Eine andere Möglichkeit bietet der ADAM Scratch Sensor von Sibel Health, ein „Wearable“, das kürzlich in der Schlafforschung bei AD erstmalig eingesetzt wurde (84). So genannte „Wearables“ revolutionieren neben Apps und Telemedizin aktuell die Dermatologie. Die in unseren Untersuchungen verwendete Polygraphie ist eine Methode, die es ermöglicht schon mit mittlerweile kleinen Medizinprodukten, in reduzierter Qualität (aufgrund fehlender Ableitungen verglichen zu einem EEG) z.B. auch in Smart-Watches, den Schlaf im häuslichen Umfeld aufzuzeichnen (28, 35). Auch bei Kindern gibt es mittlerweile die Möglichkeit Polygraphie Geräte in die Windeln zu integrieren und so den Schlaf von Kindern mit AD zu objektivieren, ohne dabei den Schlaf zu stören (85).

Um Ursachen des nächtlichen Pruritus sowie potentielle andere schlafstörende Faktoren bei betroffenen Patienten aufzudecken, eignen sich unter anderem die Messung des transepidermalen Wasserverlusts (TEWL). In einer kleinen Pilostudie an 4 Kindern mit AD wurde gezeigt, dass der transepidermale Wasserverlust (TEWL)

insbesondere während der nächtlichen Stunden erhöht ist und u.a. Pruritus verstärkt (86).

Eine Reduktion der TEWL u.a. durch die Barriere-stärkende Maßnahme einer topischen Therapie, wie sie in unserer Studie bei AD und Pso Patienten erfolgte, wäre eine mögliche Erklärung für die verbesserte Schlafqualität(28). Um diese Annahme zu bestätigen, wäre in einer Folgestudie der Einsatz einer tragbaren analytischen Hautsonde (Wearable Analytical Skin Probe, WASP) möglich. Diese hat sich als wirksames Instrument für die kontinuierliche Messung des TEWL bei Personen mit chronischen Hauterkrankungen erwiesen (87). Ergänzend besteht die Möglichkeit die Hauttemperatur während der Nacht zu messen. Eine Dysregulation, wie sie bei entzündlichen Hauterkrankungen vorkommt, führt ebenfalls ggf auch durch vermehrtes Schwitzen und damit TEWL Erhöhung zu Schlafproblemen (88).

Zu bedenken ist weiterhin, dass Schwankungen der Konzentrationen wichtiger endokrinologischer Faktoren in der Nacht aber auch unter bestimmten Triggern wie Stress die Schlafstörungen erklären könnten. So ist gerade der Cortisol-Stoffwechsel stark Stress-abhängig und bei Patienten mit chronisch entzündlichen Hauterkrankungen häufig pathologisch erhöht. Generell kommt es physiologisch zum Absinken des Cortisolspiegels zum Abend. Fehlt diese Absenkung, resultiert Insomnie(89). Ein neu-entwickeltes, am Körper zu tragendes Pflaster ermöglicht die kontinuierliche Messung des Cortisolspiegels im Schweiß (90). Die Verwendung dieses Messinstruments zur Verfolgung des Stresslevels könnte möglicherweise durch frühzeitige Gegenmaßnahmen zur Stressreduktion führen, um sowohl den Schlaf als auch die Hauterkrankung zu verbessern. Mögliche Interventionen zur Stressreduktion wären zum Beispiel Interventionen im Lebensstil oder gezielte Entspannungsmaßnahmen (progressive Muskelrelaxation).

Noch vor einigen Jahren waren die weitreichenden gesundheitlichen Folgen von Insomnie inklusive Schlafapnoe unbekannt. Mittlerweile erschließen sich immer neue Zusammenhänge mit unterschiedlichen Erkrankungen.

Ziel ist es durch klinische Forschung Zusammenhänge zwischen Hauterkrankungen und Schlafstörungen aufzudecken, um durch frühzeitige Intervention dem „Cumulative Life Course Impairment“ (CLCI) dieser Patienten entgegenzuwirken (91). Dies involviert auch die Entwicklung zielgerichteter Therapiekonzepte und die Etablierung

von Schlafqualität als neuen Biomarker für Krankheitskontrolle und Lebensqualität in der Dermatologie.

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CLINICAL REPORT

Sleep Disturbance in Patients with Urticaria and Atopic Dermatitis: An Underestimated Burden

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This study examined the relationship between insomnia and the frequent itching skin diseases, atopic dermatitis and chronic urticaria. Patients with chronic inflammatory dermatological diseases with pruritus were evaluated for insomnia (Insomnia Severity Index; ISI) and impairment in dermatological quality of life (Dermatology Life Quality Index; DLQI). Disease activity was measured using validated scores. A total of 61 patients participated in the study. Patients with atopic dermatitis had a mean ISI score of 8.7 before flares and 16 when a flare occurred. The mean DLQI score in atopic dermatitis was 11.4. The mean ISI score in patients with chronic urticaria was 6.8 before flares and 14.9 when a flare occurred. In patients with chronic urticaria the mean DLQI score was 8.5. An increase in insomnia during a disease flare was demonstrated in both groups. Thus, sleep is a factor to consider during treatment of itching skin diseases. The results of this pilot study indicate that pruritus may not be the only reason for insomnia in patients with atopic dermatitis or chronic urticaria.

Key words: sleep disturbance; urticaria; atopic dermatitis; insomnia; quality of life.

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SIGNIFICANCE

Interactions between sleep and skin diseases are considered clinically relevant. Quality of sleep can positively or negatively influence the course of skin diseases. However, the impact of the interaction between dermatological diseases and sleep disturbance, especially with regard to chronicity, remains to be elucidated. The aim of this pilot study was to identify possible interactions between sleep disturbance and skin diseases, which may be an underestimated aetiopathological aspect.

Insomnia is the most common sleep disturbance among the general population, with an incidence of 10–20% (1). Although the pathophysiology of insomnia is diverse, its definition involves the following aspects: difficulty falling asleep, staying asleep, waking up early or a lack of sleep despite opportunities to sleep (2). Insomnia can be a symptom, or even a cause of other underlying medical disorders and may lead to an increase in interleukins (3). Individual assessment of insomnia is often divergent from the measurement of actual sleep deprivation by polysomnography (1).

Atopic dermatitis (AD) is a common inflammatory skin disease, which affects almost 3% of the German population in adulthood (4, 5). AD is multifactorial and can be triggered by various endogenous and exogenous stimuli. The reaction of different skin types to environmental triggers varies. An individual's skin barrier dysfunction seems to play a key role, making the skin more vulnerable to environmental damage (6). Hormonal fluctuations, psychological stress, infectious diseases and further more triggers influence the condition of the skin (6). Alteration of the skin texture is often the first sign of an underlying medical problem. Early inflammation of the skin is TH2 driven and becomes TH1 driven when chronic and maintained by various interleukins (7, 8).

Urticaria, also known as hives, is defined as the spontaneous appearance of itching wheals and angioedema (9, 10). Almost 20% of the German population is affected by urticaria, lasting less than 6 weeks, at least once in their lifetime. Approximately 5% of the affected people experience urticaria for longer than 6 weeks and therefore have chronic urticaria (CU) (9). The cause of urticaria is heterogeneous, but it is mainly regarded as a mast-cell driven reaction (10).

Although itching skin disease in the general public is associated with poor sleep quality, little research has been done to better understand insomnia-associated oxidative stress and its impact on inflammatory skin diseases. This was the topic of the current investigation.

Questions about insomnia are routine when taking a medical history of dermatological patients, although this subject has not received particular attention. It is known that patients with sleep disturbance have an increased risk of cardiometabolic disease, which is associated with vascular events such as stroke, coronary artery disease and myocardial infarction, but also with obesity, impotence and depression (11, 12). In many aspects this influence is bidirectional. Insomnia has a significant impact on quality of life (QoL) as well as daytime functioning, and is especially common in elderly people. Moreover, patients with insomnia have reduced resistance to pain

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(13). These wide-ranging effects provide evidence to support a correlation between skin diseases and insomnia. The aim of this study was to elucidate to what extent insomnia influences the disease process in dermatological diseases with pruritus.

METHODS

Population and procedure

This was a paper and pencil questionnaire-based cohort study, lasting from September 2018 to February 2019 in the dermatology department of the University Medical Center in Mainz, Germany. Sex, age and body mass index (BMI) were registered for all patients. Disease diagnosis was based on clinical manifestation and validated scores for CU and Hanifin & Rajka criteria for AD (14).

All subjects provided written consent to participate in the survey. In order to increase the level of anonymity of the survey, collection of personal data was reduced to a minimum. The study design was reviewed by the ethics committee of the state of Rhineland-Palatinate, Germany.

Disease activity

For patients with AD, disease severity was evaluated using the Eczema Area and Severity Index (EASI; score 0–72, where 0 indicates no skin manifestations and 72 indicates strong infiltration, erythroderma, xerosis and excoriations), rated by the physician. A flare was defined by an increase of 6–7 points in the EASI (15).

For patients with CU, the Urticaria Control Test (UCT) was used (score 0–16, where ≥12 indicates disease control) and the Urticaria Activity Score (UAS7; score 0–42, where 0–6 indicates well-controlled urticaria with no activity and 42 indicates severe activity). The UCT and UAS7 scores evaluate disease activity and are both patient-rated. In the UAS7 activity is assessed for 7 consecutive days, asking about number of wheals (score 0–3) and pruritus intensity (score 0–3), whereas the UCT (0–16) asks about physical symptoms, QoL, treatment efficacy and urticaria control (16), which was defined by newly appearing objective symptoms like hives during the previous 7 days.

Patient-reported outcomes

The Insomnia Severity Index (ISI) is a validated 7-item questionnaire in which patients rate their current quality of sleep in order to assess the extent of insomnia. The ISI was developed in English and translated into various languages. The German version of the ISI was validated by Gerber et al. in 2016 (17).

The Dermatological Life Quality Index (DLQI) is a commonly used 10-item questionnaire with a range of 0–30, which measures the impact of different skin diseases on QoL during the previous week. A score ≥10 indicates severely impaired QoL (18).

To measure current pruritus severity patients were asked to rate their itch on a visual analogue scale (VAS) from 1 (no itch) to 10 (unbearable itch). An itch score ≥4 was rated significant (19).

Statistical analysis

All data were assessed for normal or non-normal distribution. Differences in disease scores were determined using Mann–Whitney *U* test and or Student's *t*-test with reference to the distribution of the calculated variables. Correlations were determined using Spearman's rho correlation analysis. The level of significance was set at $\alpha = 0.05$. The resulting *p*-values were considered nominally significant at $p < 0.05$. Statistical analyses were calculated with SPSS PASW23 Statistics (IBM Corp., Somers, NY, USA).

RESULTS

Demographics

A total of 61 patients (20 males, 41 females) were included; 25 with AD, and 36 with CU, including all subtypes (**Table I**). All patients were asked to complete the ISI questionnaire on admission. In addition, they rated their insomnia before the onset of the current flare, even though the questionnaire is usually used only to determine current sleep quality. The patients' ages ranged from 18 to 77 years, with a mean of 44.0 ± 17.5 years for patients with

Table I. Descriptive characteristics of the studied groups

	Atopic dermatitis		Chronic urticaria		
Item	*n*	Mean ± SD (range)	*n*	Mean ± SD (range)	*p*-value
Sex					
Total	25		36		
Women	14		27		
Men	11		9		
Age, years,		44.0 ± 17.5 (19–77)		49.2 ± 13.9 (18–76)	0.255
Body mass index, kg/m^2		24.4 ± 3.2 (17–31)		27.3 ± 4.9 (19–42)	**0.022**
Underweight	1		0		
Normal weight	13		13		
Overweight	10		11		
Obese I	1		10		
Obese II	0		0		
Obese III,	0		2		
Insomnia Severity Index no flare		8.7 ± 5.6 (0–23)		6.8 ± 4.9(0–17)	0.156
No clinically significant insomnia	11		21		
Subthreshold insomnia	11		13		
Clinical insomnia (moderate severity)	2		2		
Clinical insomnia (severe)	1		0		
Insomnia Severity Index flare		16.0 ± 6.4 (2–27)		14.9 ± 6.0 (2–28)	0.482
No clinically significant insomnia	1		4		
Subthreshold insomnia	11		17		
Clinical insomnia (moderate severity)	6		7		
Clinical insomnia (severe)	7		4		
Pruritus		6.9 ± 1.9 (2–9)		5.9 ± 2.7 (1–10)	0.174
0–3 no significant pruritus	1		9		
≥4 significant pruritus	24		27		
Dermatology Life Quality Index		14.0 ± 8.7 (1–28)		9.6 ± 8.0 (0–28)	0.051
0–10 none–moderate effect	6		13		
11–30 large effect	19		23		
Eczema Area and Severity Index		20.2 ± 10.8 (6–48)	n/a		n/a
0–7 clear to mild	2		n/a		
7.1–72 moderate to severe	23		n/a		
Urticaria Control Test	n/a			11.1 ± 3.8 (2–16)	n/a
≥12 well controlled urticaria,	n/a		20		
<12 poorly controlled urticaria	n/a		14	9.9 ± 8.2 (0–32)	
UAS7	n/a				n/a
≤6 well controlled urticaria	n/a		13		
>6 poorly controlled urticaria	n/a		21		

SD: standard deviation; n/a: not applicable; UAS7: Urticaria Activity Score. Significant value shown in bold.

AD and 49.2 ± 13.9 years for patients with CU. The BMI ranged from 17 to 42 kg/m², with a mean of 24.4 ± 3.2 kg/m² in AD and 27.3 ± 4.9 kg/m² in CU. For AD 14 persons were not overweight, whereas 11 had a BMI > 24.9 kg/m². Only 13 patients in the CU group were of normal weight, while 23 were overweight (BMI > 24.9 kg/m²). The BMI was calculated according to WHO criteria (20).

Disease activity

For patients with AD the mean EASI score (physician rated) was 20.2 ± 10.8. For patients with CU the mean UCT was 11.1 ± 3.8 and the mean UAS7 9.9 ± 8.2 (both patient rated). All patients experienced itch to a different level and as a main symptom during a flare. The pruritus score showed a mean score of 6.9 ± 1.9 for patients with AD and 5.9 ± 2.7 for patients with CU, respectively. The mean DLQI during a flare was 14.0 ± 8.7 in patients with AD and 9.6 ± 8.0 in patients with CU. There were no significant differences between the 2 groups, except for BMI, which was higher in patients with CU ($p = 0.022$). The p-value of the DLQI, at $p = 0.051$, was close to significance for both patients with AD and those with CU.

Insomnia Severity Index

The ISI score was 8.7 ± 5.6 before a flare in patients with AD and 6.8 ± 4.9 in patients with CU, and during a flare increased to 16 ± 6.4 for patients with AD and 14.9 ± 6.0 for patients with CU. Insomnia was pre-existing in 6 patients with AD and in 12 with CU. Significant change in the ISI score was found in both groups before and after treatment ($p > 0.001$). More detailed insomnia during a flare was also subtyped by the predominant symptoms, as shown in **Table II**. Thus, 16 patients with AD (2.1 ± 1.4) and 9 with CU (1.7 ± 1.3) had "problems falling asleep", 12 patients with AD (2.2 ± 1.5) and 17 with CU (2.3 ± 1.3) had "problems maintaining sleep", and 8 patients with AD (1.8 ± 1.4) and 15 with CU (2.0 ± 1.3) had "problems with waking up too early". Only 8 patients with AD (2.9 ± 0.9) and 16 patients with CU (2.4 ± 1.1) were satisfied "with their sleep pattern". A total of 16 patients with AD (2.2 ± 1.1) and 29 with CU (1.7 ± 1.2) reported that their "sleep problems were not noticeable by others". Eleven patients with AD (2.3 ± 1.2) and 15 with CU (2.3 ± 1.1) were worried about their sleep. "Interference with daily functioning" caused by insomnia was reported by 17 patients with AD (2.7 ± 1.0) and 20 patients with CU (2.5 ± 1.0), respectively. The sub-scores did not any show differences between the 2 groups ($p > 0.05$).

Focusing on age and anthropometrical parameters, correlations were found between age and ISI score ($p = 0.036$) and between age and UCT score ($p = 0.024$); hence, older age leads to a lower UCT score. In addition, a correlation was found between higher weight and lower DLQI ($p = 0.035$).

No significant correlations were found between ISI flare and pruritus score, or between UCT, UAS7 and ISI scores. No significant interaction was found between BMI and ISI score during a flare in either group of patients.

The correlations between relevant variables for both disease groups are shown in **Table III**. In the AD group there was a positive correlation between ISI flare score and DLQI score ($p = 0.017$), and between ISI flare and EASI score ($p = 0.032$). There was a significant correlation between DLQI score and pruritus score ($p = 0.020$), whereas no significant correlation was found between ISI and pruritus scores. No other parameters were statistically significant in patients with AD.

In patients with CU during a flare correlations were detected between ISI and DLQI scores ($p = 0.029$) and between pruritus score and DLQI score ($p > 0.001$).

In patients with AD when focusing on the 7 subscores of the ISI during a flare (**Table IV**), a significant correlation was found between DLQI score and "difficulties falling asleep" ($p = 0.007$). Being "worried about sleep" ($p = 0.003$) and "interference with daily functioning" ($p = 0.017$) correlated significantly with the DLQI score. "Difficulties staying asleep" was associated with an increased EASI score ($p = 0.014$). Younger patients reported, that their "sleep problem was noticeable to others in terms of impaired QoL" ($p = 0.010$).

In patients with CU, "waking up too early" was correlated with DLQI score ($p = 0.012$). Patients with CU with a higher

Table II. Descriptive characteristics of the Insomnia Severity Index

	Atopic dermatitis		Chronic urticaria		
Insomnia problem	*n*	Mean ± SD (range)	*n*	Mean ± SD (range)	*p*-value
Difficulty falling asleep		2.1 ± 1.4 (0–4)		1.7 ± 1.3 (0–4)	0.293
None-existing	9		27		
Existing	16		9		
Difficulty staying asleep		2.2 ± 1.5 (0–4)		2.3 ± 1.3 (0–4)	0.738
None-existing	13		19		
Existing	12		17		
Problems waking up too early		1.8 ± 1.4 (0–4)		2.0 ± 1.3 (0–4)	0.406
None-existing	17		21		
Existing	8		15		
Satisfaction of sleep pattern		2.9 ± 0.9 (1–4)		2.4 ± 1.1 (0–4)	0.107
Satisfied	8		16		
Not satisfied	17		20		
Noticeable to others sleep problem is in terms of impairing quality of life		2.2 ± 1.1 (0–4)		1.7 ± 1.2 (0–4)	0.108
Not noticeable	16		29		
Noticeable	9		7		
Worried about sleep		2.3 ± 1.2 (0–4)		2.3 ± 1.1 (0–4)	0.973
Not worried	14		21		
Worried	11		15		
Interference with daily functioning		2.7 ± 1.0 (1–4)		2.5 ± 1.0 (1–4)	0.433
Not interfering	8		16		
Interfering	17		20		

SD: standard deviation.

