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# Patogeneza i obraz kliniczny świądu w różnych postaciach łuszczycy

**Rozprawa doktorska w dziedzinie nauk medycznych i nauk o zdrowiu, w dyscyplinie nauki medyczne**

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*Składam serdeczne podziękowania Promotorowi pracy*
*Panu prof. dr hab. n. med. Adamowi Reichowi*
*za wskazanie drogi zawodowej, wszelką pomoc oraz przekazaną wiedzę.*

*Szczególe podziękowania kieruję również do moich najbliższych,*
*którzy nieustannie mnie wspierają.*

## Spis treści

## Rozdział 1. Wykaz publikacji stanowiących rozprawę doktorską

**Prace przeglądowe:**

1. Jaworecka K, Muda-Urban J, Rzepko M, Reich A. Molecular Aspects of Pruritus Pathogenesis in Psoriasis. *Int J Mol Sci.* 2021;22(2):858.

**Prace oryginalne:**

1. Jaworecka K, Kwiatkowska D, Marek L, Tamer F, Stefaniak A, Szczegielniak M, Chojnacka-Purpurowicz J, Matławska M, Gulekon A, Szepietowski JC, Narbutt J, Owczarczyk-Saczonek A, Reich A. Characteristics of Pruritus in Various Clinical Variants of Psoriasis: Results of the Multinational, Multicenter, Cross-Sectional Study. *Life (Basel).* 2021;11(7):623.

2. Jaworecka K, Rzepko M, Marek-Józefowicz L, Tamer F, Stefaniak AA, Szczegielniak M, Chojnacka-Purpurowicz J, Gulekon A, Szepietowski JC, Narbutt J, Owczarczyk-Saczonek A, Reich A. The Impact of Pruritus on the Quality of Life and Sleep Disturbances in Patients Suffering from Different Clinical Variants of Psoriasis. *J Clin Med.* 2022;11(19):5553.

3. Jaworecka K, Kwiatkowska D, Marek L, Tamer F, Stefaniak A, Szczegielniak M, Chojnacka-Purpurowicz J, Gulekon A, Szepietowski JC, Narbutt J, Owczarczyk-Saczonek A, Reich A. Characteristics of pruritus in various clinical variants of psoriasis: Final report of the binational, multicenter, cross-sectional study. *J Eur Acad Dermatol Venereol*. 2023;37(4):787-795.

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## Rozdział 2. Zestawienie publikacji doktoranta (z wyłączeniem prac będących częścią rozprawy doktorskiej)

1. Żychowska M, Jaworecka K, Mazur E, Słomka K, Marszałek W, Rzepko M, Czarny W, Reich A. COVID-19 and Postural Control-A Stabilographic Study Using Rambling-Trembling Decomposition Method. *Medicina (Kaunas).* 2022;58(2), 305.
2. Żychowska M, Muda-Urban J, Jaworecka K, Kaznowska E, Reich A. Multiple Keratoacanthoma Centrifugum Marginatum in a Patient with Primary Myelofibrosis: A Case Report with Dermoscopic Findings. *Acta Derm Venereol.* 2021;101(10).
3. Sawińska E, Szczęch JM, Jaworecka K, Reich A. Choroby wysypkowe u dzieci. Część II - osutki krostkowe. *Standardy Medyczne Pediatria.* 2020;17(2).
4. Jaworecka K, Szczęch JM, Sawińska E, Samotij D, Reich A. Choroby wysypkowe u dzieci. Część III - osutki grudkowe i rumieniowo-grudkowe. *Standardy Medyczne Pediatria*. 2020;17(3):312-325.
5. Jaworecka K, Kijowski R, Ostańska E, Mazur-Chromiak P, Reich A. Pierwotna amyloidoza skórna - opis przypadku. *Forum Dermatologicum.* 2020;6(3):126-129.
6. Szczęch JM, Samotij D, Jaworecka K, Tobiasz A, Reich A. Quality of Life in Patients with Morphea : A Cross-Sectional Study and a Review of the Current Literature. *Biomed Res Int.* 2020;2020:9186274.
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8. Jaworecka K, Pojawa-Gołąb M, Otto-Buczkowska E, Reich A. Injection Site Reaction during Liraglutide Therapy. *J Dermatol Plast Surg.* 2019;3(1):1023.
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10. Żuk G, Jaworecka K, Samotij D, Ostańska E, Reich A. Rheumatoid neutrophilic dermatitis. *Reumatologia*. 2019;57(6):350-353.

11. Jaworecka K, Samotij D, Reich A. Trądzikopodobna osutka u chorego leczonego cetuksymabem z powodu raka jelita grubego. *Forum Dermatologicum.* 2018;4(2):78-80.
12. Wyglądacz D, Głowaczewska A, Jaworecka K, Pięt M, Reich A. Analiza przypadków kiły wśród chorych hospitalizowanych w Klinice Dermatologii, Wenerologii
i Alergologii we Wrocławiu w latach 2009-2016. *Forum Dermatologicum*. 2017;3(4):143-146.
13. Ligęza M, Wyglądacz D, Tobiasz A, Jaworecka K, Reich A. Natural cold pressed oils as cosmetic products. *Family Medicine & Primary Care Review*. 2016;18(4):443–447.
14. Ligęza M, Wyglądacz D, Tobiasz A, Jaworecka K, Franiczek R, Krzyżanowska B, Aniołowska M, Reich A. Ocena składu i czystości mikrobiologicznej olejów zimnotłoczonych firmy OleoWita. *Forum Dermatologicum.* 2016;2(2):85-89.
15. Ligęza M, Wyglądacz D, Tobiasz A, Jaworecka K, Reich A. Ocena skuteczności kremu pielęgnacyjnego zawierającego kwas azelainowy i laktobionowy u chorych z trądzikiem. *Dermatologia Praktyczna*. 2015;7(6):57-62.

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| | Liczba | Impact Factor | Punktacja MNiSW |
|---|---|---|---|
| Prace włączone do rozprawy doktorskiej | **4** | **24.217** | **490** |
| Prace, które nie zostały włączone do rozprawy doktorskiej | **15** | **12.995** | **480** |
| Razem | | **37.212** | **970** |

## Rozdział 3. Wykaz stosowanych skrótów

BSA – wskaźnik procentowy zajętej powierzchni ciała (ang. *body surface area*)

DLQI – wskaźnik jakości życia (ang. *dermatology life quality index*)

GPPSI – wskaźnik rozległości i nasilenia łuszczycy krostkowej uogólnionej (ang. *general pustular psoriasis severity index*)

IL – interleukina (ang. *interleukin*)

NGF – czynnik wzrostu nerwów (ang. *nerve growth factor*)

PASI – wskaźnik rozległości i nasilenia łuszczycy (ang. *psoriasis area and severity index*)

PPSI – wskaźnik rozległości i nasilenia łuszczycy krostkowej dłoni i stóp (ang. *palmoplantar pustulosis severity index*)

VEGF – czynnik wzrostu śródbłonka naczyniowego (ang. *vascular endotelial growth factor*)

10-PSS – 10-punktowy kwestionariusz nasilenia świądu (ang. *10-item pruritus severity scale*)

# Rozdział 4. Wstęp

Łuszczyca jest przewlekłą, zapalną chorobą skóry dotyczącą ponad 100 mln ludzi na całym świecie [1]. Charakteryzuje się wzmożoną proliferacją keratynocytów i licznymi zaburzeniami immunologicznymi, a swój udział w patogenezie mają również czynniki genetyczne i środowiskowe [2]. Klasycznie łuszczyca manifestuje się obecnością symetrycznych, dobrze odgraniczonych blaszek, pokrytych srebrzysto-szarymi łuskami. Jednak poza opisaną powyżej postacią plackowatą łuszczycy, istnieje szereg innych podtypów choroby, o nieco odmiennym fenotypie, wśród których można wymienić łuszczycę pieniążkowatą i grudkową, różniące się przede wszystkim wielkością pojedynczych wykwitów łuszczycowych, czy też erytrodermiczną, zajmującą z definicji ponad 90% powierzchni skóry [3]. Z uwagi na szczególną lokalizację zmian skórnych oraz predylekcję do zajmowania określonych jej obszarów wymienić można także łuszczycę skóry owłosionej głowy, łuszczycę dłoni i podeszew oraz łuszczycę odwróconą, inaczej zwaną łuszczycą wyprzeniową. Kolejne odmiany charakteryzują się obecnością sterylnych krost na rumieniowym podłożu, a ich dystrybucja determinuje odmianę krostkową uogólnioną lub łuszczycę krostkową dłoni i podeszew.

Niezależnie od rodzaju analizowanej dermatozy, zmianom skórnym bardzo często towarzyszą objawy subiektywne, które mogą powodować u chorych znaczny dyskomfort i wpływać na ich codzienne funkcjonowanie. Jednym z najczęściej zgłaszanych objawów subiektywnych, towarzyszących łuszczycy, jest świąd skóry. Niestety, niejednokrotnie zdarza się, że jest on bagatelizowany przez lekarzy, bądź też leczony nieskutecznie. Mimo bardzo licznych badań, nadal istnieje wiele niepewności dotyczących świądu w łuszczycy, które przekładają się na niepowodzenia terapeutyczne, skutkujące frustracją pacjentów, których jakość życia jest znacznie obniżona z uwagi na odczuwany świąd. Zaburzenia snu, pojawiające się u chorych, u których świąd występuje wieczorami i w nocy skutkują natomiast zmęczeniem, sennością, trudnościami w koncentracji i problemami w nawiązywaniu kontaktów międzyludzkich.

W przeszłości uważano, że łuszczyca nie swędzi. Stanowisko to zaczęło się zmieniać w latach osiemdziesiątych ubiegłego stulecia, jednak wówczas rozpatrywano świąd jako sporadyczny objaw, towarzyszący tylko części pacjentów chorujących na

łuszczycę. W chwili obecnej dysponujemy wynikami wielu niezależnych badań, z których jednoznacznie wynika, że świąd jest częstym, nierzadko najbardziej problematycznym objawem łuszczycy, dotyczącym 70-93% chorych [4-10]. Możliwość kontrolowania świądu łuszczycowego jest istotna, ponieważ zapobiega powstawaniu nowych zmian skórnych w mechanizmie objawu Koebnera, a ponadto zdecydowanie poprawia komfort życia pacjentów.

Mimo postępu, jaki dokonał się w ostatnim czasie w zakresie wiedzy na temat patogenezy łuszczycy, wciąż dysponujemy niewielką ilością danych dotyczących podłoża molekularnego świądu towarzyszącego tej jednostce chorobowej. Ograniczona jest także nasza wiedza na temat czynników wpływających na nasilenie świądu oraz wstępowanie objawów mu towarzyszących. W pracy przeglądowej wchodzącej w skład rozprawy doktorskiej dokonano systematycznego przeglądu piśmiennictwa na temat czynników mogących determinować na poziomie molekularnym występowanie świądu w łuszczycy [11]. Lepsze poznanie mechanizmów leżących u jego podłoża ma szansę przyczynić się do odkrycia bezpieczniejszych, a przede wszystkim bardziej skutecznych leków przeciwświądowych.