Table III. Correlations of the relevant variables for both diseases

	Atopic dermatitis						Chronic urticaria						
	Age	BMI	ISI flare	Pruritus	DLQI	EASI	Age	BMI	ISI flare	Pruritus	DLQI	UCT	UAS7
Age													
Correlation coefficient		0.321	−0.188	−0.143	−0.145	0.030		0.297	−0.35	−0.158	−0.230	−0.385	0.259
p-value		0.117	0.367	0.496	0.489	0.887		0.078	**0.036**	0.358	0.176	**0.024**	0.140
BMI													
Correlation coefficient	0.321		0.142	−0.160	−0.084	0.059	0.297		−0.142	−0.081	−0.353	−0.287	0.269
p-value	0.117		0.500	0.446	0.690	0.779	0.078		0.410	0.637	**0.035**	0.100	0.125
ISI flare													
Correlation coefficient	−0.188	0.142		0.074	0.472	0.43	−0.35	−0.142		0.205	0.364	0.172	−0.076
p-value	0.367	0.500		0.726	**0.017**	**0.032**	**0.036**	0.410		0.230	**0.029**	0.330	0.667
Pruritus													
Correlation coefficient	−0.143	−0.160	0.074		0.463	0.103	−0.158	−0.081	0.205		0.726	−0.249	0.169
p-value	0.496	0.446	0.726		**0.020**	0.625	0.358	0.637	0.230		**0.000**	0.156	0.339
DLQI													
Correlation coefficient	−0.145	−0.084	0.472	0.463		0.296	−0.230	−0.353	0.364	0.726		−0.064	0.184
p-value	0.489	0.690	**0.017**	**0.020**		0.151	0.176	**0.035**	**0.029**	**0.000**		0.717	0.298
EASI													
Correlation coefficient	0.030	0.059	0.43	0.103	0.296		n/a	n/a	n/a	n/a	n/a	n/a	n/a
p-value	0.887	0.779	**0.032**	0.625	0.151								
UCT													
Correlation coefficient	n/a	n/a	n/a	n/a	n/a	n/a	−0.385	−0.287	0.172	−0.249	−0.064		−0.513
p-value							**0.024**	0.100	0.330	0.156	0.717		**0.002**
UAS7													
Correlation coefficient	n/a	n/a	n/a	n/a	n/a	n/a	0.259	0.269	−0.076	0.169	0.184	−0.513	
p-value							0.140	0.125	0.667	0.339	0.298	**0.002**	

Body mass index; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; UCT: Urticaria Control Test; UAS7: Urticaria Activity Score. Significant values shown in bold ($p < 0.05$).

DLQI score ($p = 0.003$) and a higher pruritus score ($p = 0.018$) were less satisfied with their sleep pattern. "Interference with daily functioning" was reported by patients with CU with a lower DLQI ($p = 0.040$). Patients who were "worried about sleep" had a higher UCT score ($p = 0.022$). In younger patients "difficulties staying asleep" ($p = 0.039$), and "interference with daily functioning" ($p = 0.026$) were noticed. Furthermore, younger patients found that their "sleep problem was noticeable by others" ($p = 0.005$).

DISCUSSION

Insomnia is a well-known phenomenon worldwide, which is thought to play an important role in increasing disease activity in inflammatory and itching skin diseases.

This pilot study revealed an association between insomnia and disease activity by evaluating sleep disturbances in 2 different skin diseases. The results demonstrate that disease severity in AD, measured by the EASI score, influences sleep quality. Examining the individual questions of the ISI, a high EASI score, and therefore

Table IV. Correlations with the subscales of the Insomnia Severity Index for both diseases

	Atopic dermatitis					Chronic urticaria					
	Age	BMI	Pruritus	DLQI	EASI	Age	BMI	Pruritus	DLQI	UCT	UAS7
Difficulty falling asleep											
Correlation coefficient	−0.292	−0.107	0.203	0.525	0.197	−0.135	−0.035	−0.044	0.092	0.060	−0.177
p-value	0.157	0.612	0.329	**0.007**	0.345	0.434	0.841	0.801	0.593	0.736	0.317
Difficulty staying asleep											
Correlation coefficient	−0.076	0.138	−0.045	0.288	0.487	−0.345	−0.251	0.167	0.267	0.289	−0.183
p-value	0.718	0.512	0.831	0.163	**0.014**	**0.039**	0.141	0.331	0.115	0.098	0.300
Problems waking up too early											
Correlation coefficient	0.158	0.090	−0.119	0.007	0.172	−0.227	−0.121	0.227	0.412	−0.079	0.134
p-value	0.450	0.669	0.572	0.974	0.411	0.183	0.484	0.184	**0.012**	0.656	0.451
Satisfaction of sleep pattern											
Correlation coefficient	−0.278	0.087	0.224	0.386	0.286	−0.075	−0.078	0.391	0.474	0.155	0.010
p-value	0.179	0.680	0.282	0.057	0.165	0.662	0.651	**0.018**	**0.003**	0.381	0.956
Noticeable to others sleep problem is in terms of impairing quality of life											
Correlation coefficient	−0.507	0.111	−0.079	0.374	0.334	−0.457	−0.083	0.013	0.239	0.213	−0.172
p-value	**0.010**	0.598	0.707	0.066	0.103	**0.005**	0.629	0.942	0.160	0.226	0.330
Worried about sleep											
Correlation coefficient	−0.123	0.206	0.149	0.566	0.385	−0.300	−0.123	0.076	0.299	0.391	−0.204
p-value	0.559	0.323	0.478	**0.003**	0.058	0.075	0.474	0.660	0.076	**0.022**	0.247
Interference with daily functioning											
Correlation coefficient	−0.099	0.080	0.004	0.472	0.266	−0.37	−0.221	0.172	0.343	0.304	−0.064
p-value	0.638	0.703	0.986	**0.017**	0.199	**0.026**	0.195	0.316	**0.040**	0.080	0.720

ISI: Insomnia Severity Index; BMI: body mass index; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; UCT: Urticaria Control Test; UAS7: Urticaria Activity Score. Significant values shown in bold ($p < 0.05$).

a high disease activity, was associated with interrupted sleep. This could be explained by subconscious itching during the night, as is often reported by patients' partners. However, the UCT and UAS7 did not show a correlation between UCT and UAS7 score with insomnia severity. However, a significant difference was seen in ISI scoring before and during a disease flare. This suggests that the UCT and UAS7 instruments are not sufficiently strong to reflect the influence of sleep disturbances. Nonetheless, the sub-score of the ISI "worried about sleep" correlated significantly with the UCT score in patients with CU and showed that impaired sleep has an effect on perception of disease severity in patients with CU.

Although the DLQI did not ask specifically about insomnia, the results of this study show a correlation between insomnia severity and quality of life. Moreover, questions about sleep quality in the ISI revealed a significant correlation with the DLQI (Table IV). In patients with AD "difficulties falling asleep" had a higher correlation with DLQI score. In patients with CU, QoL was more affected by early awakening. This emphasizes the relevance of sleep disturbances on daily functioning in each individual and shows consistency and interaction between the parameters surveyed. Although insomnia is more common in the older population (21), the current study did not find any correlation between advanced age and ISI score. In contrast, the results revealed difficulties staying asleep and interference with daily functioning especially in younger patients with CU. In both groups, but especially in patients with CU, younger patients seemed to be troubled by impaired sleep. This association was also found in other studies dealing with the assessment of QoL in adolescents with insomnia (22). The current study showed that patients with AD and those with CU have different manifestations of sleep disturbances, although both AD and CU are inflammatory diseases with pruritus as a main symptom. However, in both diseases the relevance of insomnia with regard to QoL is manifested.

Recent studies have examined skin diseases and insomnia (23–25). With psoriasis, for example, itch and pain appear to affect both QoL and sleep (26). Patients with AD or psoriasis were scanned for insomnia, demonstrating that, with AD, there was a higher level of insomnia compared with patients with psoriasis (24). This was explained by pruritus. Likewise, the current study showed that 25 patients with AD appeared to be more affected by insomnia than those with CU. The current study showed that the more the patients were affected by pruritus, the higher was the impact on their QoL. This was also confirmed when examining the ISI sub-scores. Patients with CU with a higher pruritus score were less satisfied about their sleep pattern. Interestingly patient-rated insomnia itself did not increase significantly with pruritus. Unlike other studies, we were unable to identify itch as the most reliant predictor for sleep impairment (23, 26). This means that there must be additional relevant factors for poor sleep in this group of patients. The BMI did not have an impact on the outcome of the ISI in this cohort, therefore obstructive sleep apnoea could be ruled out as potential bias. One possible explanation for insomnia in AD could be impaired thermoregulation during sleep and fluid loss due to decreased skin barrier function (6).

CU can be subdivided into different subgroups; however, this pilot study focussed on sleep as the primary endpoint. In contrast to patients with AD, those with CU did not show permanent symptoms and were exposed to specific triggers during the course of the day. The level of histamine release increases in the evening and again in the early hours of the morning, which could explain the higher rating of the question "problems waking up too early" in patients with CU (27). Our results show that, even with a low UAS7 score in patients with CU, which also includes a rating of pruritus severity (16), clinically significant insomnia was observed during a flare. The pruritus documented in the UAS7 score, might vary between patients, as it is known, that some subjects document their worst pruritus during the day, while others document their mean pruritus intensity (28). In addition, symptoms of angioedema are not included in the UAS7, but might contribute to insomnia and explain the high ISI score (29).

The amount of research into intensive pruritus reflects its relevance and need for further workup. However, insomnia has similar psychological and physiological effects and is enhanced by pain (23). It is known that insomnia increases the risk of metabolic syndrome, hypertension, coronary artery disease and depression (1). On a molecular level, initial studies show an association between poor sleep and an increase in pro-inflammatory cytokines, such as TNF alpha and interleukin-6, both playing an important role in inflammatory skin diseases, such as AD and CU (3, 30). Moreover, an increase in reactive oxygen species, due to sleep disturbance, has been shown to be of relevance in the pathogenesis of inflammatory skin diseases, such as AD and CU (31–33).

It remains to be elucidated how much cytokines are elevated during sleep deprivation in patients with skin disease. Sleep deprivation has been shown to result in cortisol release (34). Cortisol has various effects and is known to have a negative influence on skin barrier function and homeostasis (35). Nerve growth factor, for example, is increased in chronic stress, as seen in patients with sleep deprivation. This NGF results in increased inflammation and skin thinning (34). Sleep deprivation leads to a diminished skin barrier function (36, 37).

The current study indicates that there is a high likelihood of sleep disturbance in patients with AD and those with CU. In particular, patients with AD experienced poor sleep during acute episodes. Sleep was less affected in patients with CU. In contrast to other studies, the current results indicate that pruritus is not the only

reason for insomnia in patients with AD and those with CU, and further research is needed. The current pilot study indicates that patients with dermatological diseases have different manifestations of sleep disturbance and should therefore be individually assessed, as each sleep disturbance may mandate a different treatment. The current study showed that sleep disturbances are indeed an underestimated burden among patients with dermatological diseases and should be considered and treated in patients with AD and CU in order to improve outcomes.

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REFERENCES

1. Buysse DJ. Insomnia. JAMA 2013; 309: 706–716.
2. Roth T. Insomnia: definition, prevalence, etiology, and consequences. J Clin Sleep Med 2007; 3: S7–10.
3. Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. Biol Psychiatry 2016; 80: 40–52.
4. Schmitt J, Bauer A, Meurer M. Atopisches Ekzem im Erwachsenenalter. Hautarzt 2008; 59: 841–852.
5. Wollenberg A, Feichtner K. Atopic dermatitis and skin allergies – update and outlook. Allergy 2013; 68: 1509–1519.
6. Levin J, Friedlander SF, Del Rosso JQ. Atopic dermatitis and the stratum corneum: part 2: other structural and functional characteristics of the stratum corneum barrier in atopic skin. J Clin Aesthet Dermatol 2013; 6: 49–54.
7. Kuo IH, Yoshida T, De Benedetto A, Beck LA. The cutaneous innate immune response in patients with atopic dermatitis. J Allergy Clin Immunol 2013; 131: 266–278.
8. Werfel T. The role of leukocytes, keratinocytes, and allergen-specific IgE in the development of atopic dermatitis. J Invest Dermatol 2009; 129: 1878–1891.
9. Deacock SJ. An approach to the patient with urticaria. Clin Exp Immunol 2008; 153: 151–161.
10. Radonjic-Hoesli S, Hofmeier KS, Micaletto S, Schmid-Grendelmeier P, Bircher A, Simon D. Urticaria and angioedema: an update on classification and pathogenesis. Clin Rev Allergy Immunol 2018; 54: 88–101.
11. Grandner MA, Jackson NJ, Pak VM, Gehrman PR. Sleep disturbance is associated with cardiovascular and metabolic disorders. J Sleep Res 2012; 21: 427–433.
12. Murphy MJ, Peterson MJ. Sleep disturbances in depression. Sleep Med Clin 2015; 10: 17–23.
13. Olfson M, Wall M, Liu SM, Morin CM, Blanco C. Insomnia and impaired quality of life in the United States. J Clin Psychiatry 2018; 79. pii: 17m12020.
14. Hanifin M, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol 1980; suppl 92: 44–47.
15. Schram ME, Spuls PI, Leeflang MM, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. Allergy 2012; 67: 99–106.
16. Hawro T, Ohanyan T, Schoepke N, Metz M, Peveling-Oberhag A, Staubach P, et al. The Urticaria activity score – validity, reliability, and responsiveness. J Allergy Clin Immunol Pract 2018; 6: 1185–1190.e1181.
17. Gerber M, Lang C, Lemola S, Colledge F, Kalak N, Holsboer-Trachsler E, et al. Validation of the German version of the insomnia severity index in adolescents, young adults and adult workers: results from three cross-sectional studies. BMC Psychiatry 2016; 16: 174.
18. Kulthanan K, Chiawsirikajorn Y, Jiamton S. Acute urticaria: etiologies, clinical course and quality of life. Asian Pac J Allergy Immunol 2008; 26: 1–9.
19. Reich A, Heisig M, Phan NQ, Taneda K, Takamori K, Takeuchi S, et al. Visual analogue scale: evaluation of the instrument for the assessment of pruritus. Acta Derm Venereol 2012; 92: 497–501.
20. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000; 894: i–xii, 1–253.
21. Miner B, Kryger MH. Sleep in the aging population. Sleep Med Clin 2017; 12: 31–38.
22. Amaral MO, de Almeida Garrido AJ, de Figueiredo Pereira C, Master NV, de Rosario Delgado Nunes C, Sakellarides CT. Quality of life, sleepiness and depressive symptoms in adolescents with insomnia: a cross-sectional study. Aten Primaria 2017; 49: 35–41.
23. Kaaz K, Szepietowski JC, Matusiak L. Influence of itch and pain on sleep quality in patients with hidradenitis suppurativa. Acta Derm Venereol 2018; 98: 757–761.
24. Kaaz K, Szepietowski JC, Matusiak L. Influence of itch and pain on sleep quality in atopic dermatitis and psoriasis. Acta Derm Venereol 2019; 99: 175–180.
25. Jensen P, Zachariae C, Skov L, Zachariae R. Sleep disturbance in psoriasis: a case-controlled study. Br J Dermatol 2018; 179: 1376–1384.
26. Gupta MA, Simpson FC, Gupta AK. Psoriasis and sleep disorders: a systematic review. Sleep Med Rev 2016; 29: 63–75.
27. Oliver ET, Sterba PM, Saini SS. Interval shifts in basophil measures correlate with disease activity in chronic spontaneous urticaria. Allergy 2015; 70: 601–603.
28. Hawro T, Ohanyan T, Schoepke N, Metz M, Peveling-Oberhag A, Staubach P, et al. Comparison and interpretability of the available urticaria activity scores. Allergy 2018; 73: 251–255.
29. Sussman G, Abuzakouk M, Berard F, Canonica W, Oude Elberink H, Gimenez-Arnau A, et al. Angioedema in chronic spontaneous urticaria is underdiagnosed and has a substantial impact: analyses from ASSURE-CSU. Allergy 2018; 73: 1724–1734.
30. Altemus M, Rao B, Dhabhar FS, Ding W, Granstein RD. Stress-induced changes in skin barrier function in healthy women. J Invest Dermatol 2001; 117: 309–317.
31. Okayama Y. Oxidative stress in allergic and inflammatory skin diseases. Curr Drug Targets Inflamm Allergy 2005; 4: 517–519.
32. Young CN, Koepke JI, Terlecky LJ, Borkin MS, Boyd Savoy L, Terlecky SR. Reactive oxygen species in tumor necrosis factor-alpha-activated primary human keratinocytes: implications for psoriasis and inflammatory skin disease. J Invest Dermatol 2008; 128: 2606–2614.
33. Ji H, Li XK. Oxidative stress in atopic dermatitis. Oxid Med Cell Longev 2016; 2016: 2721469.
34. Leproult R, Copinschi G, Buxton O, Van Cauter E. Sleep loss results in an elevation of cortisol levels the next evening. Sleep 1997; 20: 865–870.
35. Chen Y, Lyga J. Brain-skin connection: stress, inflammation and skin aging. Inflamm Allergy Drug Targets 2014; 13: 177–190.
36. Yoshizaki T, Kimira Y, Mano H, Ota M, Iwatsuki K, Oishi Y, et al. Association between skin condition and sleep efficiency in Japanese young adults. J Nutr Sci Vitaminol (Tokyo) 2017; 63: 15–20.
37. Oyetakin-White P, Suggs A, Koo B, Matsui MS, Yarosh D, Cooper KD, et al. Does poor sleep quality affect skin ageing? Clin Exp Dermatol 2015; 40: 17–22.

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UCOMB-real life data: treatment strategies for chronic urticaria patients with comorbidities

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ABSTRACT

Background: There is a lack of real-life safety data on treatment options for chronic urticaria in the presence of comedication and comorbidities.

Methods: We present a single-center UCARE pilot study of 212 outpatients with chronic urticaria. Patients were divided into three groups according to different CU therapies according to international guidelines.

Results: Of 212 patients, 108 (mean age 48.9 years, 71.3% female) had 59 comorbidities, including cardiovascular, autoimmune and malignant diseases. Patients were followed for a mean of 24.6 months (SD ± 21.3). Urticaria therapies were divided into three groups: A: 105 (97.2%) with omalizumab and 2nd generation antihistamines), B: 16 patients (14.8%): dual therapy with antihistamines and cyclosporine in 10 (9.3%), montelukast in five (4. 6%), dapsone in four (3.7%), hydroxychloroquine in one patient (0.9%), C: 12 (11.1%) patients received a third drug for 4.9 months (SD ± 3.2) and one quadruple therapy (2.1 months). 10 out of 12 (83.3%) patients received montelukast, two (16.7%) cyclosporine, two (16.7%) dapsone and one (8.3%) hydroxychloroquine as a third drug for chronic urticaria.

Conclusions: Combining treatment modalities for chronic urticaria and comorbidities are available and feasible with a good safety profile.

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Chronic spontaneous urticaria; wheals; angioedema; systemic therapy; comedication; comorbidity; real-life

1. Introduction

Chronic urticaria (CU) afflicts a significant portion of the world population, with a lifetime prevalence of 1.4%, resulting in negative impacts on patients' quality of life (1,2).

The primary treatment for CU is a second-generation antihistamine (sgAH) administered at dosages up to four-fold. If signs and symptoms continue to recur, add-on treatment with omalizumab (OMA), an anti-IgE antibody, should be considered (3). OMA is effective and mostly well-tolerated by patients (4). However, some CU patients do not benefit from OMA and need more effective therapy (5–7). Moreover, CU is connected with coexisting conditions like atopic dermatitis, autoimmune and cardiovascular disorders, and psychological disorders, as well as sleep disturbances, which, in many cases, necessitate medication (8–10). However, data on the safety of combined therapeutic approaches and long-term treatment for CU in such cases is limited (11).

2. Materials and methods

Retrospective analyses were performed at the Urticaria Center of Reference and Excellence (UCARE) of the Department of Dermatology and Allergy at the University Medical Center in Mainz, Germany. The data was collected using a questionnaire created by UCARE members of UCARE Centers, who have coauthored this manuscript. Overall, 212 CU outpatients were examined for the following inclusion criteria: treatment with a higher than standard-dosed antihistamine and receiving at least one more systemic drug with at least one comorbidity and comedication or receiving a triple therapy (TT). Demographic data and treatment plans were documented. A special questionnaire, developed by experts, was used for this purpose. The assessment of side effects was based on patient reports documented during patient visits. Different treatment strategies were compared: Group A=Double treatment (DT): sgAH and OMA; Group B=sgAH combined with another therapeutic agent different

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from OMA; Group C=Triple therapy (TT) with a sgAH, OMA and another drug, or quadruple therapy (QT) consisting of a sgAH, OMA, montelukast, and hydroxychloroquine.