Analizując aktualne piśmiennictwo poświęcone tematyce świądu łuszczycowego spostrzeżono, że dotychczas przeprowadzonych zostało niewiele badań podejmujących zagadnienie świądu w różnych postaciach klinicznych łuszczycy, a te, których wyniki opublikowano, odnosiły się w większości do najczęściej występującej łuszczycy plackowatej. Brak jest wyników rzetelnych badań oceniających nasilenie, lokalizację oraz częstotliwość świądu, a także współwystępowanie objawów subiektywnych i czynników modyfikujących świąd w kontekście określonych odmian klinicznych łuszczycy. Z klinicznego punktu widzenia jest to istotne zagadnienie, ponieważ umożliwia lepsze poznanie świądu, jak również pozwoli na skuteczniejsze kontrolowanie tego objawu.

Świadomość społeczna na temat chorób skóry jest wciąż niewielka, dlatego chorzy są często stygmatyzowani. Rola lekarza prowadzącego terapię pacjenta z łuszczycą nie ogranicza się zatem do leczenia objawów przedmiotowych, ale konieczne jest także kontrolowanie objawów podmiotowych. Chorzy, u których udało się zredukować ilość zmian skórnych oraz odczuwane dolegliwości, mają szansę

skoncentrować się na innych aspektach życia niż choroba, a co za tym idzie prawidłowo funkcjonować w społeczeństwie.

W codziennej praktyce klinicznej, podczas oceny pacjenta z łuszczycą należy pamiętać o konieczności zwrócenia uwagi na obecność objawów subiektywnych towarzyszących tej jednostce chorobowej, w szczególności świądu.

## Rozdział 5. Cele pracy

1. Analiza czynników molekularnych biorących udział w patogenezie świądu w łuszczycy w oparciu o przegląd piśmiennictwa.
2. Ocena częstości występowania świądu w różnych postaciach łuszczycy.
3. Charakterystyka i porównanie świądu w różnych odmianach klinicznych łuszczycy na podstawie wieloośrodkowego badania przeprowadzonego na grupie 295 chorych.
4. Ocena wpływu świądu na jakość życia i zaburzenia snu u pacjentów cierpiących na łuszczycę oraz porównanie tych zależności w odniesieniu do poszczególnych podtypów klinicznych łuszczycy.

## Rozdział 6. Materiał i metody

Niniejsza rozprawa doktorska została przygotowana w oparciu o cykl czterech powiązanych tematycznie publikacji pełnotekstowych poświęconych problematyce świądu w łuszczycy ze szczególnym uwzględnieniem różnic w jego nasileniu i percepcji pomiędzy poszczególnymi wariantami klinicznymi tej jednostki chorobowej.

W pracy przeglądowej pt. "*Molecular Aspects of Pruritus Pathogenesis in Psoriasis*" dokonano przeglądu piśmiennictwa celem usystematyzowania dotychczasowej wiedzy na temat czynników molekularnych biorących udział w patogenezie świądu w łuszczycy [11]. W tym celu przeszukano bazy danych PubMed, Mendeley i Science Direct uzyskując ponad 10 tys. rekordów zawierających słowa kluczowe, którymi były kombinacje terminów łuszczyca i łuszczyca krostkowa oraz świąd. Z analizy wykluczono prace nie na temat, artykuły napisane w języku innym niż angielski, badania przeprowadzane na modelach zwierzęcych oraz opisy przypadków i doniesienia zjazdowe. Finalnie wyodrębniono 13 oryginalnych prac, w których opublikowano wyniki badań nad czynnikami mogącymi mieć istotny wpływ na powstawanie świądu łuszczycowego oraz usystematyzowano ich najważniejsze rezultaty.

Pierwszym etapem pracy badawczej było stworzenie autorskiego kwestionariusza, zawierającego dane demograficzne, podstawowe parametry antropometryczne, pytania dotyczące współchorobowości i aktualnie stosowanego leczenia oraz zagadnienia odnoszące się do obecności i charakterystyki świądu. Załączniki do ankiety stanowiły skale oceniające nasilenie zmian skórnych tj. PASI, BSA, GPPSI, PPSI, skala oceniająca jakość życia - DLQI oraz 10-punktowy kwestionariusz nasilenia świądu - 10-PSS. Następnie przeprowadzono przekrojowe, prospektywne badanie ankietowe na pacjentach w wieku powyżej 16 lat, z rozpoznaną na podstawie charakterystycznego obrazu klinicznego bądź, w wątpliwych przypadkach, potwierdzoną histologicznie łuszczycą. Kryteria wyłączenia obejmowały aktualne bądź niedawno zakończone systemowe (<4 tyg.) lub miejscowe (<2 tyg.) leczenie łuszczycy, obecność innego schorzenia mogącego modyfikować odczuwanie świądu, a także stosowanie leków mających potencjalny wpływ na świąd. W zależności od dominującego rodzaju zmian skórnych i/lub ich lokalizacji wyodrębniono dziewięć klinicznych podtypów łuszczycy: łuszczyca plackowata wielkoogniskowa, łuszczyca pieniążkowata,

łuszczyca grudkowa, łuszczyca owłosionej skóry głowy, łuszczyca zwyczajna dłoni i podeszew, łuszczyca wyprzeniowa (odwrócona), łuszczyca erytrodermiczna, łuszczyca krostkowa uogólniona i łuszczyca krostkowa dłoni i podeszew. Badanie zostało zaprojektowane, a także zainicjowane przez zespół Kliniki Dermatologii w Rzeszowie, natomiast dane zbierane były we współpracy z Klinicznymi Ośrodkami Dermatologii mieszczącymi się w Bydgoszczy, Łodzi, Olsztynie, Wrocławiu i Ankarze. Koordynatorem całego projektu była Klinika Dermatologii w Rzeszowie, która następnie podjęła się analizy zebranych danych oraz przygotowała wszystkie trzy publikacje.