The aim of this investigation was to assess the treatments recommended for CU by the international guideline in a real-life setting. Specifically, we assessed if the recommended treatments are suitable for CU patients with comorbidities and/or comedications in a real life settings.

Mobility exists within groups A, B and C. Patients in whom, for example, DT consisting of OMA and sgAH was not sufficient can also appear in group B after changing the second CU drug and/or in group C after adding a third drug.

2.1. Results

Of 212 patients with CU, 108 (50.9%) fulfilled the inclusion criteria. In the other 104 patients no comorbidity was recorded and/or no DT (no up-dosed sgAH and/or no second systemic treatment) was used. The mean age of the included patients was 48.9 years (SD ± 15.0), ranging from 14.1 to 78.5 years. The average duration of CU until therapy initiation was 4.6 years (SD ± 5.6). Most patients were female (77 of 108, 71.3%), and 67 (62.0%) and 38 (62.0%) patients had standalone CSU and CSU combined with CIndU, respectively. Three patients (2.8%) had mast cell mediator-associated angioedema (AE) without wheals (Table 1).

Group A: 105 of 108 (97.2%) patients received standard therapy with up-dosed sgAH and OMA. Three of 108 (2.8%) were in group B or C. Of these, 104 (99.0%) patients had at least one comorbidity and 100 (95.2%) had at least one co-medication, in addition to their CU therapy with a sgAH and OMA and sgAH)

Group B: 16 of 108 (14.8%) patients were treated by different CU therapies. Due to the fact, that patients were non-responders in Group A, they were treated with sgAH and instead omalizumab they received in 10 patients (9.3%) cyclosporine, in five patients (4.6%) montelukast, in four patients (3.7%) dapsone, and in one patient hydroxychloroquine. 13 of 16 (81.3%) had at least one comorbidity and 12 of 16 (75.0%) at least one co-medication alongside the different combinations mentioned above (Supplement Figure S1).

The mean duration for a DT in either group A or B was 24.6 months (SD ± 21.3).

Group C: A total of 12 of 108 patients (11.1%) received additional to sgAH and OMA a third therapeutic agent for a mean duration of 4.9 months (SD ± 3.2). 10 of these 12 patients (83.3%), received montelukast, two patients (16.7%) cyclosporine, two patients (16.7%) dapsone and one patient (8.3%) hydroxychloroquine.

In seven out of 12 patients (58.3%) who received TT, comorbidities were present. In five out of 12 (41.6%) co-medication was given (Supplement Figure S2).

In one case a QT consisting of sgAH, OMA, montelukast, and hydroxychloroquine was necessary for 2.1 months.

The number of therapies exceeds the number of patients, because in some cases therapeutic strategies were changed for the same patient.

Table 1. Patient demographics.

Patient characteristic	
Age, in years, mean ± SD	48.9 ± 15.0
Gender	
Female, n (%)	77 (71.3%)
Male, n (%)	31 (28.7%)
Urticaria type	
Standalone CSU, n (%)	67 (62.0 %)
CSU & CIndU, n (%)	38 (35.2%)
Isolated AE, n (%)	3 (2.8%)
Duration of dual therapy for CU in months, mean ± SD	24.6 ± 21.3
Duration of triple therapy for CU in months, mean ± SD	4.9 ± 3.2

CSU = chronic spontaneous urticaria, CIndU = chronic inducible urticaria, AE = angioedema; *n* = 108.

2.2. CU therapy in the presence of comorbidities

Our 108 CU patients with comorbidities had 59 distinct coexisting conditions, most commonly hypothyroidism, hypertension and atopic diseases (Table 2). Common co-medications included L-thyroxine (41.7%), beta-blockers (18.5%), AT-1 receptor antagonists (13.9%), antiplatelet drugs (10.2%), statins (7.4%) and selective

Table 2. Comorbidities of patients.

	n	%
Comorbidity		
Hypothyroidism	50	46,3%
Hypertension	47	43,5%
Atopies	**27**	25,0%
Allergic rhinoconjunctivitis	21	19,4%
Allergic bronchial asthma	10	9,3%
Atopic dermatitis	3	2,8%
Depression	16	14,8%
Sleep disorders	14	13,0%
Dyslipidemia	12	11,1%
Diabetes I and II	12	11,1%
Allergies	12	11,1%
Autoimmune diseases	**12**	11,1%
Psoriasis	3	2,8%
Ulcerative colitis	2	1,9%
Lupus erythematosus	2	1,9%
Celiac	2	1,9%
Crohn's disease	1	0,9%
Myasthenia gravis	1	0,9%
Vitiligo	1	0,9%
Subacute cutaneous lupus erythematosus	1	0,9%
Bechterew's disease	1	0,9%
Family Mediterranean fever	1	0,9%
Chronic pain	9	8,3%
Coronary artery disease	5	4,6%
Malignancies	**4**	3,7%
Active breast cancer	1	0,9%
State after breast cancer	1	0,9%
Chronic lymphatic leukemia	1	0,9%
Myeloproliferative Syndrome	1	0,9%
Cardiac arrhythmia	4	3,7%
Chronic gastritis	4	3,7%
COPD	4	3,7%
Restless legs-syndrome	3	2,8%
Hyperuricemia	3	2,8%
Iron deficiency	3	2,8%
Anxiety disorder	3	2,8%
Sleep apnea	3	2,8%
Benign prostatic hyperplasia	2	1,9%
Migraine	2	1,9%
Factor- V- Leiden mutation	2	1,9%
Hepatitis C	1	0,9%
Chronic hepatitis B	1	0,9%
Peripheral arterial occlusive disease	1	0,9%
von-Willebrand-syndrome	1	0,9%
Osteoporosis	1	0,9%
Kallmann-syndrome	1	0,9%
Bladder hyperactivity	1	0,9%
Hypoparathyroidism	1	0,9%
Adrenocortical insufficiency	1	0,9%
Thalassemia minor	1	0,9%
Eosinophilic esophagitis	1	0,9%
Endometriosis	1	0,9%
Onychomycosis	1	0,9%
Polycystic ovary syndrome	1	0,9%
Diverticulosis	1	0,9%
Chronic diverticulitis	1	0,9%
Fructose intolerance	1	0,9%
Protein S-deficiency	1	0,9%
Vitamin D-deficiency	1	0,9%
Acid reflux	1	0,9%
Herpes labialis	1	0,9%
Chronic Bronchitis	1	0,9%
Hyperthyroidism	1	0,9%

Table 3. Duration of co-medication of the most frequent comorbidities.

Co-medication	Mean of co-medication duration ± SD next to DT for CU in months, *median*	95% confidence interval Mean
Co-medication of thyroid dysfunction	22.1 ± 18.5, *16.9*	17.0–27.1
Co-medication of hypertension	26.4 ± 23.2, *21.4*	20.0–32.8
Co-medication of cardiovascular prophylaxis	25.5 ± 23.8, *15.6*	12.8–38.2
Co-medication of dyslipidaemia	17.2 ± 20.1, *7.7*	6.1–28.3
Co-medication of diabetes	19.0 ± 22.6, *9.0*	5.9–32.0
Co-medication of depression	16.2 ± 15.7, *11.3*	9.4–22.9
Co-medication of sleep disorders	6.4 ± 6.8, *3.8*	1.2–11.7

serotonin reuptake inhibitors (5.6%). Supplementary Table 1a, 1b and 1c illustrates the distribution of comedication combinations for comorbidity in conjunction with various forms of CSU treatment. When comorbidities such as malignancies, chronic inflammatory diseases, and hepatitis C are present, the duration of comedications is carefully monitored and described in detail. Tables 2 and 3 provide additional specific information.

Thyroid disorders were observed in 50 out of 108 patients (46.3%). Of the 50 patients, 49 (98.0%) were from group A, while 6 (12.0%) and 4 (8.0%) were from groups B and C, respectively. Among the 50 patients, 18 (36.0%) reported a diagnosis of Hashimoto's thyroiditis (HT).

2.2.1. Metabolic syndrome/disorders/cardiovascular comorbidity

Of the 108 patients observed, 47 suffered from arterial hypertension, representing 43.5% of the sample. In group A, 45 of 47 patients (95.8%) had arterial hypertension, while in group B and group C, the numbers were 6 of 47 (12.8%) and 2 of 47 (4.3%), respectively. 15 patients receiving cardiovascular prophylactic treatment belonged to group A, with only one of these patients (6.7%) also belonging to group B. Of the total sample, 15 patients (13.9%) received cardiovascular prophylaxis. Furthermore, 4 of the patients (26.7%) who were given prophylaxis had coronary artery disease. Out of 108 patients, 12 (11.1%) had dyslipidaemia, with all cases occurring in group A and three of the 12 (25.0%) also presenting In group B. Among the group, 11 (10.2%) patients were identified as suffering from diabetes mellitus type II, while one patient (0.9%) had diabetes mellitus type I. Moreover, 12 of the diabetes mellitus patients were in group A, with two found to be in group B as well.

2.2.2. Depression

Out of the 108 patients, 16 (14.8%) experienced depression alongside chronic spontaneous urticaria. All 16 of these patients belonged to group A, with two out of the 16 (12.5%) belonging to group B, and one out of the 16 (6.25%) belonging to group C. Due to this comorbidity, the only decision taken was to discontinue one treatment, as a preventive measure. The therapy in this patient involving sgAH was stopped due to depression but OMA was continued.

2.2.3. Sleep disorders

14 of 108 (13.0%) patients reported sleep disturbances. 13 in group A and one of 108 (0.9%) in group B.

2.2.4. Malignancies

In Group A, four out of 108 patients (3.7%) disclosed malignancies prior to or during treatment for CU. Amongst those patients, two suffered from breast cancer and received anti-cancer therapy: epirubicin and cyclophosphamide (19.6 m), and in the second case, anastrozole (14.3 m) was prescribed. One patient with myeloproliferative syndrome was treated with an antiplatelet agent (56.4 m). One patient with chronic lymphatic leukemia did not receive any co-medication.

2.2.5. Chronic inflammatory diseases

One patient, comprising 0.9% of the total of 108, in Group A required systemic treatment for atopic dermatitis, leaving to parallel use of dupilumab with DT. This combination lasted for 4.4 months. OMA was discontinued after CU control.

2.2.6. Chronic infections

One patient in Group A, comprising 108 individuals (0.9%), exhibited hepatitis C symptoms whilst being treated with anti-viral drugs sofosbuvir and ledipasvir for 5.2 months, alongside DT. However, complete remission of the condition transpired.

2.3. Side effects to CU medication and adverse events

In general, 80 of 108 patients (74.1%) reported adverse events and/or side effects during the monitored period. 42 of 108 patients (38.9%) reported side effects due to CU therapy. 36 of 105 (34.2%) patients in group A, 8 of 16 (50.0%) patients in group B and one of 12 (8.3%) patient in group C (Supplement Tables 2 and 3). It should be noted that there were no significant side effects that led to the discontinuation of CU medication, unless otherwise specified.

The most frequent side effects were related to sgAH in 28 patients (25.9%), 27 in Group A and one in Group B mentioning adverse events like fatigue in 20 of 28 (71.4%), headache, abdominal pain and weight gain (7.1%). In 18 of 28 patients these side effects subsided or disappeared after changing to another sgAH, combination therapy for CU with sgAH and OMA was continued.

In 12 out of 105 patients in group A (11.4%), the following side effects associated with OMA were observed: Therapy stopped in one case due to muscle, joint pain, and fatigue after a single OMA injection. Dapsone and sgAH were used for treatment instead. In another patient, uncertified angina pectoris symptoms occurred shortly after OMA injection, but no pathology was found. 12 (11.4%) patients reported the following side effects after OMA: Headache and fatigue were reported by seven patients each (6.7%), while heat sensation, nausea, and muscle and joint pain were observed in a single case each. One patient (0.9%) experienced idiopathic facial paralysis one day after receiving the OMA injection, although a direct correlation was ruled out. In 10 of the 12 cases, treatment could be sustained.

Overall, in Group B, 10 out of 16 patients (62.5%) were administered dual therapy for CU, comprising CsA and sgAH. Furthermore, two more patients were given CsA as part of a triple therapy in Group C. Out of the CsA patients, 8 (66.7%) reported side effects. Side effects reported include gastrointestinal problems in three patients (25.0%), gingival hyperplasia, hypertrichosis and hypertension in two patients (16.7%), as well as sensory disturbances, weight gain, fatigue, creatinine increase, headache, dizziness and gingival bleeding in a single patient (8.3%). There was also one undefined anaphylactoid reaction in DT, which resulted in immediate discontinuation of CsA. Due to safety concerns, six out of ten patients (60.0%) were discontinued and switched. The average duration of DT treatment with CsA was 5.3 ± 6.2 months.

Six out of 16 patients (37.5%) in group B were administered dapsone for CU. Among these, four out of six patients (66.7%) received dapsone in combination with sgAH as part of DT, while the remaining two (33.3%) received it as part of TT. Two cases (33.3%) reported side effects, with one patient experiencing occasional shortness of breath and the other developing methemoglobinemia, which led to discontinuation of therapy and subsequent switching to OMA and sgAH. No anemia was associated in these cases.

Two out of the 16 (12.5%) patients in Group B were administered hydroxychloroquine. One patient received a combination of hydroxychloroquine with sgAH, while the other was given hydroxychloroquine as part of TT. However, the treatment with hydroxychloroquine for the latter was halted due to visual impairment. Five out of 16 (31.3%) patients received montelukast as part of DT for Group B. In Group C, montelukast was used as the third component of TT for 10 out of 12 patients (83.3%). There were no reports of side effects due to the use of montelukast.

3. Discussion

Chronic spontaneous urticaria is an inflammatory systemic disease with a high burden of disease and high prevalence of comorbidities (8–10). Within our cohort of 108 CU patients with comorbidities, we identified 59 distinct comorbidities.

Although the gold standard therapeutic option for CSU is OMA combined with up-dosed sgAH (12,13) at least approximately 10–15% of patients with CSU, remain insufficiently treated (5–7). This is in line with our data: 12 out of 108 patients (11.1%), received TT because of insufficient treatment. Limited information is available regarding the successful use of sgAH with OMA and a third therapy, such as CsA (14). One study describes the use of immune suppressants (CsA in 16 patients, MTX and azathioprine in one patient each) in combination with high-dose OMA, for 14 months (SD ± 8) as safe. In our study, the duration of DT with CsA was 5.3 months (SD ± 6.2), which is consistent with the data obtained from another trial, where 72.7% of patients on CsA experienced side effects at two months and 64.5% at four months of therapy (15). Two studies with a limited number of patients, describe the use of OMA alongside with CsA or MTX as safe in the majority of patients ($n=15$ and $n=21$) (6,14) However, in our cohort six of 12 (50,0%) therapies with CsA were discontinued due to side effects.

Another study described three cases where dapsone and colchicine were safely added to the sgAH and OMA therapy regimen (16). In our cohort, two cases received dapsone in addition to sgAH and OMA (one case of TT with comorbidities and co-medication and one case colchicine for familial Mediterranean fever).

The findings of this study demonstrate that DT is a safe treatment option for CU/CSU patients with comorbidities or co-medication, even when used in combination with other therapeutic agents. With the exception of one case, DT treatment did not require complete discontinuation due to comorbidity, medication, or concomitant therapy. In one instance, OMA was discontinued as a result of suspected side effects. In addition to being able to use a third drug for CU (TT) for a duration of 4.9 months (SD ± 3.2) without interference, it is noteworthy that seven out of 108 patients (6.4%) had comorbidities and co-medications along with TT (Supplement Figure S1). Side effects under OMA were reported by 11.4% of patients who were undergoing OMA and sgAH treatment. Only one case resulted in OMA being discontinued due to suspected side effects. Similarly, in the OMA phase III trial, 11% of patients reported experiencing at least one adverse reaction with identical side effects to those in our cohort (17). Consequently, our real-life data indicate that the frequency of side effects of OMA in a patient population with comorbidities and co-medication is similar, with an average treatment period of 27.7 months.

3.1. Comorbidities with Co-medication and CU

In order to place the prevalence of the comorbidities in the epidemiological context of CU we refer to the total of 212 patients with CU.

In our cohort four of 212 patients (1.9%) with CU had malignancies, two breast-cancer, two haemato-oncological. Therapy consisted of epirubicine/cyclophosphamide respectively anastrozole as chemotherapy as well as an antiplatelet agent. There were no limitations in regard of cancer or cancer therapy during the time of observation, which is of great importance as there are only few published data regarding the effects of OMA on malignant diseases or impaired efficacy of OMA in cancer treatment (18,19). In case of cancer and its treatment, a CU therapy consisting of sgAH and OMA was safe, possible and feasible given a close monitoring.

In 12 of 212 patients (5.7%) autoimmune diseases other than Hashimoto's thyroiditis and type I diabetes mellitus were reported, i.e. psoriasis, ulcerative colitis, systemic lupus erythematosus(SLE), celiac disease, Crohn's disease, myasthenia gravis, vitiligo, subacute cutaneous lupus erythematosus(SCLE), Bechterews disease and familial Mediterranean fever. The prevalence of ulcerative colitis in CSU patients is described as 0.9%, which is in concordance with our data. For vitiligo (0.9%), our proportion differs by 0.1%. The proportions for celiac disease (1.9%), SLE (1.9%) and psoriasis (2.8%) are comparable (20). OMA was paused precautionary for six months in one case of SLE due to an episodic disease flare with vasculitic complaints and chilblain-like symptomatology. However, there was no sign of OMA being the cause. If there is a need to proceed or initiate CU therapy in patients with chronic inflammatory diseases, our data shows that a concomitant (co)-medication despite the intake of sgAH and OMA is safe and possible.

The percentage of thyroid dysfunction is reported as 0–42.6% (clinical) and 0–31% (subclinical), the proportion of Hashimoto Thyroiditis (HT) as 0.5–27.5% (21). The proportion without differentiation between clinical and subclinical SD dysfunction in our cohort is 23.6%, with 8.5% for HT. Simultaneous co-medication was possible in group A, B and C.

Hypertension is a prevalent comorbidity in CU, with a prevalence ranging from 18.1% to 41.3% (11,22–25). This is consistent with our research, indicating a hypertension prevalence of 22.2%. Furthermore, DM type II was found to be prevalent in 5.2%, in keeping with the findings of two recent studies (5.2% or 13.9% respectively) (23,24). Regarding dyslipidaemia, values of 22% and 41.6% can be found in the literature (11,23), our rate of 5.7% is far below this. Our findings indicate a possible underreporting, despite regular assessment of comedication changes. Based on our data and the available literature, the estimated prevalence of coronary artery disease (CAD) in patients with urticaria ranges from approximately 1.7% to 1.9% (24).

The prevalence of CAD in our patient group is lower compared to the worldwide average of 5–8% (26). This could be attributed to the younger age of our patients, which is comparable to other studies on CSU or CU. A DT for CU is safe and possible in patients with existing cardiovascular comorbidity/co-medication.

Anxiety disorders are present in 30% and depression in 17% of patients with CSU (27). In our current evaluation, depression

represented 7.5%, sleep disorders 6.6% and anxiety disorders 1.4% of the population. The prevalence is significantly lower compared to literature, which also could be partially explained by underreporting. This implicates, that physicians need to actively ask about mental health symptoms (3). 13 out of 16 patients safely received pharmacological treatment for depression, however a possible effect of sgAH therapy was closely monitored and led to a precautionary discontinuation in one case.

The medication with the most side effects was sgAH ($n = 28$) (25.9%). In 18 of the 108 patients (16.7%), the sgAH was changed to another. However, considering the treatment length (24.6 months; SD ± 21.3) with regular follow-up visits, may alone increases the probability of several symptoms being interpreted as side effects. The most common reported symptom was fatigue in 20 (18.5%) patients. The sgAHs used were: rupatadine, fexofenadine, loratadine, desloratadine, bilastine, cetirizine, levocetirizine and ebastine.

Dapsone, a second-line treatment option, was administered to six patients within our cohort. Co-administration of both montelukast and dapsone, as a third therapeutic agent, did not entail any risk to DT. Hydroxychloroquine was administered to two patients, even as part of a QT (sgAH, OMA, montelukast and hydroxychloroquine). One patient had to stop therapy after 4.7 months due to a decline in visual acuity. Apart from this, TT or escalation thereof was feasible and safe, and DT remained uncompromised. Patients receiving dapsone for CU presented a range of comorbidities, including diabetes, hypertension, hypercholesterolemia, hypothyroidism, chronic gastritis, sleep disorders, adrenal insufficiency, and Factor V-Leiden Syndrome. Dapsone has a confirmed track record as a medication for various other autoimmune/autoinflammatory diseases.

3.2. Strengths and limitations

Our data are summarized based on the physician's documentation during each visit in average every 3 months and patient's history only. However, by embedding our data in the context of previous literature, the validity of our registered prevalence becomes evident. The strength of this observation is the exact documentation of duration of urticaria medication as well as co-medications and comorbidities, suggesting the safety in both patient groups. Furthermore, this study offers essential real-world data concerning the occurrence of comorbidities in CU patients that can only be obtained in a real-life environment, especially in patients not responding adequately to standard treatment where no approved treatment is available for now. These findings lend support to physicians in their daily practice for optimal CU patient treatment. However, additional data is needed to reinforce these discoveries, for example, through multi-center non-interventional studies or registries. Consequently, an international UCARE-project is currently being prepared worldwide.

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Disclosure statement

Petra Staubach: Has served as a consultant, in clinical studies and/or speaker to AbbVie, Almirall-Hermal, Amgen, Beiersdorf, Biocryst, BMS, Boehringer-Ingelheim, CSL-Behring, Eli-Lilly, Galderma, Hexal, Janssen, Kalvista, LEO-Pharma, L'Oreal, Novartis, Octapharma, Pfizer, Pflüger, Regeneron, Shire, Takeda, Regeneron, Sanofi-Genzyme und UCB Pharma. She has no conflicts of interest related to the content of this article.

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References

1. Gonçalo M, Gimenéz-Arnau A, Al-Ahmad M, et al. The global burden of chronic urticaria for the patient and society. Br J Dermatol. 2020;184(2):1–7. doi: 10.1111/bjd.19561.
2. Fricke J, Ávila G, Keller T, et al. Prevalence of chronic urticaria in children and adults across the globe: systematic review with meta-analysis. Allergy. 2020;75(2):423–432. doi: 10.1111/all.14037.
3. Zuberbier T, Abdul Latiff AH, Abuzakouk M, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022;77(3):734–766. doi: 10.1111/all.15090.
4. Zuberbier T, Maurer M. Omalizumab for the treatment of chronic urticaria. Expert Rev Clin Immunol. 2015;11(2):171–180. doi: 10.1586/1744666x.2015.993971.
5. Vena GA, Maurer M, Cassano N, et al. Alternative treatments for chronic spontaneous urticaria beyond the guideline algo-

rithm. Curr Opin Allergy Clin Immunol. 2017;17(4):278–285. doi: 10.1097/aci.0000000000000372.
6. Rutkowski K, Wagner A, Jui-Lin Choo K, et al. "Omalizumab plus": combining omalizumab with immunosuppression for treatment of refractory chronic urticaria: a multicenter UK series. J Allergy Clin Immunol Pract. 2021;9(3):1400–1401. doi: 10.1016/j.jaip.2020.10.056.
7. Maoz-Segal R, Levy T, Haj-Yahia S, et al. Combination therapy with omalizumab and an immune-suppressive agent for resistant chronic spontaneous rrticaria - A real-life experience. World Allergy Organ J. 2020;13(8):100448. doi: 10.1016/j.waojou.2020.100448.
8. Staubach P, Mann C, Peveling-Oberhag A, et al. Epidemiology of urticaria in german children. J Dtsch Dermatol Ges. 2021;19(7):1013–1019. doi: 10.1111/ddg.14485.
9. Papapostolou N, Xepapadaki P, Katoulis A, et al. Comorbidities of chronic urticaria: a glimpse into a complex relationship. Front Allergy. 2022;3:1008145. doi: 10.3389/falgy.2022.1008145.
10. Zbiciak-Nylec M, Wcisło-Dziadecka D, Kasprzyk M, et al. Overweight and obesity may play a role in the pathogenesis of chronic spontaneous urticaria. Clin Exp Dermatol. 2018;43(5):525–528. doi: 10.1111/ced.13368.
11. Vollono L, Piccolo A, Lanna C, et al. Omalizumab for chronic spontaneous urticaria in "complex" patients: data from real-life clinical practice. Drug Des Devel Ther. 2019;13:3181–3186. doi: 10.2147/dddt.S214307.
12. Ke X, Kavati A, Wertz D, et al. Real-World characteristics and treatment patterns in patients with urticaria initiating omalizumab in the United States. J Manag Care Spec Pharm. 2018;24(7):598–606. doi: 10.18553/jmcp.2018.24.7.598.
13. Giménez-Arnau A, Velasco M, Armario Hita JC, et al. Omalizumab: what benefits should we expect? Eur J Dermatol. 2016;26(4):340–344. doi: 10.1684/ejd.2016.2809.
14. Sánchez J, Alvarez L, Cardona R. Cyclosporine and omalizumab together: a new option for chronic refractory urticaria. J Allergy Clin Immunol Pract. 2020;8(6):2101–2103. doi: 10.1016/j.jaip.2020.02.012.
15. Vena GA, Cassano N, Colombo D, et al. Cyclosporine in chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. J Am Acad Dermatol. 2006;55(4):705–709. doi: 10.1016/j.jaad.2006.04.078.
16. Salman A, Ergun T, Gimenez-Arnau AM. Real-life data on the effectiveness and safety of omalizumab in monotherapy or combined for chronic spontaneous urticaria: a retrospective cohort study. J Dermatolog Treat. 2020;31(2):204–209. doi: 10.1080/09546634.2019.1589639.
17. Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. J Allergy Clin Immunol. 2013;132(1):101–109. doi: 10.1016/j.jaci.2013.05.013.
18. Hayama K, Fujita H, Asai-Sato M, et al. Successful treatment of intractable chronic spontaneous urticaria with omalizumab in a patient with ovarian cancer. Eur J Dermatol. 2021;31(1):100–101. doi: 10.1684/ejd.2020.3959.
19. Türk M, Carneiro-Leão L, Kolkhir P, et al. How to treat patients with chronic spontaneous urticaria with omalizumab: questions and answers. J Allergy Clin Immunol Pract. 2020;8(1):113–124. doi: 10.1016/j.jaip.2019.07.021.
20. Kolkhir P, Borzova E, Grattan C, et al. Autoimmune comorbidity in chronic spontaneous urticaria: a systematic review. Autoimmun Rev. 2017;16(12):1196–1208. doi: 10.1016/j.autrev.2017.10.003.
21. Kolkhir P, Metz M, Altrichter S, et al. Comorbidity of chronic spontaneous urticaria and autoimmune thyroid diseases: a systematic review. Allergy. 2017;72(10):1440–1460. doi: 10.1111/all.13182.
22. Maurer M, Staubach P, Raap U, et al. H1-antihistamine-refractory chronic spontaneous urticaria: it's worse than we thought - first results of the multicenter real-life AWARE study. Clin Exp Allergy. 2017;47(5):684–692. doi: 10.1111/cea.12900.
23. Shalom G, Magen E, Babaev M, et al. Chronic urticaria and the metabolic syndrome: a cross-sectional community-based study of 11 261 patients. J Eur Acad Dermatol Venereol. 2018;32(2):276–281. doi: 10.1111/jdv.14548.
24. Goldstein S, Gabriel S, Kianifard F, et al. Clinical features of adolescents with chronic idiopathic or spontaneous urticaria: review of omalizumab clinical trials. Ann Allergy Asthma Immunol. 2017;118(4):500–504. doi: 10.1016/j.anai.2017.02.003.
25. Martina E, Damiani G, Grieco T, et al. It is never too late to treat chronic spontaneous urticaria with omalizumab: real-life data from a multicenter observational study focusing on elderly patients. Dermatol Ther. 2021;34(2):e14841. doi: 10.1111/dth.14841.
26. Bauersachs R, Zeymer U, Brière JB, et al. Burden of coronary artery disease and peripheral artery disease: a literature review. Cardiovasc Ther. 2019;2019:8295054–8295059. doi: 10.1155/2019/8295054.
27. Staubach P, Dechene M, Metz M, et al. High prevalence of mental disorders and emotional distress in patients with chronic spontaneous urticaria. Acta Derm Venereol. 2011;91(5):557–561. doi: 10.2340/00015555-1109.

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ORIGINAL ARTICLE

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

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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 Severity 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

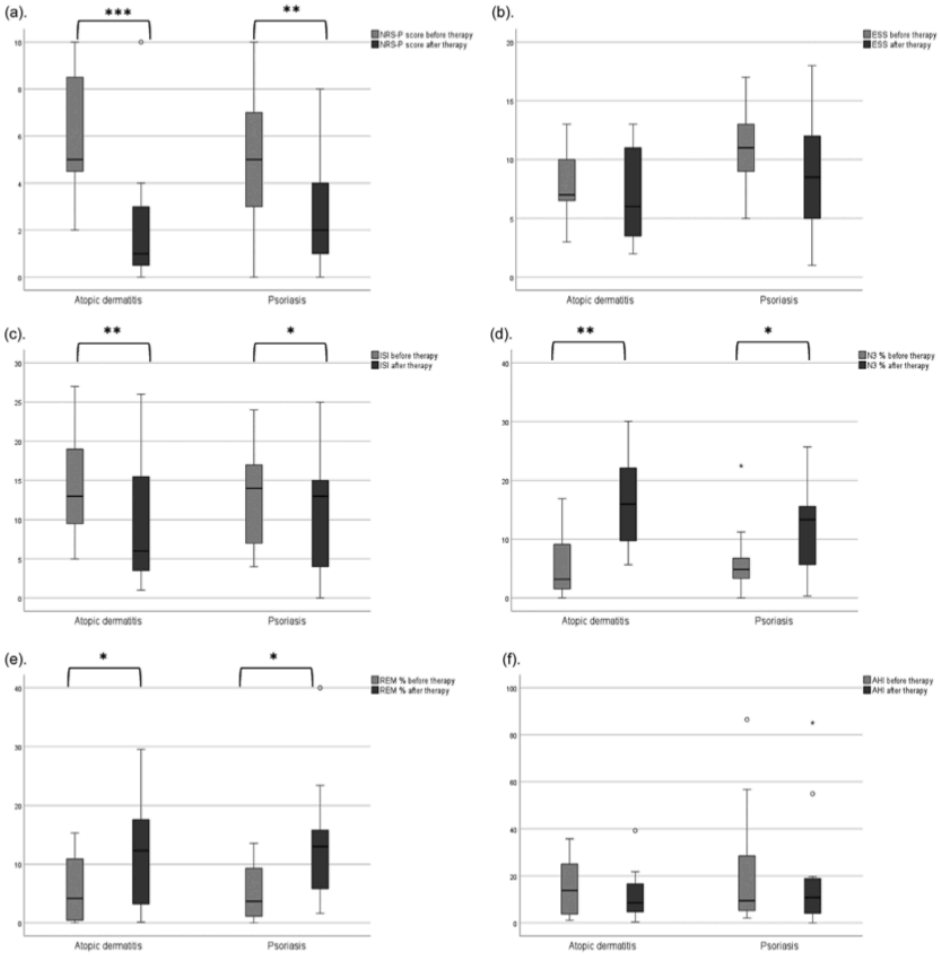

FIGURE 1 Boxplots showing changes before and after therapy. x-axis: Atopic Dermatitis (left) and psoriasis (right) patients y-axis: Scores of patient-rated outcomes (a–c) and polygraphy data (d–f) *p < 0.05, **p < 0.01, ***p < 0.0001 *Abbr.*: NRS-P, Numeric Rating Scale Pruritus; ESS, Epworth Sleepiness 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.

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CONFLICT OF INTEREST STATEMENT

None.

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REFERENCES

1. Mann C, Gorai S, Staubach-Renz P, Goldust M. Sleep disorders in dermatology – a comprehensive review. *J Dtsch Dermatol Ges*. 2023;21(6):577-584.
2. Mann C, Dreher M, Weeß HG, Staubach P. Sleep disturbance in patients with urticaria and atopic dermatitis: an underestimated burden. *Acta Derm Venereol*. 2020;100(6):adv00073.
3. Rangel SM, Kim T, Sheth A, et al. Prevalence and associations of fatigue in childhood atopic dermatitis: A cross-sectional study. *J Eur Acad Dermatol Venereol*. 2023;37(4):763-771.
4. Silverberg JI, Garg NK, Paller AS, et al. Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study. *J Invest Dermatol*. 2015;135(1):56-66.
5. Birkner T, Siegels D, Heinrich L, et al. Itch, sleep loss, depressive symptoms, fatigue, and productivity loss in patients with moderate-to-severe atopic dermatitis: Analyses of TREATgermany registry data. *J Dtsch Dermatol Ges*. 2023;21(10):1157-1168.
6. Boyce R, Glasgow SD, Williams S, Adamantidis A. Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. *Science*. 2016;352(6287):812-816.
7. Leminen MM, Virkkala J, Saure E, et al. Enhanced memory consolidation via automatic sound stimulation during non-REM sleep. *Sleep*. 2017;40(3):zsx003.
8. Unnikrishnan D, Jun J, Polotsky V. Inflammation in sleep apnea: an update. *Rev Endocr Metab Disord*. 2015;16(1):25-34.
9. Paller AS, Lai JS, Jackson K, et al. Generation and Validation of the patient-reported outcome measurement information system Itch Questionnaire-Child (PIQ-C) to measure the impact of itch on life quality. *J Invest Dermatol*. 2022;142(5):1309-1317.e1.
10. Hawro T, Hawro M, Zalewska-Janowska A, et al. Pruritus and sleep disturbances in patients with psoriasis. *Arch Dermatol Res*. 2020;312(2):103-111.
11. Hess A, Axmann R, Rech J, et al. Blockade of TNF-α rapidly inhibits pain responses in the central nervous system. *Proc Natl Acad Sci USA*. 2011;108(9):3731-3736.
12. Grandner MA, Jackson NJ, Pak VM, Gehrman PR. Sleep disturbance is associated with cardiovascular and metabolic disorders. *J Sleep Res*. 2012;21(4):427-433.
13. Krause K, Kessler B, Weller K, et al. German version of ItchyQoL: validation and initial clinical findings. *Acta Derm Venereol*. 2013;93(5):562-568.
14. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540-545.
15. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med*. 2001;2(4):297-307.
16. Iber C, Ancoli-Israel S, Chesson AL, Quan, SF for the American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications*. AASM. 2007.
17. Executive summary on the systematic review and practice parameters for portable monitoring in the investigation of suspected sleep apnea in adults. *Am J Respir Crit Care Med*. 2004;169(10):1160-1163.
18. Kukwa W, Migacz E, Lis T, Ishman SL. The effect of in-lab polysomnography and home sleep polygraphy on sleep position. *Sleep Breath*. 2021;25(1):251-255.
19. Patel AK, Reddy V, Shumway KR, Araujo JF. Physiology, Sleep Stages. 2024 Jan 26. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 30252388.
20. Cohen J. A power primer. *Psychol Bull*. Jul 1992;112(1):155-159.
21. Becker HF, Ficker J, Fietze J, et al. S3-Leitlinie Nicht erholsamer Schlaf/Schlafstörungen (DGSM). *Somnologie*. 2009;13:4-160.
22. Leshem YA, Hajar T, Hanifin JM, Simpson EL. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. *Br J Dermatol*. 2015;172(5):1353-1357.

23. Papaconstantinou E, Cancelliere C, Verville L, et al. Effectiveness of non-pharmacological interventions on sleep characteristics among adults with musculoskeletal pain and a comorbid sleep problem: a systematic review. *Chiropr Man Therap*. 2021;29(1):23.
24. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9(2):105-121.
25. Morin CM, Jarrin DC. Epidemiology of insomnia: prevalence, course, risk factors, and public health burden. *Sleep Med Clin*. 2022;17(2):173-191.
26. Kaaz K, Szepietowski JC, Matusiak Ł. Influence of itch and pain on sleep quality in atopic dermatitis and psoriasis. *Acta Derm Venereol*. 2019;99(2):175-180.
27. Patel S, Kon SSC, Nolan CM, et al. The Epworth Sleepiness Scale: Minimum clinically important difference in obstructive sleep apnea. *Am J Respir Crit Care Med*. 2018;197(7):961-963.
28. Elewski B, Alexis AF, Lebwohl M, et al. Itch: an under-recognized problem in psoriasis. *J Eur Acad Dermatol Venereol*. 2019;33(8):1465-1476.
29. O'Neill JL, Chan YH, Rapp SR, Yosipovitch G. Differences in itch characteristics between psoriasis and atopic dermatitis patients: results of a web-based questionnaire. *Acta Derm Venereol*. 2011Sep;91(5):537-40.
30. Ishikawa O, Oks M. Central Sleep Apnea. *Clin Geriatr Med*. 2021;37(3):469-481.
31. Maniaci A, Iannella G, Cocuzza S, et al. Oxidative stress and inflammation biomarker expression in obstructive sleep apnea patients. *J Clin Med*. 2021;10(2):277.
32. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev*. 2010;90(1):47-112.
33. Emami E, Heydecke G, Rompré PH, et al. Impact of implant support for mandibular dentures on satisfaction, oral and general health-related quality of life: a meta-analysis of randomized-controlled trials. *Clin Oral Implants Res*. 2009;20(6):533-544.
34. Kim J, Tran K, Seal K, et al. Interventions for the treatment of obstructive sleep apnea in adults: a health technology assessment [Internet]. Ottawa (ON). Available from: https://www.ncbi.nlm.nih.gov/books/NBK535532/ [Last accessed February 27, 2024].
35. Shalom G, Dreiher J, Cohen A. Psoriasis and obstructive sleep apnea. *Int J Dermatol*. 2016;55(11):e579-e584.
36. Liu X, Ma Y, Ouyang R, et al. The relationship between inflammation and neurocognitive dysfunction in obstructive sleep apnea syndrome. *J Neuroinflammation*. 2020;17(1):229.

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RESEARCH ARTICLE

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Self-management-competency as a new target in Hidradenitis suppurativa care

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ABSTRACT

Background: Hidradenitis suppurativa affects approximately 1% of the population.
Objective: Highlighting the relevance of self-management-competency as a new therapeutic target.
Method: 258 patients from the 'Epidemiology and Care in Acne inversa (EpiCAi)' project were included in the study. Disease burden was measured by patient-rated questionnaires in terms of disease activity, pain, quality of life, depression and insomnia and correlated with the domains of the health education impact questionnaire (heiQ) measuring self-management-competency.
Results: 66 male (25.6%) and 192 female (74.4%) patients, with a mean age of 40.3±10.24years were included. Mean scores of pain on the numeric rating scale (NRS), Dermatology Life Quality Index (DLQI) and Hospital Anxiety and Depression Scale (HADS) were 5.11±2.68, 11.35±7.79 and 13.71±7.57, respectively. The Insomnia severity index (ISI) showed a mean of 9.58±5.76. The HADS has the highest increased total risk across all heiQ domains. With respect to the heiQ domains, the highest exposure can be attributed to improving constructive attitudes and approaches as well as decreasing emotional distress.
Conclusion: There is a clear association of self-management-competency with overall disease burden, which underlines the need for psychoeducational support. This study provides ideas to develop new possible strategies of care.

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1. Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition characterized by recurrent episodes of the formation of inflammatory nodules, abscesses, fistulas, pain, and drainage in the inverse skin regions (1). HS is an immense burden of disease (2).