Dokumenty dotyczące opisanego badania nieinterwencyjnego zostały przedłożone Komisji Bioetycznej przy Okręgowej Izbie Lekarskiej w Rzeszowie, która poinformowała, że eksperyment ten nie wymaga formalnej zgody Komisji Bioetycznej. Ponadto wszyscy uczestnicy badania wyrazili pisemną świadomą zgodę na udział w nim.

Zebrane dane zostały poddane analizie statystycznej przy użyciu oprogramowania Statistica® 13.0 (Statsoft, Kraków). Obliczono średnie, odchylenia standardowe (SD), mediany i częstotliwości. Różnice pomiędzy osiągniętymi wynikami zostały przeanalizowane przy pomocy testu t Studenta, testu U Manna-Whitneya lub analizy wariancji powtarzalnych pomiarów dla rang Friedmana (ANOVA). W celu weryfikacji uzyskanych zależności wyliczono współczynnik korelacji rang Spearmana, natomiast aby określić, czy istnieje istotna różnica między częstościami oczekiwanymi i obserwowanymi w jednej lub większej liczbie kategorii, zastosowano test $X^2$. Wartości p mniejsze niż 0,05 uznano za istotne.

W pracach oryginalnych pt. „*Characteristics of Pruritus in Various Clinical Variants of Psoriasis: Results of the Multinational, Multicenter, Cross-Sectional Study*" i „*Characteristics of pruritus in various clinical variants of psoriasis: final report of the binational, multicenter, cross-sectional study*" przedstawiono porównanie pod względem klinicznego obrazu świądu, wyróżnionych na podstawie fenotypu, dziewięciu podtypów łuszczycy [9,10]. Skupiono się w nich na ocenie nasilenia, lokalizacji oraz częstotliwości świądu, a także współwystępowaniu objawów subiektywnych, sposobie określania świądu przez pacjentów i czynnikach go modyfikujących. W publikacji pt. „*Characteristics of Pruritus in Various Clinical Variants of Psoriasis: Results of the Multinational, Multicenter, Cross-Sectional Study*" przedstawiono wstępne wyniki badania, analizując ankiety zebrane od 212 chorych [9]. Natomiast praca

pt. „*Characteristics of pruritus in various clinical variants of psoriasis: final report of the binational, multicenter, cross-sectional study*" stanowiła analizę danych zebranych od 295 pacjentów, odnoszących się do różnic i podobieństw w nasileniu, częstotliwości, lokalizacji oraz subiektywnych odczuciach dotyczących świądu w poszczególnych klinicznych wariantach łuszczycy [10]. W grupie 295 badanych znalazło się: 45 osób z łuszczycą plackowatą wielkoogniskową, 32 z łuszczycą pieniążkowatą, 31 z łuszczycą grudkową, 32 z łuszczycą owłosionej skóry głowy, 33 z łuszczycą zwyczajną dłoni i podeszew, 23 z łuszczycą wyprzeniową (odwróconą), 33 z łuszczycą erytrodermiczną, 23 z łuszczycą krostkową uogólnioną i 42 z łuszczycą krostkową dłoni i podeszew [10,12]. Tę samą grupę chorych opisano w artykule pt. „*The Impact of Pruritus on the Quality of Life and Sleep Disturbances in Patients Suffering from Different Clinical Variants of Psoriasis*" zwracając szczególną uwagę na jakość życia i zaburzenia snu u tych pacjentów. Dodatkowo zwrócono uwagę na różnice między tymi parametrami w zależności od klinicznego podtypu łuszczycy, a także poddano analizie czynniki mogące na nie wpływać, między innymi świąd [12].

## Rozdział 7. Wyniki

Na podstawie analizy wyników badań dostępnych w bazach danych PubMed, Mendeley i Science Direct wyróżniono kilka czynników molekularnych biorących udział w patogenezie świądu łuszczycowego. Należą do nich histamina, substancja P i inne neuropeptydy, czynnik wzrostu nerwów (NGF), naczyniowo-śródbłonkowy czynnik wzrostu (VEGF), interleukiny (IL-2, IL-4, IL-31), endogenne opioidy i ich receptory oraz lipokalina-2. Istotne znaczenie mają również zaburzenia w unerwieniu i unaczynieniu skóry pacjentów z łuszczycą. Stwierdzono, że patogeneza świądu łuszczycowego jest niezwykle złożona i nie do końca poznana. Z uwagi na to, iż dotychczas nie udało się wyróżnić kluczowego mediatora świądu w tej jednostce chorobowej, nadal trudne jest dobranie odpowiedniej i skutecznej farmakoterapii.