When establishing treatment plans, disease status and impact must be evaluated. There are numerous validated scores as e.g., Hurley-stage (3) or the International Hidradenitis Suppurativa Severity Score System (IHS4) (4) as well as quality of life (e.g., Dermatology Life Quality Index (DLQI)) (5) and treatment guidelines building on these scores to initiate physical, medicinal and surgical therapies (6). In contrast, dealing with the disease burden by means of improving mental wellbeing has been addressed in HS only sparsely.

To treat the disease holistically and to implement successful disease management, it is necessary to identify key targets in self-management and education that can be addressed. Possible topics include information on the reduction of triggers and risk factors, as well as techniques to reduce symptoms, overcome distress and improve coping with the disease. There is a validated instrument, the health education impact questionnaire (heiQ), for adults with chronic diseases which proved to be effective in evaluating self-management-competency in various publications (7). The heiQ consists of eight independent core domains in relation to living and coping with the illness: Positive and active life engagement (active), health-focused activities (health), skill acquisition (skill), constructive attitudes and approaches (const), self-observation (self), navigating health care (coop), social integration and support (social), and emotional distress (emo).

The aim of this study was to explore whether the heiQ is a sensitive tool to identify relevant target points in self-management-competency of HS-patients to influence disease activity and burden.

2. Materials and methods

The data for this publication stem from the EpiCAi-project. EpiCAi (Epidemiology and Care in Acne inversa) is a project of an international consortium of experts led by the Department of Dermatology of the University Medical Center Mainz in cooperation with LENICURA GmbH. The aim is to combine data from the everyday care of a large number of HS patients with additional digital surveys. All HS-diagnosed patients, who have agreed to the documentation of their LAight therapy (physical treatment option in Germany performed in outpatient offices) in the manufacturer's software (LENICURA GmbH, Germany), were invited to participate in EpiCAi. Invitation was performed by mailing to the address provided by patients for research purposes and on the other hand by

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displaying flyers at the treatment sites of the LAight therapy as well as an announcement on the project website (www.epicai.de). After logging into their own account, patients were shown questionnaires on different topics. It was not mandatory to fill out all questionnaires, but once a questionnaire was started, it automatically closed after 7 days, saving the most recent status. All available data was analyzed. The present study focuses on the self-management-competency of patients and includes a subset of validated endpoints derived from EpiCAi-questionnaires.

Self-management-competency was measured by the heiQ. Each domain of the heiQ consists of four to six questions and a total of 40 questions on a 4-point scale ('strongly disagree' to 'strongly agree'). By calculating the mean value of the respective items, the domain values are formed (on a scale from 1–4). The higher the score, the stronger the ability to cope with the chronic disease in the respective domain. The domain 'emo' is an exception, as it is rated negatively.

Disease severity was measured by Hurley-staging which was assessed by the physician in the outpatient centers. Moreover, patients were asked to rate their disease activity as a sum of inflammatory nodules + 2 x abscesses + 4 x draining fistulas (PRDA). For this purpose, patients were provided with a description of each lesion typical of HS (8). For measuring the disease burden, the current pain on the Numeric Rating Scale (Pain-NRS: no pain = 0 to worst pain imaginable = 10), the DLQI with 10 items (0 to 3 points allocated per question) as well as the Hospital Anxiety and Depression Scale (HADS), an instrument to measure psychological distress in patients consisting of 14 items, 7 for each subscale anxiety and depression (0 to 3 points allocated per question) (9) were derived. Sleep quality was assessed by the Insomnia Severity Index (ISI), a 7-item patient-rated questionnaire (scoring from 0–28) depicting the quality of sleep in the past 14 days (10). Moreover, patients were also asked about their wishes for information to be displayed if a digital application/app for patients with HS was available.

2.1. Statistical methods

The study follows an explorative design to identify target points for the education of HS-patients. All available data of patients was used for the statistical analysis. To show the impact of the different domains of the heiQ on disease activity, disease burden and sleep impairment, odds-ratios were calculated. For the heiQ, patients with a score in the lower third (L3) received a binary value of 1, while patients in the upper third (U3) received a 0 (Table 1).

The following cut-of criteria were used for the allocation of a binary value of 1 in the disease related endpoints: PRDA severe (PRDA > 10); at least moderate pain (pain-NRS > 3) (11); very strong influence on quality of life (DLQI > 19 points); alarming values of HADS (HADS total score > 14) and at least moderate sleep problems (ISI > 14). The significance level was set at 5%. All analyses were performed using SPSS (IBM, New-York, United States).

Table 1. Criteria on heiQ for patients with HS, compared to other diseases.

	Mean	SD	Lower third (L3)	Upper third (U3)	Cohen's d[a] to bowles disease	Cohen's d[1)] to rheuma	Cohen's d[1)] to oncology
heiQ_Activ	2.87	0.61	≤ 2.40	≥ 3.20	0.21	0.05	0.41
heiQ_Health	2.49	0.73	≤ 2.00	≥ 2.75	0.36	0.52	0.97
heiQ_Skill	2.73	0.55	≤ 2.25	≥ 3.00	0.01	0.07	0.71
heiQ_Const	3.06	0.61	≤ 2.40	≥ 3.20	0.16	0.08	0.44
heiQ_Self	2.91	0.47	≤ 2.67	≥ 3.17	0.46	0.33	0.67
heiQ_Coop	2.93	0.60	≤ 2.60	≥ 3.20	0.39	0.22	0.92
heiQ_Social	2.80	0.66	≤ 2.40	≥ 3.00	0.19	0.02	0.93
heiQ_Emo	2.65	0.73	≤ 2.17	≥ 3.00	−0.42	0.06	−0.55

[a]Calculated as difference between mean of other disease [1] and HS-mean divided by SD of HS-value.
Schwarze M. Übersetzung, Adaption und Validierung des HeiQ – eines generischen Instruments zur Bewertung von Patientenschulungen (PS) und Selbstmanagementprogrammen (SM). In. Abschlussbericht. Hannover. 2011.

3. Results

3.1. Study population

Patients were recruited for EpiCAi from 3rd December 2021 until 3rd June 2022. In total 3,513 patients had a valid HS-diagnosis and thus were eligible to fill out the digital questionnaires. Of those 277 filled out the informed consent.

A total of 258 patients, 66 male (25%) and 192 female (74.4%), with a mean age of 40.3 ± 10.24 years answered the questionnaire for self-management at baseline and thus were included in this study. Most patients suffered from HS with Hurley stage II (60.5%), while 16.3% showed Hurley stage I and 23.2% were evaluated as Hurley stage III (Table 2). PRDA scores were available for 182 patients, showing a mean score of 16.96 ± 16.45 points. Overall, the disease burden was high with mean values of pain-NRS, DLQI and HADS of 5.11 ± 2.68 points, 11.35 ± 7.79 points and 13.71 ± 7.57 points, respectively. Moreover, the ISI was completed by 179 patients, showing a mean of 9.58 ± 5.76 points.

3.2. heiQ domains

Table 1 shows the mean values for the heiQ domains as well as the cutoffs for the L3 and U3. To gain an idea about the initial level of self-management competency in HS, the mean values were compared to those reported for other diseases like

Table 2. Baseline characteristics.

Characteristics	mean ± SD or absolute/relative numbers are shown
Age in years	40.30 ± 10.24
Gender	
Male	66 (25.6%)
Female	192 (74.4%)
Hurley Stage	
Hurley I	42 (16.3%)
Hurley II	156 (60.5%)
Hurley III	60 (23.3%)
PRDA (n = 182)	16.96 ± 16.45
Pain NRS (n = 198)	5.11 ± 2.68
DLQI (n = 194)	11.35 ± 7.79
HADS (n = 194)	13.71 ± 7.57
ISI (n = 179)	9.58 ± 5.76
Smoking behavior (n = 181)	
Non-smoker	48 (26.5%)
Former smoker	52 (28.7%)
Smoker	68 (37.6%)
Vaping with nicotine	13 (0.7%)
Cigarettes/day (n = 68)	14.01 ± 7.66
BMI	32.47 ± 7.40
Living site (n = 181)	
Rural	95 (52.5%)
City	86 (47.5%)
Work status (n = 182)	
Employed	144 (79.12%)
Not employed*	51 (20.88%)
SHG activity	
No	130 (50.4%)
Yes	128 (49.6%)

*Including student, retired, 'erwerbsunfähig', 'arbeitsunfähig', unemployed, other.

inflammatory bowel disease, rheumatologic and oncologic diseases using Cohens' d (12) (a measurement for effect size mean difference divided by standard deviation). Especially in comparison to oncologic disease, the mean difference almost consistently shows a medium (> 0.5) to strong (> 0.8) effect in difference toward lower values for HS-patients.

3.3. Association of heiQ domains with disease activity and burden

Table 3 shows the odds-ratio of high values in relevant HS-endpoints with L3 performers in heiQ domains as well as risk factors 'smoking' and 'obesity'. It can be obtained that the heiQ domains show many significant associations with a higher risk in disease activity and burden (e.g., a 9 times higher risk for a critical HADS value if patients belong to the L3 of heiQ_Coop and thus are under the impression to not be able to communicate properly with their caregivers). The different magnitudes of effects are highlighted in different colors and received different index points (e.g., 4 points for an odds-ratio bigger than 6 or smaller than 0.167, see Table 3).

From the magnitude of the odds-ratios, an index score was calculated for each endpoint as well as for each heiQ domain by summing up the respective index points to illustrate which endpoint has the highest overall association to self-management-competency and which heiQ domain has the highest impact across all endpoints.

Following this method, index scores for endpoints show that the HADS (26 index points) has the highest increased total risk for L3 scorers across all heiQ domains, followed by the DLQI and ISI (each 15 index points), pain-NRS (13 index points) and finally PRDA (12 index points).

Index scores for heiQ domains show that patients performing in the L3 in the domains heiQ_Const and heiQ_Emo (15 index points) have the highest risk for a high disease impact. Those two domains are followed by heiQ_Activ and heiQ_Social (13 index points), heiQ_Coop (9 index points) and finally heiQ_Health and heiQ_Self (4 index points).

3.4. Categories of supportive recommendations and information

In the study, patients were asked about which kind of information and support they would mostly benefit from, once a specific digital application for HS would become available. Results are depicted in Table 4. Among the suggested information categories, tips for cleansing and skin care are the most frequently selected (47.0%) by respondents, followed by wound care (40.7%), treatment options and disease understanding (35.5%) as well as knowledge on trigger and risk factors (29.0%).

After that, the project team associated the different requests with heiQ domains. From all suggestions, 'stress reduction and personal time-outs spending on things you enjoy' achieved 47 summed index points. This can be assigned to heiQ_Const and heiQ_Emo with a referral to mental coping and self-aid groups as well as to heiQ_Activ with suggestions for different personalized

Table 3. Odds ratios between heiQ domains and HS-relevant endpoints.

heiQ domains		PRDA	Pain-NRS	DLQI	HADS	ISI	
		12	13	15	26	15	Derived index
heiQ_Activ	Odds-Ratio	2.689	3.197	3.158	32.727	4.714	13
	95% CI	[1.20 ; 6.02]	[1.38 ; 7.40]	[1.17 ; 8.54]	[11.74 ; 91.28]	[1.77 ; 12.56]	
	N_{U3} / N_{L3}	62 / 45	68 / 53	67 / 52	67 / 52	62 / 48	
heiQ_Health	Odds-Ratio	2.995	1.672	2.051	3.141	1.593	4
	95% CI	[1.38 ; 6.50]	[0.75 ; 3.73]	[0.76 ; 5.57]	[1.48 ; 6.65]	[0.63 ; 4.07]	
	N_{U3} / N_{L3}	54 / 58	61 / 62	60 / 61	60 / 61	52 / 56	
heiQ_Skill	Odds-Ratio	2.111	3.726	3.065	2.297	1.614	8
	95% CI	[1.06 ; 4.21]	[1.75 ; 7.93]	[1.23 ; 7.63]	[1.20 ; 4.42]	[0.76 ; 3.44]	
	N_{U3} / N_{L3}	78 / 61	85 / 70	83 / 69	83 / 69	76 / 63	
heiQ_Const	Odds-Ratio	2.256	2.748	8.164	45.600	3.947	15
	95% CI	[1.10 ; 4.63]	[1.33 ; 5.67]	[2.31 ; 28.84]	[15.56 ; 133.62]	[1.54 ; 10.11]	
	N_{U3} / N_{L3}	58 / 68	63 / 76	62 / 75	62 / 75	61 / 65	
heiQ_Self	Odds-Ratio	1.788	2.204	0.917	2.748	0.837	4
	95% CI	[0.87 ; 3.70]	[1.00 ; 4.85]	[0.39 ; 2.18]	[1.36 ; 5.56]	[0.36; 1.95]	
	N_{U3} / N_{L3}	72 / 52	76 / 60	75 / 59	75 / 59	68 / 55	
heiQ_Coop	Odds-Ratio	1.792	2.498	2.605	9.059	4.219	9
	95% CI	[0.82 ; 3.90]	[1.11 ; 5.60]	[0.98 ; 6.93]	[3.87 ; 21.22]	[1.60 ; 11.11]	
	N_{U3} / N_{L3}	53 / 52	58 / 59	56 / 59	56 / 59	52 / 53	
heiQ_Social	Odds-Ratio	2.780	2.096	5.385	29.597	7.453	13
	95% CI	[1.24 ; 6.22]	[0.94 ; 4.70]	[1.66 ; 17.46]	[10.57 ; 82.86]	[2.32 ; 23.99]	
	N_{U3} / N_{L3}	54 / 49	61 / 55	60 / 54	60 / 54	57 / 50	
heiQ_Emo	Odds-Ratio	0.276	0.212	0.074	0.040	0.266	15
	95% CI	[0.12 ; 0.62]	[0.09 ; 0.49]	[0.02 ; 0.26]	[0.015 ; 0.11]	[0.09 ; 0.80]	
	N_{U3} / N_{L3}	54 / 55	58 / 61	57 / 59	57 / 59	52 / 56	
Obesity	Odds-Ratio	0.907	0.779	1.000	1.043	0.947	
	95% CI	[0.50 ; 1.64]	[0.43 ; 1.42]	[0.48 ; 2.06]	[0.59 ; 1.84]	[0.46 ; 1.97]	
	N_{nad} / N_{ad}	87 / 91	98 / 97	96 / 96	96 / 96	85 / 84	
Smoker	Odds-Ratio	1.992	1.841	1.078	1.108	1.556	
	95% CI	[1.06 ; 3.75]	[0.97 ; 3.51]	[0.50 ; 2.33]	[0.61 ; 2.03]	[0.76 ; 3.17]	
	N_{NS} / N_{S}	86 / 76	95 / 79	94 / 78	94 / 78	98 / 81	
1 – 1.99 / 1 – 0,499	**1 index point**						
2 – 3.99 / 0,5 – 0,251	**2 index points**						
4 – 5.99 / 0,25 – 0,167	**3 index points**						
> 6 / < 0,167	**4 index points**						

The upper third (U3) of respondents in heiQ serves as 0, the lower third (L3) as 1. For endpoints the following binary conditions are used to classify for 1: PRDS > 10, pain-NRS > 3, DLQI >19, HADS > 14, ISI > 14.

Table 4. Patients wishes for the content of an HS-App.

Patient wishes for possible functions in an HS-App	Proportion
Cleansing and skin care (e.g., tips for hair removal, soothe itching, suitable toiletries and soaps) → Cleansing and skin care	47.0%
Wound care and scar care incl. adequate dressings (when to call a doctor?) → Wound care	40.5%
Treatment options (ointments, drugs, surgery, alternative treatments, mode of action and side effects) → Treatment options and disease understanding	35.5%
Trigger factors and preventive measures (e.g., food, smoking, alcohol, supplements, period, stress) → Trigger and risk factors	29.0%
Expert contact (identification, consultation, information) → Expert finder and suggestion	18.0%
Forum for affected persons / exchange of experiences (private chat function) → Mental coping and self-aid groups	17.0%
Everyday tips (e.g., tips for clothing, 'household remedies', sleep improvement, self-care, hot weather and sweating) → Treatment options and disease understanding → Cleansing and skin care	14.5%
Diary (incl. treatments and pictures) → Diary	12.0%
Comorbidities and their effect (e.g., depression or diabetes) → Treatment options and disease understanding	8.0%
Pain management (acute inflammation and chronic pain) → Pain management	7.0%
Explanation of pathogenesis of HS and explanation of lesion types and Hurley stages → Treatment options and disease understanding	7.0%
Communication health insurance and regulatory authorities (apply for reimbursement of new therapies or disability status) → Communication health insurance and regulatory authorities	6.5%
Types of sport (e.g., swimming, yoga) → Treatment options and disease understanding	4.0%
How to talk to family and friends (suggestion for couple therapy and sex-life) → Communication with family and friends	2.5%
Social Interaction with employer and colleagues concerning HS (info sheet on what HS is) → Communication with employer and colleagues	2.0%

heiQ domains	Suggestions derived from patient wishes by the study team (added index*)
heiQ_Const (15 index points)	Stress reduction and personal time-outs spending on things you enjoy (47) Mental coping and self-aid groups (38)
heiQ_Emo (15 index points)	Stress reduction and personal time-outs spending on things you enjoy (47) Mental coping and self-aid groups (38)
heiQ_Activ (13 index points)	Stress reduction and personal time-outs spending on things you enjoy (47) Suggestions for sport (17)
heiQ_Social (13 index points)	Mental coping and self-aid groups (38) Communication with family and friends (13) Communication with employer and colleagues (13)
heiQ_Coop (9 index points)	Treatment options and disease understanding (21) Diary (13) Expert finder and suggestion (9) Communication health insurance and regulatory authorities (9)
heiQ_Skill (8 index points)	Treatment options and disease understanding (21) Cleansing and skin care (12) Wound care (8) Pain management (8)
heiQ_Self (4 index points)	Treatment options and disease understanding (21) Diary (13) Cleansing and skin care (12) Trigger and risk factors (4)
heiQ_Health (4 index points)	Stress reduction and personal time-outs spending on things you enjoy (47) Suggestions for sport (17)

*Sum of all index points of the domains, where the suggestion is associated.

activities or workout plans as a possible method to address patient's needs (Table 4).

4. Discussion

HS is a progressive, life-defining disease that can lead to physical limitations, inability to work, and social isolation. Due to the relatively low awareness and understanding for HS, educational opportunities and support structures for patients are scarce. A recent study by Kirby et al. (13) on the real-world patient journey found that people with HS remain frustrated with their disease management (13).

Our explorative study is the first to evaluate whether relevant target points in self-management-competency of HS-patients could be identified with a validated tool, the heiQ-questionnaire.

The instrument has been successfully used in various studies on dermatological diseases (e.g., psoriasis, atopic dermatitis) to evaluate the self-management-competency of patients as well as the effect of educational programs (14–16).

The results of our explorative study show that there is a clear association of self-management-competency, measured by the heiQ, with overall disease burden; including diseases activity, pain level, mental condition and insomnia. There are other conditions, especially in the oncological field, for which social and psychological support programmes have been established (17). Studies find that this improves the handling and acceptance of the disease by those affected. So far, these structures are often missing in HS, which is clearly reflected in the results of the heiQ, were HS patients score consistently lower in self-management-competency (Table 1).

Patient empowerment embodies the idea of shifting the therapy focus toward a higher patient-autonomy to achieve better disease outcomes. When looking at inflammatory skin diseases like atopic dermatitis and psoriasis, the positive effect of empowering heliotherapy has been shown and psychotherapy in patients has been long recognized as helpful to reduce triggers (18–20).

The odds-ratios between the domains of the heiQ and HS-relevant endpoints shown in Table 3 can be used to identify priorities when creating support structures and educational programs for patients. They can also be used to determine specific target points to positively influence disease activity and burden.

Our results suggest that patients performing in the L3 in the domains heiQ_Const and heiQ_Emo have the highest risk (15 index points) for a high disease impact and thus the implementation of constructive attitudes and suggestions toward approaches in disease management should be aimed for. Considering the gathered patient feedback, this can be achieved by recommending stress reduction and personal time-outs, providing information on mental coping or referral to self-aid groups (Table 4). According to odds-ratios in Table 3 a higher self-management competency in these domains is highly associated with better life quality and less depression and anxiety.