Zarówno wstępne, jak i końcowe wyniki naszego wieloośrodkowego, prospektywnego badania potwierdziły, iż niezależnie od podtypu klinicznego łuszczycy świąd jest bardzo częstym jej objawem, raportowanym przez 86,1% – 100% pacjentów. Co więcej, zdecydowana większość z nich odczuwała go codziennie lub kilka razy w tygodniu. Dominujący rodzaj zmian skórnych nie wpływał jednak na jego nasilenie. Intensywność świądu nie była również związana z wiekiem pacjentów, ani z czasem, jaki upłynął od zachorowania. Świąd dotyczył głównie obszarów skóry zajętych przez wykwity łuszczycowe, a jedyną populacją wyróżniającą się w tym aspekcie byli chorzy w erytrodermii, którzy najczęściej raportowali świąd całego ciała.

Analizując zależność pomiędzy nasileniem zmian skórnych a intensywnością odczuwanego świądu, okazało się, iż w przypadku chorych cierpiących z powodu łuszczycy zwykłej wielkoogniskowej, grudkowej, wyprzeniowej i erytrodermicznej większe nasilenie zmian skórnych nie korelowało z bardziej intensywnym świądem. W pozostałych podtypach zależność ta była obserwowana.

Przeprowadzone badanie wykazało, iż odczucie świądu jest indywidualne i trudno jest je jednoznacznie scharakteryzować, nawet w przypadku tej samej odmiany klinicznej łuszczycy. Niemniej jednak, w każdej z badanych populacji, świąd był najczęściej określany jako piekący, szczypiący i mrowiący. Ponadto, chorzy ze zmianami dominującymi w obrębie rąk i stóp, bez względu na to czy były to klasyczne zmiany

grudkowo-złuszczające, czy zmiany krostkowe, spójnie określali świąd jako głęboki, kłujący, a nawet bolesny.

Jakość życia zdecydowanej większości badanych była obniżona. Wykazano, iż spośród czynników ją determinujących wymienić należy nasilenie zmian skórnych, obecność, rozległość oraz intensywność świądu, a także występowanie zaburzeń snu. Potwierdzono, że z uwagi na częste nasilenie świądu wieczorami i w nocy, nierzadko, bo u 50-66% osób, powodował on trudności z zasypianiem lub wybudzenia nocy [5,12-15]. Problemy ze snem były istotnie większe u pacjentów odczuwających bardziej intensywny świąd, ale u większości badanych nie były one na tyle znaczące, żeby skutkować potrzebą przyjmowania leków nasennych. U ponad 60% chorych, łuszczyca wywierała bardzo duży, a nawet ekstremalnie duży wpływ na jakość życia. Porównując analizowane podtypy kliniczne stwierdzono, iż populacja chorych cierpiący na odmianę erytrodermiczną charakteryzowała się istotnie wyższymi wynikami wskaźnika DLQI, a co za tym idzie bardziej obniżoną jakością życia niż pozostałe podtypy łuszczycy. Jednakże w tym przypadku, tak samo jak w podtypie łuszczycy grudkowej, nasilenie świądu nie było kluczowym czynnikiem determinującym jakość życia. Największy wpływ nasilenia świądu na jakość życia odnotowano u pacjentów w podgrupie łuszczycy skóry owłosionej głowy i łuszczycy krostkowej dłoni i podeszew. Nie obserwowano istotnych różnic w zaburzeniach snu pomiędzy pacjentami cierpiącymi na różne warianty kliniczne łuszczycy.

## Rozdział 8. Wnioski

1. W patogenezie świądu łuszczycowego istotną rolę odgrywają liczne czynniki molekularne oraz złożone interakcje pomiędzy układem nerwowym, neuroendokrynnym, immunologicznym i naczyniowym.
2. Świąd jest bardzo częstym objawem subiektywnym podawanym przez większość pacjentów chorujących na łuszczycę.
3. Odczucie świądu u chorych cierpiących z powodu łuszczycy jest indywidualne, przez co trudno w jednoznaczny sposób je scharakteryzować.
4. Świąd jest czynnikiem, który w istotny sposób obniża jakość życia oraz powoduje zaburzenia snu u pacjentów chorujących na łuszczycę.

## Rozdział 9. Kopie publikacji wchodzących w skład rozprawy doktorskiej

International Journal of
*Molecular Sciences*

MDPI

*Review*

# Molecular Aspects of Pruritus Pathogenesis in Psoriasis

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**Abstract:** Psoriasis is a chronic, systemic inflammatory disease with a genetic background that involves almost 3% of the general population worldwide. Approximately, 70–90% of patients with psoriasis suffer from pruritus, an unpleasant sensation that provokes a desire to scratch. Despite the enormous progress in understanding the mechanisms that cause psoriasis, the pathogenesis of psoriasis-related pruritus still remains unclear. In order to improve patients' quality of life, development of more effective and safer antipruritic therapies is necessary. In turn to make it possible, better understanding of complexed and multifactorial pathogenesis of this symptom is needed. In this article we have systematized the current knowledge about pruritus origin in psoriasis.

**Keywords:** psoriasis; palmoplantar pustulosis; pruritus; itch; itching



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## 1. Introduction

Psoriasis is a chronic, inflammatory, immune-mediated skin and joint disease with genetic background, affecting even 3% of general population. The most characteristic skin lesion of psoriasis is erythematosus plaque covered with silvery scales. Approximately 70–90% of patients with psoriasis suffer from pruritus, an unpleasant sensation that provokes a desire to scratch [1]. Due to the systemic inflammation that characterizes psoriasis, several comorbidities have been recently linked with this disease and they may also contribute to triggering, maintaining or even worsening of the psoriasis-related pruritus. The subjective and multidimensional nature of this symptom renders it challenging for clinicians and researchers to measure it appropriately and to provide optimal therapy. However, it is important to be able to control pruritus in psoriasis to prevent Koebner phenomenon (i.e., development of new psoriatic lesions due to minor trauma to apparently healthy skin) [2] and worsening of skin lesions as well as to improve patients' quality of life. Remarkably, itching is often considered by patients as the most troublesome and unpleasant symptom of psoriasis. Pruritus in subjects with psoriasis most often appears at night and in the evening, but less frequently in the morning or around noon. According to various studies, pruritus causes difficulty in falling asleep in approximately 50–66% of patients [1,3–5]. Approximately 70% of patients experience itching at the sites of the lesions, in the remaining 30% it also affects unchanged skin [1,3]. More than 70% of patients experience itching on a daily basis [1,3]. The most important factors that exacerbate itching in psoriasis patients are dry skin and emotional stress, but other factors also may play a significant role [4,6]. In order to develop more effective and safer antipruritic therapies, better understanding of complexed and multifactorial pathogenesis of pruritus in psoriasis is needed. In this article we have systematized the current knowledge about pruritus origin in psoriasis.

## 2. Data Sources and Study Selection

This review was conducted using a systematic electronic literature search of the PUBMED, Mendeley and Science Direct databases. Index words included combinations

of terms: "psoriasis" or "palmoplantar pustulosis" coupled with "pruritus", "itch" or "itching". All articles published until 1 December 2020 were taken into consideration. Our search yielded a total of 1308 results while browsing PUBMED, 2398 results containing the mentioned keywords while searching the Mendeley database and 10,808 results while browsing Science Direct. All results were checked for relevance. First, duplications and articles published in languages other than English were excluded ($n$ = 9870). In the next step, non-human studies, non-clinical trials and off-topic publications were eliminated ($n$ = 159). Finally, review articles, case reports, conference abstracts were excluded ($n$ = 69). Ultimately, 13 research articles, focused on the pathogenesis of pruritus were included in this review (Table 1).

**Table 1.** Studies on mechanisms of pruritus in psoriasis (↓—decreased, ↑—increased, ↔—the same, BDNF—brain-derived neurotrophic factor, CGRP—calcitonin-gene related peptide, ELAM-1—endothelial leukocyte adhesion molecule 1, ICAM-1—intercellular adhesion molecule 1, INF—interferon, IL—interleukin, KOR—κ-opioid receptor, LCN2—lipocalin 2, MOR—μ-opioid receptor, NEP—neutral endopeptidase, NGF—nerve growth factor, NK-1R–neurokinin-1 receptor, NK-2R—neurokinin-2 receptor, NKA—neurokinin A, NPY—neuropeptide Y, NT-3—neurotrophin 3, OPRK1—opioid receptor kappa 1, OPRM1—opioid receptor mu 1, PECAM-1—platelet endothelial cell adhesion molecule-1, p75NTR—p75 neurotrophin receptor, PACAP—pituitary adenylate cyclase-activating peptide, PGP 9.5—protein gene product 9.5, PMN—polymorphonuclear leukocytes, Sema3A—semaphorin 3A, SOM—somatostatin, SP—substance P, TNF-α—tumor necrosis factor α, TRPM8—transient receptor potential melastatin 8, TRPV—transient receptor potential vanilloid, Trk A—tropomyosin-related kinase A, VCAM-1—vascular cell adhesion molecule 1, VIP–vasoactive intestinal peptide, VPACR–vasoactive intestinal peptide receptor).

| Study | Number of Included Patients | What Was Evaluated? | Major Findings |
| --- | --- | --- | --- |
| Nakamura M et al., 2003 [7] | Psoriasis: $n$ = 38 (23 with pruritus and 15 without pruritus) | Number of mast cells, Langerhans cells, macrophages, as well as expression of PGP 9.5, SP, CGRP, VIP, SOM, NPY, NGF, NGF-receptor (Trk A), BDNF, NT-3, NEP, angiotensin-converting enzyme, INF-γ, TNF-α, IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, PMN, PECAM-1, ICAM-1, ELAM-1, VCAM-1 in pruritic vs. non-pruritic psoriatic skin | ↑ mast cells in the dermis of pruritic vs. non-pruritic psoriatic skin<br>↑ NGF-immunoreactive keratynocytes,<br>↑ expression of Trk A in the epidermis and dermal nerve fibres, ↑ PGP 9.5-immunoreactive nerve fibers in the epidermis and in the upper dermal areas,<br>↑ SP-containing nerves in the perivascular areas of pruritic in comparison to non-pruritic psoriatic skin<br>↑ IL-2-immunoreactive cells in pruritic vs. non-pruritic psoriatic skin<br>↑ ELAM-1-positive venules in pruritic compared to non-pruritic psoriatic skin<br>↓ expression of NEP in the epidermal basal layer and in the endotelia of blood vessels in pruritic vs. non-pruritic samples<br>↔ expression of CGRP, SOM<br>↔ INF-γ, TNF-α, IL-1α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 expression in the epidermis and infiltrating mononuclear cells<br>↔ ICAM-1 and VCAM-1-immunoreactive vessels in the upper dermis and ICAM-1-positive vessels in the epidermis of pruritic and non-pruritic psoriatic skin |
| Wisnicka B et al., 2004 [8] | Psoriasis: $n$ = 59 (43 with pruritus and 16 without pruritus)<br>Healthy controls: $n$ = 32 | Plasma level of histamine, SP, CGRP | ↑ CGRP plasma levels in pruritic psoriatic patients vs. healthy controls<br>↔ histamine and SP plasma concentration in all the group<br>No correlations between CGRP, histamine or SP levels and pruritus intensity |
| Chang SE et al., 2007 [9] | Psoriasis: $n$ = 20 (10 with pruritus and 10 without pruritus)<br>Healthy controls: $n$ = 10 | Expression of NGF, TrkA, p75NTR, NT4, CGRP, CGRP receptor, SP, NK-1R, VIP, PACAP, VPACR, NEP, PGP 9.5, collagen VII in lesional pruritic psoriatic skin vs. non-pruritic psoriatic skin, non-lesional psoriatic pruritic skin and healthy skin | ↑ expression of SP receptors, TrkA and CGRP receptors in keratynocytes and number of dermal nerves in pruritic compared with non-pruritic lesional psoriatic skin<br>↔ expression of assessed neuropeptides and NEP between the pruritus and non-pruritus groups |