When looking at sleep impairment a positive effect is expected with increased social integration (heiQ_Social) and empowerment of patients to communicate confidently with their caregivers (heiQ_Coop). This could be achieved by providing them with knowledge about treatment options thus increasing their disease understanding. An association between insomnia and poor social integration was also seen in the Covid-19 pandemic (21). Furthermore, physical activity has shown to be of relevant importance to improve sleep quality (22). Vice versa improving sleep quality should also help decrease disease burden.

HS requires a high level of self-management from those affected, however according to our data, this is exactly what most patients struggle with, seemingly thereby influencing their disease outcome. Our ultimate goal for patients should be to help them gain competency by making them experts in their own disease and thus positively influence their daily life. We consider the heiQ a valuable, sensitive tool to detect weaknesses and monitor patients' capabilities.

4.1. Limitations and biases

It must be pointed out that the study-cohort was already under treatment in an outpatient center. So participants were most likely well informed about HS at the time of the survey. This implies that we expect an even more substantial burden of disease and lower self-management-competency in the general HS-population.

Patients collected the PRDA-score based on the validated lesion identification scheme (LISAI). Although it has been shown that patients can correctly classify their lesions in the anatomical region with the help of the LISAI, a validation of the quantitative measurement by patients has not yet been performed (8).

4.2. Outlook

Although the implementation of basic educational programs and support groups seems obvious, our study reveals that the importance for HS-care might be underestimated. Implementing supportive measures like e.g., a specific HS-App designed to analyze specific patient's needs to come up with an individualized plan is one way to improve self-management-competency.

Further studies are needed to evaluate whether individual performance of patients in heiQ domains can be used to give associated suggestions (Table 4) and whether these suggestions eventually lead to improved disease activity and burden.

Authors' contributions

C.M., M.S. drafted the manuscript and designed the figures with K.H. K.H. performed the analysis. PS and SG were involved in planning and supervised the work. All coauthors participated in the study, helped interpreting the results and worked on the manuscript. All authors discussed the results, commented and agreed on the final version of the manuscript.

Ethics statement

The research complied with the guidelines for human studies and was conducted according to the ethical principles of the Declaration of Helsinki and in line with the principles of Good Clinical Practice (ICH-GCP) and was registered at the German Clinical Trials Registry (DRKS00025315) before recruitment of the first patient. The study protocol was approved by the independent ethics committees and informed consent was obtained from each patient before any study specific procedures.

Disclosure statement

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Data availability statement

All data is available from the authors upon reasonable request.

References

1. Zouboulis CC, Bechara FG, Fritz K, et al. [S1 guideline for the treatment of hidradenitis suppurativa/acne inversa * (number ICD-10 L73.2)]. J Dtsch Dermatol Ges. 2012 Oct;10:1–8. doi: 10.1111/j.1610-0387.2012.08006.x.
2. Schultheis M, Staubach P, Nikolakis G, et al. A Centre-based, ambulatory care concept for hidradenitis suppurativa improves disease activity, burden, and patient satisfaction: results from the randomised controlled trial EsmAiL. Br J Dermatol. 2023;189(2):170–179. doi: 10.1093/bjd/ljad135.
3. Hurley H. Dermatologic surgery, principles and practice. Dermatologic surgery, principles and practice. New York: Marcel Dekker; 1989, p. 729–739.
4. Zouboulis CC, Tzellos T, Kyrgidis A; European Hidradenitis Suppurativa Foundation Investigator Group, et al. Development and validation of the international hidradenitis suppurativa severity score system (IHS4), a novel dynamic scoring system to assess HS severity. Br J Dermatol. 2017 Nov;177(5):1401–1409. doi: 10.1111/bjd.15748.
5. Basra MK, Fenech R, Gatt RM, et al. The dermatology life quality index 1994-2007: a comprehensive review of validation data and clinical results. Br J Dermatol. 2008 Nov;159(5): 997–1035.
6. Gulliver W, Zouboulis CC, Prens E, et al. Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the european guidelines for hidradenitis suppurativa. Rev Endocr Metab Disord. 2016 Sep;17(3):343–351. doi: 10.1007/s11154-016-9328-5.
7. Osborne RH, Elsworth GR, Whitfield K. The health education impact questionnaire (heiQ): an outcomes and evaluation measure for patient education and self-management interventions for people with chronic conditions. Patient Educ Couns. 2007 May;66(2):192–201. doi: 10.1016/j.pec.2006.12.002.
8. Schultheis M, Staubach-Renz P, Grabbe S, et al. Can hidradenitis suppurativa patients classify their lesions by means of a digital lesion identification scheme? J Dtsch Dermatol Ges. 2023 Jan;21(1):27–32. doi: 10.1111/ddg.14926.
9. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361–370. doi: 10.1111/j.1600-0447.1983.tb09716.x.
10. Dieck A, Morin C, Backhaus J. A german version of the insomnia severity index: validation and identification of a cut-off to detect insomnia. Somnologie. 2018;22(1):27–35. doi: 10.1007/s11818-017-0147-z.
11. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. J Pain. 2003 Sep;4(7):407–414. doi: 10.1016/s1526-5900(03)00716-8.

12. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale (NJ): Erlbaum Associates; 1988.
13. Kirby JS, Martorell A, Sayed CJ, et al. Understanding the real-world patient journey and unmet needs of people with hidradenitis suppurativa through social media research. Br J Dermatol. 2023 Apr;189(2):228–230. doi: 10.1093/bjd/ljad104.
14. Wahl AK, Langeland E, Larsen MH, et al. Positive changes in self-management and disease severity following climate therapy in people with psoriasis. Acta Derm Venereol. 2015 Mar;95(3):317–321. doi: 10.2340/00015555-1939.
15. Wahl AK, Osborne RH, Langeland E, et al. Making robust decisions about the impact of health education programs: psychometric evaluation of the health education impact questionnaire (heiQ) in diverse patient groups in Norway. Patient Educ Couns. 2016 Oct;99(10):1733–1738. doi: 10.1016/j.pec.2016.05.001.
16. Ammerlaan JW, van Os-Medendorp H, Sont JK, et al. Validation of the dutch version of the health education impact questionnaire (HEIQ) and comparison of the dutch translation with the english, german and french HEIQ. Health Qual Life Outcomes. 2017 Jan 31;15(1):28. doi: 10.1186/s12955-017-0601-4.
17. Bergholdt SH, Hansen DG, Johnsen AT, et al. A NEw MOdel of individualized and patient-centered follow-up for women with gynecological cancer (the NEMO study)-protocol and rationale of a randomized clinical trial. Trials. 2023 Feb 1;24(1):74. doi: 10.1186/s13063-022-07022-0.
18. Cole WC, Roth HL, Sachs LB. Group psychotherapy as an aid in the medical treatment of eczema. J Am Acad Dermatol. 1988 Feb;18(2 Pt 1):286–291. doi: 10.1016/s0190-9622(88)70041-9.
19. Karppinen TT, Ylianttila L, Kautiainen H, et al. Empowering heliotherapy improves clinical outcome and quality of life of psoriasis and atopic dermatitis patients. Acta Derm Venereol. 2015 May;95(5):579–582. doi: 10.2340/00015555-2028.
20. Zhang X-J, Wang A-P, Shi T-y, et al. The psychosocial adaptation of patients with skin disease: a scoping review. BMC Public Health. 2019;19(1):1404. doi: 10.1186/s12889-019-7775-0.
21. Chin BN, Tracy EL, Lehrer HM, et al. Social integration and sleep quality during the COVID-19 pandemic: prospective evidence from a study of retired older adults. Behav Sleep Med. 2022 May-Jun;20(3):337–342. doi: 10.1080/15402002.2021.2021203.
22. Passos GS, Poyares DL, Santana MG, et al. Is exercise an alternative treatment for chronic insomnia? Clinics (Sao Paulo). 2012;67(6):653–660. doi: 10.6061/clinics/2012(06)17.

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Pathobiology of Second-Generation Antihistamines Related to Sleep in Urticaria Patients

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Simple Summary: Sleep is a restorative state that is crucial for all human beings. Sleep is important for many biological processes in the body and has a huge impact on quality of life. According to previous studies, we know that patients with hives report sleep impairments. However, there are no data objectifying the sleep pattern. Guideline-based therapy for hives includes second-generation antihistamines of up to fourfold dosage. It is known that first-generation antihistamines lead to changes in sleep pattern and increased daytime sleepiness. However, the effect of second-generation antihistamines on sleep is not known. This pilot study was conducted to better understand the pathobiology of sleep in patients suffering from hives, who are medicated with high-dosed second-generation antihistamines. As healthy sleep in many dermatologic patients is still an unmet need, it is of utmost importance to raise awareness and eventually include sleep improvement in the therapy of urticaria patients.

Abstract: Background: Standard treatment options for urticaria are second-generation antihistamines; however, their effect on sleep is uncertain. This study measures the influence of different antihistamines on the biologic sleep pattern of urticaria patients and the relevance of sleep in urticaria patients. Methods: Ten patients with chronic spontaneous urticaria (CSU) and uncontrolled symptoms under a single dose of second-generation antihistamines were included. Two nights were monitored: the first night after 5 days on single dosage and the second night after 5 days on fourfold dosage. Patient-rated questionnaires were used and sleep was monitored using polygraphy. Results: The patients' rated daytime sleepiness decreased ($p = 0.0319$), as did their insomnia severity ($p = 0.0349$). The urticaria control (UCT) improved ($p = 0.0007$), as did the quality of life ($p < 0.0001$). There was no significant change of nightly pruritus ($p = 0.1173$), but there was an improvement of daytime pruritus ($p = 0.0120$). A significant increase in rapid eye movement (REM) sleep was seen ($p = 0.0002$) (from a mean of 3.9% to 14.3%). The deep sleep state (N3) also improved (8.7% to 12.3%) ($p = 0.1172$). Conclusion: This study has demonstrated an improvement of the sleep pattern in CSU patients under up-dosed second-generation antihistamines, without increased daytime sleepiness, alongside an improvement of urticaria symptoms and quality of life.

Keywords: sleep; urticaria; antihistamines; quality of life

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1. Introduction

Chronic spontaneous urticaria (CSU) is a common inflammatory dermatological disease with a high burden of disease. Symptoms include hives, pruritus and/or angioedema, resulting in a decrease in quality of life [1].

In previous studies, among others, we were able to show that sleep disturbances in patients with urticaria and atopic dermatitis is an underestimated burden [2–5]. However, there is great need for any data that can objectify sleep patterns in patients with chronic

inflammatory skin diseases and pruritus, such as chronic urticaria. It is known that impaired sleep carries the risk of vascular events, i.e., stroke, coronary artery disease and myocardial infarction, and is also associated with obesity, impotence, and depression [6,7]. To what extent skin diseases have an influence on the sleep quality or vice versa is a matter of debate.

Sleep cycles can be measured with electroencephalography (EEG). It is part of polygraphy, a diagnostic tool that records multiple parameters during sleep [8]. The sleep architecture is characterized by the following stages [9]: non-rapid eye movement (NREM) sleep (which is defined by stages N1, N2 and N3) and rapid eye movement (REM) sleep. The waking stage is defined by high frequency (EEG waves 40–339 Hz), whereas light sleep (N1 and N2) is characterized by theta waves (4–8 Hz). Slow-wave sleep (N3) is characterized by low-frequency waves (0.5–4 Hz) and was found to be important for cognitive performance and memory consolidation [10]. REM sleep is characterized by predominant theta 6–9 Hz and gamma waves (30–300 Hz), with the disappearance of muscle tone and the occurrence of REM muscle twitches [9,11]. REM sleep is also known as the dream state and is crucial for memory consolidation and processing of sensory impressions [11,12]. The average sleep cycle begins with the NREM stage N1, constituting 2–5% of the whole sleep cycle, followed by N2, which constitutes about 45–55%, N3 (SWS), with 10–15%, and then REM, with 20–25% [8,11]. First-generation antihistamines are known to have a sedating effect, as a result of passing the brain–blood barrier and their anticholinergic side effects due to poor H1 receptor selectivity. Yanai et al. claim that the blocking of the H1 receptor by antihistamines is crucial for their sedative effect [13]. There are studies on first-generation antihistamines that show their use is associated with a decrease in REM sleep and REM-sleep latency [14,15]. Furthermore, there was an increase in daytime sleepiness, divided attention and vigilance [13,16]. Second-generation antihistamines have been developed to reduce these side effects [17]. The less sedating effect of second-generation antihistamines is explained by a lower H1-receptor occupancy [13] and a lower concentration in the central nervous system, following an active efflux through a pump in the blood–brain barrier [18]. There are reports based on patient-rated questionnaires [19,20] that show that even second-generation antihistamines, such as rupatadine and cetirizine, especially if up-dosed, lead to daytime sleepiness nonetheless. Second-generation antihistamines, up to fourfold dosage, are the first-line therapy for urticaria [21]. However, there is a lack of objective data showing the influence on the sleep quality under fourfold dosage of second-generation antihistamines in patients with chronic spontaneous urticaria.

2. Materials and Methods

The study protocol was approved by the ethics committee of the state of Rhineland-Palatinate, Germany.

In our pilot study, 10 patients with CSU and uncontrolled symptoms under single doses of different second-generation antihistamines were recruited from October to November, 2020 from the Department of Dermatology at the University Medical Center in Mainz. No comorbidities or intake of comedication were reported. Each patient's previously taken and well-tolerated antihistamine was continued (rupatadine in 7 patients, loratadine in 1 patient, desloratadine in 1 patient and cetirizine in 1 patient).

The patients were asked to fill out the following patient-reported outcomes.

2.1. Subjective Patient-Related Outcomes

Epworth Sleepiness Scale (ESS): Assesses daytime sleepiness. The ESS is an 8-item questionnaire, asking the patient to rate the likelihood of falling asleep during daily activities with low degrees of stimulation. The score ranges from 0 to 24 (with a score from 6 to 10 showing a higher normal daytime sleepiness, and 11 to 12 a mild excessive daytime sleepiness) (minimal clinical important difference (MCID) of 2–3 points) [22].

The Insomnia Severity Index (ISI) is a validated 7-item questionnaire (scoring from 0 to 28) asking patients to rate their current quality of sleep in order to assess the extent

of insomnia. Quality of sleep as well as troubles "falling asleep", "staying asleep" or "waking up too early" are rated by the patient. A score ranging from 8 to 14 would indicate subthreshold insomnia. The German version was validated by Gerber et al. in 2016 [23].

The Dermatological Life Quality Index (DLQI) is a common 10-item questionnaire with a range from 0 to 30 that measures the impact of different kinds of skin diseases on the quality of life during the previous week. A score value $\geq$10 indicates a severe impaired quality of life [24] (MCID of 3.3 points).

The UCT is a score that evaluates disease activity (0–16, with a score value $\geq$12 indicating disease control and a MCID of 3 points) [25]. The UCT score asks for physical symptoms, quality of life, treatment efficacy and urticaria control [5,26].

To score the pruritus severity, a numeric rating scale from 0–10 (NRS) was used for both daytime and nighttime pruritus (1: 0–2.9 = mild, 2: 3–6.9 = moderate, 3: 7–8.9 = severe, 4: 9–10 = very severe pruritus) (MCID of 3 points) [27].

All questionnaires were completed for both nights.

2.2. Objective Diagnostic Outcomes

Sleep was monitored for two nights, using a polygraphic device (Homesleep® by somnomedics), an American Academy of Sleep Medicine (AASM)-certified and criteria-conformant device. The device is able to register 11 signals (3 frontoparietal EEG, 2 EOG, EMG, snoring, light, activity, head position and electrode impedance) [28]. The first evaluation was registered while patients were on a single-dosage of antihistamines and the second on day 6, after 5 days of fourfold dosage. All polygraphic channels were sampled with high- and low-pass filters. To avoid bias, the analysis of the polygraphic recordings was independent and blindly evaluated.

To eliminate the so-called "first night effect", which can occur when patients spend their first night in a sleep laboratory, which potentially leads to restless sleep, the sleep was recorded at home in their usual surroundings [29].

3. Statistics

All data were assessed for normal or non-normal distribution. Differences in disease scores were determined using a paired *t*-test. The level of significance was set at $\alpha = 0.05$. The resulting *p*-values were considered nominally significant at $p \leq 0.05$. Statistical analyses were calculated with GraphPad Prism version 6.

4. Results

In our pilot study, 10 patients (8 female, 2 male) with an average age of 42.7 (SD $\pm$ 13.1) years, and a mean body mass index (BMI) of 26.9 (SD $\pm$ 4.5) were included. Fifty percent of the patients were overweight, and fifty percent had normal weight. Mean disease duration was 2.4 years (Table 1). There were no comorbidities or co-medications registered.

Table 1. Descriptive characteristics (mean $\pm$ SD) of the studied group.

Item	
Sex, n	
total	10
women	8
men	2
Age, years, mean $\pm$ SD	42.7 $\pm$ 13.1
range	27–63
BMI, kg/m^2, mean $\pm$ SD	26.9 $\pm$ 4.5
range	21.8–36.7
urticaria duration, years, mean $\pm$ SD	2.4 $\pm$ 1.7
range	0.5–4

Questionnaires: The ESS score for daytime sleepiness significantly decreased from 11.5 under a single dosage to 9.5 under a fourfold dosage of antihistamines (Figure 1a) ($p = 0.0319$).

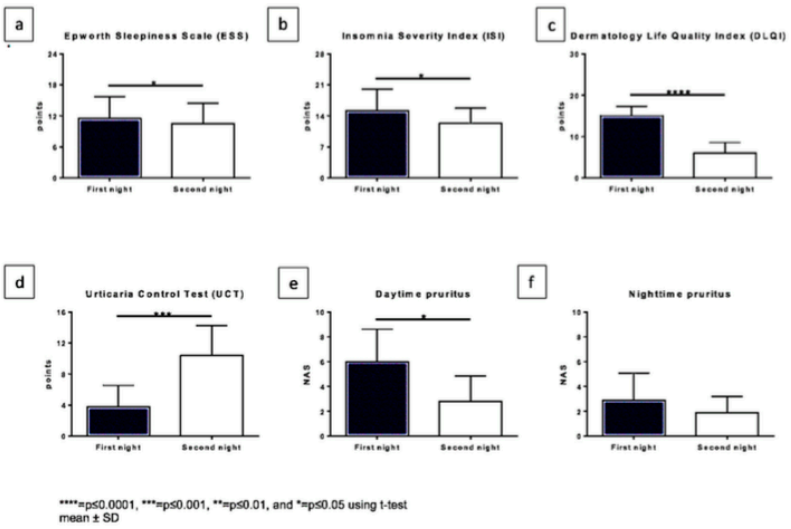

Figure 1. Changes in subjective patient-related outcomes comparing both nights. The x-axis displaying both nights and y-axis the score which was reached for: (**a**). Epworth sleepiness score, (**b**). Insomnia Severity Index (ISI), (**c**). Dermatology Life Quality Index (DLQI), (**d**). Urticaria Control Test (UCT) (a higher score in this case represents better symptom control), (**e**). Daytime pruritus NRS, (**f**). nighttime pruritus NRS.

The ISI score also showed a significant change from 15.2 to 12.3 (8–14 indicating subthreshold insomnia and 15–21 clinical insomnia (moderate severity)) ($p = 0.0349$) (Figure 1b).

The DLQI significantly improved ($p < 0.0001$) (Figure 1c) from a mean value of 15.0 to 6.0 under up-dosed antihistamines.

The UCT significantly increased from a mean of 3.8 to a mean of 10.4 ($p = 0.0007$) after 5 days (Figure 1d).

The pruritus during the night on the NRS changed from a mean value of 2.9 to 1.9 ($p = 0.1173$), whereas the pruritus during the daytime significantly improved from 6.0 under a single dosage to 2.8 under up-dosed antihistamines ($p = 0.0120$) (Figure 1e,f).