**Table 1.** *Cont.*

| Study | Number of Included Patients | What Was Evaluated? | Major Findings |
|---|---|---|---|
| Reich A et al., 2007 [10] | Psoriasis: *n* = 59 (43 with pruritus, 16 without pruritus) Healthy controls: *n* = 32 | Plasma concentration of SP, CGRP, VIP and NPY | ↓ NPY plasma levels in patients with pruritus vs. without pruritus ↔ SP, CGRP and VIP plasma concentration in pruritic and non-pruritic psoriatic patients Negative correlation between pruritus intensity and SP or VIP plasma levels No correlation between pruritus intensity and CGRP or NPY plasma levels |
| Remröd C et al., 2007 [11] | Psoriasis: *n* = 13 | Expression of SP and the NK-1R in involved and noninvolved psoriatic skin | No correlation between SP-positive nerve fibers nor SP-positive cells and the level of pruritus |
| Amatya B et al., 2010 [12] | Psoriasis: *n*=15 (with pruritus) Healthy controls: *n* = 15 | Pruritus, flare and wheal after injection of SP, saline and histamine | SP induced pruritus, flare and wheal in both psoriasis patients and healthy controls (no significant differences between studied groups) |
| Amatya B et al., 2011 [13] | Psoriasis: *n* = 28 Healthy controls: *n* = 10 | Expression of SP, NKA, NK-1R and NK-2R in lesional, non-lesional and healthy skin | Positive correlation between the pruritus intensity and the number of SP-positive nerve fibers and number of NK-2R-immunoreactive cells in the lesional skin |
| Taneda K et al., 2011. [14] | Psoriasis: *n* = 24 Healthy controls: *n* = 5 | Number of epidermal nerve fibers, the levels of Sema3A and the expression patterns of μ- and κ-opioid systems in pruritic and non-pruritic psoriatic skin and healthy skin | ↔ expression of μ-opioid receptor and expression levels of β-endorphin in the epidermis of all analyzed groups ↓ expression of κ -opioid receptor in psoriatic pruritic skin compared to healthy skin ↓ dynorphin-A levels in the epidermis of pruritic psoriatic patients compared with healthy controls |
| Kupczyk P et al., 2017. [15] | Psoriasis: *n* = 20 Healthy controls: *n* = 20 | Opioid receptor genes (OPRM1, OPRK1) and protein (MOR, KOR) expression in lesional and non-lesional psoriatic skin and healthy control | ↓ expression of KOR in lesional psoriatic skin with itch in comparison with lesional skin without itch ↔ OPRK1 expression in groups with and without pruritus ↔ expression of OPRM1/MOR system in groups with or without pruritusNegative correlation between OPRK1/KOR pathway and intensity of pruritus. No correlation between the OPRM1/MOR expression and severity of pruritus |
| Peres LP et al., 2018 [16] | Psoriasis: *n* = 29 | Number of mast cells in the dermis of lesional-skin | No correlation between the intensity of pruritus and mast cell count |
| Nattkemper LA et al., 2018 [17] | Psoriasis: *n* = 25 Atopic dermatitis: *n* = 25 Healthy controls: *n* = 39 | Genetic expression profiles | ↑ expression of genes for IL-17A, IL-23A, and IL-31, phospholipase A2 IVD, SP, voltage-gated sodium channel 1.7, TRPV1, TRPM8, TRPV3, phospholipase C, IL-36α/γ in pruritic psoriatic skin vs. healthy controls Overexpression of phospholipase A2 IVD, SP, voltage-gated sodium channel 1.7 and TRPV1 genes in itchy skin were positively correlated with pruritus intensity |
| Aizawa *n* et al., 2019 [18] | Psoriasis: *n* = 59 Atopic dermatitis: *n* = 47 Healthy controls: *n* = 47 | LCN2 serum concentrations | ↑ LCN2 plasma concentration correlated positively with itch intensity in psoriatic patients |
| Bodoor K et al., 2020. [19] | Psoriasis: *n* = 59 Atopic dermatitis: *n* = 56 Healthy controls: *n* = 49 | Serum levels of IL-4, IL-13, IL-31, IL-33 | The levels of measured interleukins in psoriasis did not correlate with itch severity |