5. Polygraphy

Polygraphic results are displayed in Figure 2 and Table S1. The sleep duration showed a mean value of 7 h for all patients. We saw a significant ($p = 0.0002$) increase in REM sleep when comparing the first night under single dosage (mean of 3.9%) to the second night under fourfold dosage (14.3%) (Figure 2a). The deep sleep state (N3) also showed an increase (Figure 2b). There was only a slight difference in the sleep efficacy, (the first night with a mean of 93.1%, to the second night with a mean of 94.2%) (Figure 2c). The sleep latency significantly decreased ($p = 0.0217$) from a mean of 10.7 min on the first night to 5.4 min on the second night (Figure 2d).

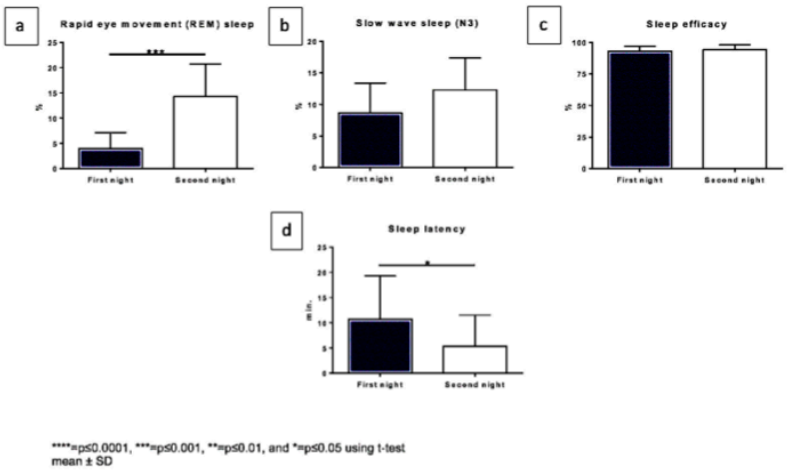

Figure 2. Changes in diagnostic polygraph outcomes comparing both nights. The x-axis displaying both nights, the y-axis: (**a**). REM sleep in % (**b**). Slow wave sleep (N3) in % (**c**). Sleep efficacy in %, (**d**). sleep latency in min.

6. Discussion

Improving sleep in patients with chronic inflammatory and itchy dermatological diseases, such as urticaria, is a highly worthwhile goal [30]. To best of our knowledge, there have been no data qualifying or quantifying sleep in chronic urticaria patients; however, sleep and quality of life are shown to be impaired.

Second-generation antihistamines can be up-dosed for the effective treatment of urticaria without increasing daytime sleepiness. Increasing their daily dosage up to fourfold, if necessary, is the recommended standard therapy for patients with chronic spontaneous urticaria, as per international guidelines [21]. Even at this elevated dosage, we did not notice any increase in daytime sleepiness in this pilot study, as documented with the ESS. In contrast, there was a reduction in the sleepiness score from 11.5 to 9.5, thus meeting the MCID criteria [31]. A reduction in daytime sleepiness might also hint at a more restful sleep.

It should be noted that both examinations were run in one week, and bigger differences could be expected after a longer intake of up-dosed antihistamines. The patients served as their own control group. Five of our ten patients had an elevated BMI; however, in only two of them was snoring recorded, which would make them candidates for obstructive sleep apnea, but this was not the topic of this study. Nonetheless, there was no difference in the sleep quality observed in these patients.

The ISI score showed a significant improvement in sleep quality but was still found to be elevated at 12.3 (8–14 subthreshold insomnia). This subjective rating was not reflected in the sleep architecture, as recorded with the EEG and EOG. However, this was also seen in other studies, who reported that subjective and objective quality of sleep often differ [32]. A potential placebo effect due to an increased number of tablets couldn't be documented in our pilot study, as the ISI did not show a tremendous improvement [33].

In the literature, a first night effect is seen in patients undergoing polysomnograpy in a sleep laboratory, but this effect was not seen on sleep patterns in outpatient polygraphic examinations [34].

We saw that the quality of life (DLQI) improved significantly under up-dosed antihistamines (MCID: −3.3 points) [35]. The patients reporting a more restful sleep underline this.

Up-dosed second-generation antihistamines, especially rupatadine, as it was taken by 7 of 10 patients, led to an increase in REM sleep, deep sleep and sleep efficacy. All those

details signal a more restful sleep. No difference between the various antihistamines was observed in this small cohort. Despite an increase in REM sleep, there was no increase in nightmares reported by the patients. The fact that the sleep latency decreased is a positive sign, as "falling asleep" is one of the main obstacles when it comes to insomnia. On the one hand, this could be due to less urticaria disease activity. On the other hand, there are reports that even second-generation antihistamines, especially in higher doses [36], are able to cross the blood–brain barrier and interact with histamine neurons, which are essential for wakefulness [37].

Pruritus is often considered a main factor in impaired sleep in chronic inflammatory skin diseases [4,30,38,39]. Like in a previous study, the nightly pruritus reported by the patient in this study did not seem to be as severe as the perceived daytime pruritus [5]. The pruritus during daytime was rated as more severe than during the night and showed a significant improvement under up-dosed therapy. This is confirmed by looking at the first question of the DLQI, which asks how much the skin was burning, painful, sore or pruritic in the last days, on a scale from 3 (strong) to 0 (not present), and showed an improvement from a mean of 2.2 to a mean of 0.8. However, it also has to be taken into consideration that the minimal beneficial difference of the pruritus perceived by the patient is dependent on the baseline pruritus.

Thus, a missing statistically significant change in nighttime pruritus could still be of clinical relevance to the patient [27].

It remains speculative whether disease control led to secondary improvement of sleep quality or if it was due to the direct central effect of the up-dosed antihistamines. It would be interesting to see if patients with fully controlled urticaria symptoms under a single-antihistamine dose show the same sleep pattern, which would indicate the latter reason.

In this pilot study, 5 days of up-dosing with second-generation antihistamines in CSU patients led to an improvement of not only indirect but also direct sleep conditions, as documented by questionnaires and by polygraphic measurements. Control of pruritus was seen in some patients; however, as shown before, pruritus did not seem to be the subjectively decisive factor for every patient's sleeping problem [5,40].

In some parts of the world, first-generation antihistamines are still used for the treatment of urticaria; however, this not only forms a potential risk for reduced REM sleep and daytime drowsiness, but also depression and other health problems, if overdosed [41]. Therefore, it is of great importance to advance research on second-generation antihistamines and further elaborate their benefits.

It is known that impaired sleep over time is highly associated with depression [7] and mental disorders, a frequent comorbidity in chronic urticaria patients [42]. Furthermore, quality of life is strongly associated with sleep quality [43]. Improving sleep in patients with urticaria by adequate treatment may have a broader therapeutic benefit and help to prevent further comorbidities. With this pilot study, we wanted to once more highlight the relevance of further studies to prove those findings [44]. Beyond that, investigations of sleep quality should be encouraged in new drug registration studies.

7. Conclusions

This study has demonstrated an improvement in sleep patterns in CSU patients under up-dosed second-generation antihistamines, without increased daytime sleepiness, alongside an improvement in urticaria symptoms and quality of life.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/biology11030433/s1, Table S1: Descriptive characteristics of the sleep and disease parameters comparing both nights.

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References

1. Zuberbier, T.; Abdul Latiff, A.H.; Abuzakouk, M.; Aquilina, S.; Asero, R.; Baker, D.; Ballmer-Weber, B.; Bangert, C.; Ben-Shoshan, M.; Bernstein, J.A.; et al. The international EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy* **2021**, *77*, 734–766. [CrossRef] [PubMed]
2. Jensen, P.; Zachariae, C.; Skov, L.; Zachariae, R. Sleep disturbance in psoriasis: A case-controlled study. *Br. J. Dermatol.* **2018**, *179*, 1376–1384. [CrossRef] [PubMed]
3. Kaaz, K.; Szepietowski, J.C.; Matusiak, L. Influence of Itch and Pain on Sleep Quality in Patients with Hidradenitis Suppurativa. *Acta Derm. Venereol.* **2018**, *98*, 757–761. [CrossRef] [PubMed]
4. Kaaz, K.; Szepietowski, J.C.; Matusiak, L. Influence of Itch and Pain on Sleep Quality in Atopic Dermatitis and Psoriasis. *Acta Derm. Venereol.* **2018**, *99*, 175–180. [CrossRef]
5. Mann, C.; Dreher, M.; Weeß, H.G.; Staubach, P. Sleep Disturbance in Patients with Urticaria and Atopic Dermatitis: An Underestimated Burden. *Acta Derm. Venereol.* **2020**, *100*, adv00073. [CrossRef]
6. Grandner, M.A.; Jackson, N.J.; Pak, V.M.; Gehrman, P.R. Sleep disturbance is associated with cardiovascular and metabolic disorders. *J. Sleep Res.* **2012**, *21*, 427–433. [CrossRef]
7. Murphy, M.J.; Peterson, M.J. Sleep Disturbances in Depression. *Sleep Med. Clin.* **2015**, *10*, 17–23. [CrossRef]
8. Iber, C.A.-I.S.; Chesson, A.L.; Quan, S.F. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications*; American Academy of Sleep Medicine (AASM): Westchester, NY, USA, 2007.
9. Dijk, D.-J.; Landolt, H.-P. Sleep Physiology, Circadian Rhythms, Waking Performance and the Development of Sleep-Wake Therapeutics. In *Sleep-Wake Neurobiology and Pharmacology*; Landolt, H.-P., Dijk, D.-J., Eds.; Springer International Publishing: Cham, Switzerland, 2019; pp. 441–481.
10. Leminen, M.M.; Virkkala, J.; Saure, E.; Paajanen, T.; Zee, P.C.; Santostasi, G.; Hublin, C.; Müller, K.; Porkka-Heiskanen, T.; Huotilainen, M.; et al. Enhanced Memory Consolidation Via Automatic Sound Stimulation During Non-REM Sleep. *Sleep* **2017**, *40*, zsx003. [CrossRef]
11. Institute of Medicine; Board on Health. Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem. In *Institute of Medicine (US) Committee on Sleep Medicine and Research*; National Academies Press (US): Washington, DC, USA, 2006; Volume 2.
12. Boyce, R.; Glasgow, S.D.; Williams, S.; Adamantidis, A. Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. *Science* **2016**, *352*, 812–816. [CrossRef]
13. Yanai, K.; Zhang, D.; Tashiro, M.; Yoshikawa, T.; Naganuma, F.; Harada, R.; Nakamura, T.; Shibuya, K.; Okamura, N. Positron emission tomography evaluation of sedative properties of antihistamines. *Expert Opin. Drug. Saf.* **2011**, *10*, 613–622. [CrossRef]
14. Boyle, J.; Eriksson, M.; Stanley, N.; Fujita, T.; Kumagi, Y. Allergy medication in Japanese volunteers: Treatment effect of single doses on nocturnal sleep architecture and next day residual effects. *Curr. Med. Res. Opin.* **2006**, *22*, 1343–1351. [CrossRef] [PubMed]
15. Unno, K.; Ozaki, T.; Mohammad, S.; Tsuno, S.; Ikeda-Sagara, M.; Honda, K.; Ikeda, M. First and second generation H_1 histamine receptor antagonists produce different sleep-inducing profiles in rats. *Eur. J. Pharmacol.* **2012**, *683*, 179–185. [CrossRef] [PubMed]
16. Saitou, K.; Kaneko, Y.; Sugimoto, Y.; Chen, Z.; Kamei, C. Slow wave sleep-inducing effects of first generation H1-antagonists. *Biol. Pharm. Bull.* **1999**, *22*, 1079–1082. [CrossRef] [PubMed]
17. Yanai, K.; Yoshikawa, T.; Yanai, A.; Nakamura, T.; Iida, T.; Leurs, R.; Tashiro, M. The clinical pharmacology of non-sedating antihistamines. *Pharmacol. Ther.* **2017**, *178*, 148–156. [CrossRef]
18. Hu, Y.; Sieck, D.E.; Hsu, W.H. Why are second-generation H1-antihistamines minimally sedating? *Eur. J. Pharmacol.* **2015**, *765*, 100–106. [CrossRef]
19. Ozdemir, P.G.; Karadag, A.S.; Selvi, Y.; Boysan, M.; Bilgili, S.G.; Aydin, A.; Onder, S. Assessment of the effects of antihistamine drugs on mood, sleep quality, sleepiness, and dream anxiety. *Int. J. Psychiatry Clin. Pract.* **2014**, *18*, 161–168. [CrossRef]
20. Van den Elzen, M.T.; van Os-Medendorp, H.; van den Brink, I.; van den Hurk, K.; Kouznetsova, O.I.; Lokin, A.S.H.J.; Laheij-de Boer, A.-M.; Röckmann, H.; Bruijnzeel-Koomen, C.A.F.M.; Knulst, A.C. Effectiveness and safety of antihistamines up to fourfold or higher in treatment of chronic spontaneous urticaria. *Clin. Transl. Allergy* **2017**, *7*, 4. [CrossRef]

21. Zuberbier, T.; Aberer, W.; Asero, R.; Abdul Latiff, A.H.; Baker, D.; Ballmer-Weber, B.; Bernstein, J.A.; Bindslev-Jensen, C.; Brzoza, Z.; Buense Bedrikow, R.; et al. The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy* **2018**, *73*, 1393–1414. [CrossRef]
22. Johns, M.W. A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep* **1991**, *14*, 540–545. [CrossRef]
23. Gerber, M.; Lang, C.; Lemola, S.; Colledge, F.; Kalak, N.; Holsboer-Trachsler, E.; Puhse, U.; Brand, S. Validation of the German version of the insomnia severity index in adolescents, young adults and adult workers: Results from three cross-sectional studies. *BMC Psychiatry* **2016**, *16*, 174. [CrossRef]
24. Kulthanan, K.; Chiawsirikajorn, Y.; Jiamton, S. Acute urticaria: Etiologies, clinical course and quality of life. *Asian Pac. J. Allergy Immunol.* **2008**, *26*, 1–9. [PubMed]
25. Ohanyan, T.; Schoepke, N.; Bolukbasi, B.; Metz, M.; Hawro, T.; Zuberbier, T.; Peveling-Oberhag, A.; Staubach, P.; Maurer, M.; Weller, K. Responsiveness and minimal important difference of the urticaria control test. *J. Allergy Clin. Immunol.* **2017**, *140*, 1710–1713.e1711. [CrossRef] [PubMed]
26. Hawro, T.; Ohanyan, T.; Schoepke, N.; Metz, M.; Peveling-Oberhag, A.; Staubach, P.; Maurer, M.; Weller, K. The Urticaria Activity Score-Validity, Reliability, and Responsiveness. *J. Allergy Clin. Immunol. Pract.* **2018**, *6*, 1185–1190.e1181. [CrossRef] [PubMed]
27. Riepe, C.; Osada, N.; Reich, A.; Augustin, M.; Zeidler, C.; Ständer, S. Minimal Clinically Important Difference in Chronic Pruritus Appears to be Dependent on Baseline Itch Severity. *Acta Derm. Venereol.* **2019**, *99*, 1288–1290. [CrossRef]
28. Kuula, L.; Pesonen, A.K. Heart Rate Variability and Firstbeat Method for Detecting Sleep Stages in Healthy Young Adults: Feasibility Study. *JMIR Mhealth Uhealth* **2021**, *9*, e24704. [CrossRef]
29. Byun, J.H.; Kim, K.T.; Moon, H.J.; Motamedi, G.K.; Cho, Y.W. The first night effect during polysomnography, and patients' estimates of sleep quality. *Psychiatry Res.* **2019**, *274*, 27–29. [CrossRef]
30. Gwillim, E.C.; Janmohamed, S.R.; Yousaf, M.; Patel, K.R.; Silverberg, J.I. The impact of prurigo nodularis on sleep disturbance and related impact: A systematic review. *J. Eur. Acad. Dermatol. Venereol.* **2020**, *34*, e815–e817. [CrossRef]
31. Patel, S.; Kon, S.S.C.; Nolan, C.M.; Barker, R.E.; Simonds, A.K.; Morrell, M.J.; Man, W.D. The Epworth Sleepiness Scale: Minimum Clinically Important Difference in Obstructive Sleep Apnea. *Am. J. Respir. Crit. Care Med.* **2018**, *197*, 961–963. [CrossRef]
32. Landry, G.; Best, J.; Liu-Ambrose, T. Measuring sleep quality in older adults: A comparison using subjective and objective methods. *Front. Aging Neurosci.* **2015**, *7*, 166. [CrossRef]
33. Rogev, E.; Pillar, G. Placebo for a single night improves sleep in patients with objective insomnia. *Isr. Med. Assoc. J.* **2013**, *15*, 434–438.
34. Gupta, R. Gibt es einen First Night Effect bei ambulanter Polysomnographie?: Eine Untersuchung an fünfundzwanzig schlafgesunden Probanden. Doctoral Thesis, TU Aachen, Aachen, Germany, 2005.
35. Basra, M.K.; Salek, M.S.; Camilleri, L.; Sturkey, R.; Finlay, A.Y. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): Further data. *Dermatology* **2015**, *230*, 27–33. [CrossRef] [PubMed]
36. Holgate, S.T.; Canonica, G.W.; Simons, F.E.; Taglialatela, M.; Tharp, M.; Timmerman, H.; Yanai, K. Consensus Group on New-Generation Antihistamines (CONGA): Present status and recommendations. *Clin. Exp. Allergy* **2003**, *33*, 1305–1324. [CrossRef]
37. Yu, X.; Franks, N.P.; Wisden, W. Sleep and Sedative States Induced by Targeting the Histamine and Noradrenergic Systems. *Front. Neural. Circuits* **2018**, *12*, 4. [CrossRef] [PubMed]
38. Gupta, M.A.; Simpson, F.C.; Gupta, A.K. Psoriasis and sleep disorders: A systematic review. *Sleep Med. Rev.* **2016**, *29*, 63–75. [CrossRef] [PubMed]
39. Misery, L.; Morisset, S.; Seite, S.; Brenaut, E.; Ficheux, A.S.; Fluhr, J.W.; Delvigne, V.; Taieb, C. Relationship between sensitive skin and sleep disorders, fatigue, dust, sweating, food, tobacco consumption or female hormonal changes: Results from a worldwide survey of 10,743 individuals. *J. Eur. Acad. Dermatol. Venereol.* **2021**, *35*, 1371–1376. [CrossRef] [PubMed]
40. Hawro, T.; Przybyłowicz, K.; Spindler, M.; Hawro, M.; Steć, M.; Altrichter, S.; Weller, K.; Magerl, M.; Reidel, U.; Alarbeed, E.; et al. The characteristics and impact of pruritus in adult dermatology patients: A prospective, cross-sectional study. *J. Am. Acad. Dermatol.* **2021**, *84*, 691–700. [CrossRef] [PubMed]
41. Church, M.K.; Maurer, M.; Simons, F.E.; Bindslev-Jensen, C.; van Cauwenberge, P.; Bousquet, J.; Holgate, S.T.; Zuberbier, T. Risk of first-generation H(1)-antihistamines: A GA(2)LEN position paper. *Allergy* **2010**, *65*, 459–466. [CrossRef]
42. Staubach, P.; Dechene, M.; Metz, M.; Magerl, M.; Siebenhaar, F.; Weller, K.; Zezula, P.; Eckhardt-Henn, A.; Maurer, M. High prevalence of mental disorders and emotional distress in patients with chronic spontaneous urticaria. *Acta Derm. Venereol.* **2011**, *91*, 557–561. [CrossRef]
43. Reimer, M.A.; Flemons, W.W. Quality of life in sleep disorders. *Sleep Med. Rev.* **2003**, *7*, 335–349. [CrossRef]
44. Weller, K.; Giménez-Arnau, A.; Grattan, C.; Asero, R.; Mathelier-Fusade, P.; Bizjak, M.; Hanna, M.; Maurer, M. The Chronic Urticaria Registry: Rationale, methods and initial implementation. *J. Eur. Acad. Dermatol. Venereol.* **2020**, *35*, 721–729. [CrossRef]

Abkürzungsverzeichnis

AD	Atopische Dermatitis
AHI	Apnoe/Hypopnoe Index
CU	Chronische Urtikaria
DLQI	Dermatologischer Lebensqualitäts Index
EASI	Eczema Area and Severity Index
ESS	Epworth Sleepiness Scale
heiQ	Health Education Impact Questionnaire
ISI	Insomnia Severity Index
MCID	Minimal Clinically Important Difference
NRS	Numerische Rating Skala
N3	Tiefschlaf-Phase
PASI	Psoriasis Area and Severity Index
PRO	Patient-rated Outcome
REM	Rapid-Eye Movement Phase
TIB	Time in Bed
TST	Total Sleep Time
UCT	Urticaria Control Test
UAS7	Urticaria Aktivitäts-Score 7 Tage

Literaturverzeichnis

1. Mrowietz U, Lauffer F, Sondermann W, Gerdes S, Sewerin P. Psoriasis as a Systemic Disease. Dtsch Arztebl Int. 2024(Forthcoming).

2. Ujiie H, Rosmarin D, Schön MP, Ständer S, Boch K, Metz M, et al. Unmet Medical Needs in Chronic, Non-communicable Inflammatory Skin Diseases. Front Med (Lausanne). 2022;9:875492.

3. Brunner PM, Suárez-Fariñas M, He H, Malik K, Wen HC, Gonzalez J, et al. The atopic dermatitis blood signature is characterized by increases in inflammatory and cardiovascular risk proteins. Sci Rep. 2017;7(1):8707.

4. von Stebut E, Reich K, Thaçi D, Koenig W, Pinter A, Körber A, et al. Impact of Secukinumab on Endothelial Dysfunction and Other Cardiovascular Disease Parameters in Psoriasis Patients over 52 Weeks. J Invest Dermatol. 2019;139(5):1054-62.

5. Gelfand JM, Shin DB, Alavi A, Torigian DA, Werner T, Papadopoulos M, et al. A Phase IV, Randomized, Double-Blind, Placebo-Controlled Crossover Study of the Effects of Ustekinumab on Vascular Inflammation in Psoriasis (the VIP-U Trial). J Invest Dermatol. 2020;140(1):85-93.e2.

6. Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CE, Nast A, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Arch Dermatol Res. 2011;303(1):1-10.

7. S3 Leitlinie Therapie der Psoriasis vulgaris [Internet]. Deutsche Dermatologische Gesellschaft 2021 [cited 29.12.2021]. Available from: https://www.awmf.org/uploads/tx_szleitlinien/013-001l_S3_Therapie-Psoriasis-vulgaris_2021-07.pdf.

8. Leshem YA, Hajar T, Hanifin JM, Simpson EL. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. Br J Dermatol. 2015;172(5):1353-7.

9. Prens LM, Rondags A, Volkering RJ, Janse IC, Politiek K, Zuidema YS, et al. The refined Hurley classification: the inter-rater and intrarater reliability and face validity. Br J Dermatol. 2019;181(6):1335-7.

10. Spertini F, Ballmer-Weber B, Bircher A, Ferrari G, Grabbe J, Hausmann O, et al. Urtikariamanagement in der Grundversorgung. Swiss Medical Forum – Schweizerisches Medizin-Forum. 2017;17.

11. Weller K, Groffik A, Church MK, Hawro T, Krause K, Metz M, et al. Development and validation of the Urticaria Control Test: a patient-reported outcome instrument for assessing urticaria control. The Journal of allergy and clinical immunology. 2014;133(5):1365-72, 72.e1-6.

12. Mann C, Wegner J, Weeß H-G, Staubach P. Pathobiology of Second-Generation Antihistamines Related to Sleep in Urticaria Patients. Biology. 2022;11(3):433.

13. Riepe C, Osada N, Reich A, Augustin M, Zeidler C, Ständer S. Minimal clinically important difference in chronic pruritus appears to be dependent on baseline itch severity. Acta Dermato-Venereologica. 2019;99(13):1288-90.

14. Yosipovitch G, Reaney M, Mastey V, Eckert L, Abbé A, Nelson L, et al. Peak Pruritus Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. Br J Dermatol. 2019;181(4):761-9.

15. Hinz A, Schwarz R, Herrmann C, Buss U, Snaith R. Hospital Anxiety and Depression Scale - Deutsche Version(HADS-D). Diagnostica. 2002;48:112-3.

16. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210-6.

17. Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? J Invest Dermatol. 2005;125(4):659-64.

18. Krause K, Kessler B, Weller K, Veidt J, Chen SC, Martus P, et al. German version of ItchyQoL: validation and initial clinical findings. Acta Derm Venereol. 2013;93(5):562-8.

19. Kirchhof R, Schuler M, Musekamp G, Nolte S, Osborne R, ehlebracht-koenig I, et al. Erfassung und Bewertung der Wirksamkeit von Patientenschulungen bei chronischen Erkrankungen: Übersetzung und Evaluation des Health Education Impact Questionnaire (heiQ) in Deutschland2009.

20. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2001;2(4):297-307.

21. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-5.

22. Jessica Beach SC. ItchyQol: A Pruritus-Specific Quality of Life Instrument [Listing]. Emory University Office of Technology Transfer Emory University 2009 [cited 2021 12.12.2021]. TechID 06082]. Available from: https://emoryott.technologypublisher.com/techcase/06082.

23. Love EM, Marrazzo GA, Kini S, Veledar E, Chen SC. ItchyQoL bands: pilot clinical interpretation of scores. Acta Derm Venereol. 2015;95(1):114-5.

24. Armstrong AW, Soong W, Bernstein JA. Chronic Spontaneous Urticaria: How to Measure It and the Need to Define Treatment Success. Dermatol Ther (Heidelb). 2023;13(8):1629-46.

25. Patel AK, Reddy V, Shumway KR, Araujo JF. Physiology, Sleep Stages. StatPearls. Treasure Island (FL): StatPearls Publishing
Copyright © 2023, StatPearls Publishing LLC.; 2023.

26. Boyce R, Glasgow SD, Williams S, Adamantidis A. Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. Science. 2016;352(6287):812-6.

27. Leminen MM, Virkkala J, Saure E, Paajanen T, Zee PC, Santostasi G, et al. Enhanced Memory Consolidation Via Automatic Sound Stimulation During Non-REM Sleep. Sleep. 2017;40(3).

28. Mann C, Dreher M, Rothschmidt JN, Staubach P. Burden of impaired sleep and its improvement through topical treatment in psoriasis and atopic dermatitis. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG. 2024;22(5):655-63.

29. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. Physiol Rev. 2010;90(1):47-112.

30. Desjardins S, Lapierre S, Hudon C, Desgagné A. Factors involved in sleep efficiency: a population-based study of community-dwelling elderly persons. Sleep. 2019;42(5).

31. Feinberg I, Floyd TC. Systematic trends across the night in human sleep cycles. Psychophysiology. 1979;16(3):283-91.

32. Staubach P, Bilo B, Fluhr JW, Krause K, Kulthanan K, Salman A, et al. UCOMB-real life data: treatment strategies for chronic urticaria patients with comorbidities. J Dermatolog Treat. 2024;35(1):2329784.

33. Mann C, Dreher M, Weeß HG, Staubach P. Sleep Disturbance in Patients with Urticaria and Atopic Dermatitis: An Underestimated Burden. Acta Derm Venereol. 2020;100(6):adv00073.

34. Mann C, Staubach P, Grabbe S, Wegner J, Hennig K, Nikolakis G, et al. Self-management-competency as a new target in Hidradenitis suppurativa care. J Dermatolog Treat. 2023;34(1):2245082.

35. Mann C, Wegner J, Weeß HG, Staubach P. Pathobiology of Second-Generation Antihistamines Related to Sleep in Urticaria Patients. Biology (Basel). 2022;11(3).

36. Ishikawa O, Oks M. Central Sleep Apnea. Clin Geriatr Med. 2021;37(3):469-81.

37. Emami E, Heydecke G, Rompré PH, de Grandmont P, Feine JS. Impact of implant support for mandibular dentures on satisfaction, oral and general health-related quality of life: a meta-analysis of randomized-controlled trials. Clin Oral Implants Res. 2009;20(6):533-44.

38. Kim J, Tran K, Seal K, Fernanda A, Glenda R, Messier R, et al. CADTH Optimal Use Reports. Interventions for the Treatment of Obstructive Sleep Apnea in Adults: A Health Technology Assessment. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health
Copyright © 2017 Canadian Agency for Drugs and Technologies in Health.; 2017.

39. Staubach P, Mann C, Hagenström K, Augustin M. [Care and medical costs of urticaria in children in Germany : Drugs, medical and inpatient services]. Dermatologie (Heidelb). 2024;75(7):554-61.

40. Weller K, Maurer M, Bauer A, Wedi B, Wagner N, Schliemann S, et al. Epidemiology, comorbidities, and healthcare utilization of patients with chronic urticaria in Germany. J Eur Acad Dermatol Venereol. 2022;36(1):91-9.

41. Papapostolou N, Xepapadaki P, Katoulis A, Makris M. Comorbidities of Chronic Urticaria: A glimpse into a complex relationship. Front Allergy. 2022;3:1008145.

42. Schoepke N, Asero R, Ellrich A, Ferrer M, Gimenez-Arnau A, C EHG, et al. Biomarkers and clinical characteristics of autoimmune chronic spontaneous urticaria: Results of the PURIST Study. Allergy. 2019;74(12):2427-36.

43. Su H, Kolkhir P, Scheffel J, Xiang YK, Yao X, Maurer M, et al. One in five patients with chronic spontaneous urticaria has IgE to tissue transglutaminase 2. Allergy. 2023;78(9):2537-9.

44. Boehncke WH. Systemic Inflammation and Cardiovascular Comorbidity in Psoriasis Patients: Causes and Consequences. Front Immunol. 2018;9:579.

45. Zafiriou E, Daponte AI, Siokas V, Tsigalou C, Dardiotis E, Bogdanos DP. Depression and Obesity in Patients With Psoriasis and Psoriatic Arthritis: Is IL-17-Mediated Immune Dysregulation the Connecting Link? Front Immunol. 2021;12:699848.

46. Esposito M, Amicucci G, Salfi F, Pellegrini C, De Berardinis A, Chiricozzi A, et al. Exploring the interplay of atopic dermatitis severity with sleep and mental health: a case-control study in adult patients. Postgrad Med. 2024:1-8.

47. Nutt D, Wilson S, Paterson L. Sleep disorders as core symptoms of depression. Dialogues Clin Neurosci. 2008;10(3):329-36.

48. Teichgräber F, Jacob L, Koyanagi A, Shin JI, Seiringer P, Kostev K. Association between skin disorders and depression in children and adolescents: A retrospective case-control study. Journal of Affective Disorders. 2021;282:939-44.

49. LEWIS-JONES MS, FINLAY AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. British Journal of Dermatology. 1995;132(6):942-9.

50. Weisshaar E, Kupfer JP, Bentz P, Staubach-Renz P, Legat F, Kremer AE, et al. Validation of the German Pruritus Questionnaire for the systematic assessment of chronic pruritus. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG. 2024;22(7):956-63.

51. Baiardini I, Pasquali M, Braido F, Fumagalli F, Guerra L, Compalati E, et al. A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-QoL). Allergy. 2005;60(8):1073-8.

52. Morin CM, Jarrin DC. Epidemiology of Insomnia: Prevalence, Course, Risk Factors, and Public Health Burden. Sleep Med Clin. 2022;17(2):173-91.

53. Mann C, Gorai S, Staubach-Renz P, Goldust M. Sleep disorders in dermatology - a comprehensive review. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG. 2023.

54. Caldarola G, De Luca E, Barini A, Basile U, Carnazzo V, Chiricozzi A, et al. Evaluation of the Impact of Night Shift Work on Disease Severity in Psoriatic Patients: A Case-Control Study with Clinical, Hormonal, and Immunological Evaluation. Dermatology. 2024;240(4):665-70.

55. Pace-Schott EF, Germain A, Milad MR. Sleep and REM sleep disturbance in the pathophysiology of PTSD: the role of extinction memory. Biol Mood Anxiety Disord. 2015;5:3.

56. Diekelmann S, Born J. The memory function of sleep. Nat Rev Neurosci. 2010;11(2):114-26.

57. Boyle J, Eriksson M, Stanley N, Fujita T, Kumagi Y. Allergy medication in Japanese volunteers: treatment effect of single doses on nocturnal sleep architecture and next day residual effects. Curr Med Res Opin. 2006;22(7):1343-51.

58. Unno K, Ozaki T, Mohammad S, Tsuno S, Ikeda-Sagara M, Honda K, et al. First and second generation H_1 histamine receptor antagonists produce different sleep-inducing profiles in rats. Eur J Pharmacol. 2012;683(1-3):179-85.

59. Del Brutto OH, Mera RM, Rumbea DA, Sedler MJ, Castillo PR. Poor sleep quality increases mortality risk: A population-based longitudinal prospective study in community-dwelling middle-aged and older adults. Sleep Health: Journal of the National Sleep Foundation. 2024;10(1):144-8.

60. Silverberg JI, Garg NK, Paller AS, Fishbein AB, Zee PC. Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study. J Invest Dermatol. 2015;135(1):56-66.

61. Irwin MR, Olmstead R, Carroll JE. Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. Biol Psychiatry. 2016;80(1):40-52.

62. Teramoto S, Yamamoto H, Yamaguchi Y, Namba R, Ouchi Y. Obstructive Sleep Apnea Causes Systemic Inflammation and Metabolic Syndrome. CHEST. 2005;127(3):1074-5.

63. Maniaci A, Iannella G, Cocuzza S, Vicini C, Magliulo G, Ferlito S, et al. Oxidative Stress and Inflammation Biomarker Expression in Obstructive Sleep Apnea Patients. J Clin Med. 2021;10(2).

64. Tien KJ, Chou CW, Lee SY, Yeh NC, Yang CY, Yen FC, et al. Obstructive sleep apnea and the risk of atopic dermatitis: a population-based case control study. PloS one. 2014;9(2):e89656.

65. Soundararajan V, Lor J, Fishbein AB. Sleep Apnea and Skin. Curr Sleep Med Rep. 2020;6(3):94-100.

66. Shalom G, Dreiher J, Cohen A. Psoriasis and obstructive sleep apnea. Int J Dermatol. 2016;55(11):e579-e84.

67. Liu X, Ma Y, Ouyang R, Zeng Z, Zhan Z, Lu H, et al. The relationship between inflammation and neurocognitive dysfunction in obstructive sleep apnea syndrome. J Neuroinflammation. 2020;17(1):229.

68. Unnikrishnan D, Jun J, Polotsky V. Inflammation in sleep apnea: an update. Rev Endocr Metab Disord. 2015;16(1):25-34.

69. Bringsvor HB, Langeland E, Oftedal BF, Skaug K, Assmus J, Bentsen SB. Self-management and health related quality of life in persons with chronic obstructive pulmonary disease. Qual Life Res. 2019;28(11):2889-99.

70. Bukvić Mokos Z, Miše J, Balić A, Marinović B. Understanding the Relationship Between Smoking and Hidradenitis Suppurativa. Acta Dermatovenerol Croat. 2020;28(1):9-13.

71. Barbarot S, Aubert H, Vibet MA, Leray M, Foureau A, Elan F, et al. Effectiveness of a nurse-led one-to-one education programme in addition to standard care in children with atopic dermatitis: a multicentre randomized control trial. Br J Dermatol. 2024;191(2):177-86.

72. Karppinen TT, Ylianttila L, Kautiainen H, Reunala T, Snellman E. Empowering heliotherapy improves clinical outcome and quality of life of psoriasis and atopic dermatitis patients. Acta Derm Venereol. 2015;95(5):579-82.

73. Zvulunov A, Lenevich S, Migacheva N. A Mobile Health App for Facilitating Disease Management in Children With Atopic Dermatitis: Feasibility and Impact Study. JMIR Dermatol. 2023;6:e49278.

74. Boucher A, Peters M, Jones GB. How Digital Solutions Might Provide a World of New Opportunities for Holistic and Empathic Support of Patients with Hidradenitis Suppurativa. Dermatol Ther (Heidelb). 2024.

75. Tahseen D, Nambudiri VE. Prescription digital therapeutics in dermatology. Journal of the American Academy of Dermatology. 2022;86(1):193-4.

76. Lavery MJ, Stull C, Kinney MO, Yosipovitch G. Nocturnal Pruritus: The Battle for a Peaceful Night's Sleep. Int J Mol Sci. 2016;17(3):425.

77. Bender BG, Ballard R, Canono B, Murphy JR, Leung DY. Disease severity, scratching, and sleep quality in patients with atopic dermatitis. J Am Acad Dermatol. 2008;58(3):415-20.

78. Elewski B, Alexis AF, Lebwohl M, Stein Gold L, Pariser D, Del Rosso J, et al. Itch: an under-recognized problem in psoriasis. Journal of the European Academy of Dermatology and Venereology. 2019;33(8):1465-76.

79. Kay DB, Buysse DJ, Germain A, Hall M, Monk TH. Subjective-objective sleep discrepancy among older adults: associations with insomnia diagnosis and insomnia treatment. J Sleep Res. 2015;24(1):32-9.

80. Murray CS, Rees JL. Are subjective accounts of itch to be relied on? The lack of relation between visual analogue itch scores and actigraphic measures of scratch. Acta Derm Venereol. 2011;91(1):18-23.

81. Reuveni H, Chapnick G, Tal A, Tarasiuk A. Sleep fragmentation in children with atopic dermatitis. Arch Pediatr Adolesc Med. 1999;153(3):249-53.

82. McCall WV, Blocker JN, D'Agostino R, Jr., Kimball J, Boggs N, Lasater B, et al. Insomnia severity is an indicator of suicidal ideation during a depression clinical trial. Sleep Med. 2010;11(9):822-7.

83. Barnes A, Andrews JM, Mukherjee S, Bryant RV, Bampton P, Fraser RJ, et al. Insomnia is common in inflammatory bowel disease (IBD) and is associated with mental health conditions as well as IBD activity. Intest Res. 2024;22(1):104-14.

84. Yang AF, Chun KS, Yu L, Walter JR, Kim D, Lee JY, et al. Validation of a hand-mounted wearable sensor for scratching movements in adults with atopic dermatitis. Journal of the American Academy of Dermatology. 2023;88(3):726-9.

85. de Sena S, Häggman M, Ranta J, Roienko O, Ilén E, Acosta N, et al. NAPping PAnts (NAPPA): An open wearable solution for monitoring Infant's sleeping rhythms, respiration and posture. Heliyon. 2024;10(13):e33295.

86. Iwanaszko M, Waldeck N, Anafi R, Paller AS, Zee PC, Fishbein AB. Circadian Rhythms in Skin Barrier Function in Atopic Dermatitis: A Pilot Study. Journal of Biological Rhythms. 2024;39(2):208-14.

87. Sivakumar AD, Sharma R, Thota C, Ding D, Fan X. WASP: Wearable Analytical Skin Probe for Dynamic Monitoring of Transepidermal Water Loss. ACS Sens. 2023;8(11):4407-16.

88. Hasselberg MJ, McMahon J, Parker K. The validity, reliability, and utility of the iButton® for measurement of body temperature circadian rhythms in sleep/wake research. Sleep Medicine. 2013;14(1):5-11.

89. Hirotsu C, Tufik S, Andersen ML. Interactions between sleep, stress, and metabolism: From physiological to pathological conditions. Sleep Sci. 2015;8(3):143-52.

90. D'Agostino M, Feo F, Martora F, Genco L, Megna M, Cacciapuoti S, et al. ChatGPT and dermatology. Ital J Dermatol Venerol. 2024.

91. Augustin M, Mayer A, Goepel LM, Baade K, Heyer K, Herberger K. Cumulative Life Course Impairment (CLCI): A new concept to characterize persistent patient burden in chronic wounds. Wound Medicine. 2013;1:2-6.