## 3. Results

### *3.1. Histamine and Mast Cells*

Data on histamine in psoriasis, one of the best-known pruritic mediator, remain controversial. Many investigators and experts share the opinion that histamine is not involved in pruritus associated with psoriasis. In line with this suggestion, no correlation between itch intensity and the histamine plasma level was found, and no difference in

histamine plasma levels were observed between pruritic and non-pruritic patients with psoriasis [8]. Moreover, studies which measured the number of cutaneous mast cells, the major histamine producers in the human body, have shown inconsistent results while comparing pruritic vs. non-pruritic psoriasis patients [7]. In the beginning of the 21st century, Japanese scientists, as the first in the world, performed a study documenting itch-related local markers in psoriasis by assessing the number of various dermal cell types and also performing histological and immunohistochemical analysis of the skin biopsy specimens obtained from 38 patients with psoriasis vulgaris. For the purposes of the study, patients were split into two groups based on the presence or absence of pruritus. In pruritic psoriatic skin in comparison to non-itchy skin, an increased number of mast cells was observed, and these cells showed signs of increased activity [7]. Contrary to these observations, Peres et al. did not observe any significant relationship between the number of dermal mast cells and the level of itch reported by patients [16]. However, it has to be mentioned that majority of study participants were on topical and/or systemic treatment, which might have influenced the results and should be considered as a limitation of the study [16]. The use of certain psoriasis medications, such as glucocorticosteroids, cyclosporine A or acitretin, may reduce the mast cell count [20]. Interestingly, other authors, similarly to Nakamura et al., also found increased mast cell count in psoriatic skin [21]. Furthermore, Petersen et al. observed that these mast cells are hyperactivated in active psoriasis [22]. It is thus possible that histamine can be overproduced locally in the dermis and the histamine plasma level does not necessarily reflect its content in the skin.

Despite lack of well-designed controlled studies that would confirm the effectiveness of antihistamines in psoriatic pruritus, some physicians use them to relieve itch in psoriatic patients. Authors such as Prignano et al. [23], Amatya et al. [24] or Yosipowitch et al. [25] based on their questionnaire studies, noticed some antipruritic effect of antihistamines in psoriatic patients, but each time they only paid attention to the short effectiveness of these drugs. In 2017 Domagala et al. published results of a double-blinded, randomized and placebo-controlled study evaluating the efficacy of clemastine—first generation histamine-1 receptor (H1R) antagonist, or levocetirizine—second generation H1R antagonist, in reducing pruritus in psoriasis as an addition to the standard psoriasis treatment. They found significantly higher decrease in mean visual analogue scale (VAS) scoring for the worst pruritus as well as significant reduction in the mean scoring of 12-Item Pruritus Severity Scale in clemastine and levocetirizine groups when compared to placebo. Despite favorable findings, this study had also major limitations such as a short follow-up period and the small number of observed patients ($n$ = 61) [26]. However, similar results on the effectiveness of levocetirizine was described by Mueller et al. [26]. They noted that, in addition to rapid reduction in pruritus intensity, levocetirizine had also improved dermatology-related quality of life, stress, anxiety and global level of functioning [27].

While most attention was focused on the H1R, other histamine receptor subtypes should not be overlooked. Mommert et al. [28] found that stimulation of H4 receptor, which is highly expressed on plasmocytoid dendritic cells (pDC) in psoriasis [29], increases production of interleukin 17 (IL-17), a cytokine that plays a major role in the pathogenesis of psoriasis. Recently, it has been also shown that blockade of H4R may help to ameliorate imiquimod-induced skin inflammation, diminish epidermal hyperproliferation, and inhibit spontaneous scratching behavior in mice [30]. These observations suggest that histamine relevance in the pathophysiology of pruritus in psoriasis is still uncovered and further investigations are needed.

### 3.2. Substance P and Other Neuropeptides

Neuropeptides are small proteins secreted from nerve endings in the central and peripheral nervous system in response to various factors such as stress, and modulate synaptic transmission [10,23]. They may activate dendritic cells, lymphocytes, macrophages and neutrophils, degranulate mastocytes, cause vascular changes in the skin, stimulate synthesis and release of many pro-inflammatory cytokines [31,32]. The imbalance of

neuropeptides in psoriatic skin is being suggested to play a role in perception of itching. One of the neuropeptides, namely substance P (SP), an undecapeptide of the tachykinin family, has been implicated in the pathogenesis of pruritus for many years. Furthermore, other neuropeptides are believed to be involved in pruritus mediation. It was shown that SP, neurokinin A (NKA), and vasoactive intestinal peptide (VIP) may elicit itch upon intradermal injection into normal human skin (Table 1) [33,34].

Amatya et al. [12] investigated the response to intradermally injected SP into psoriatic skin and confirmed induction of pruritus, flare and wheal in these patients. However, there were no statistically significant differences in latency period, duration or maximum intensity of itching evoked by intradermal injected SP between psoriasis and healthy control skin [12]. Almost 20 years ago it was demonstrated that, in lesional skin from pruritic psoriasis patients, contrary to non-pruritic individuals, a significantly elevated concentration of SP was observed [7]. Moreover, investigators paid attention to a positive correlation between the number of intraepidermal SP-positive fibers in perivascular areas of lesional skin and the degree of pruritus in psoriasis [7,12]. Remröd et al. [11] and then Amatya et al. [13] assessed the expression of tachykinins (SP, neurokinin A–NKA) and their receptors (NK-1R, NK-2R) in lesional and non-lesional psoriatic skin or healthy control skin and showed an increased number of tachykinins in involved area. Furthermore, Chang et al. [9] found that expression of NK-1R was increased on keratynocytes in the psoriatic plaques of patients with pruritus. These findings indicated that drugs blocking NK-1R, such as aprepitant or serlopitant, might be an interesting treatment option in psoriatic pruritus [35,36]. In 2020, results of the phase 2 randomized, double-blind, placebo controlled clinical trial, examining the effects of serlopitant for treatment of psoriatic pruritus have been published [37]. Serlopitant reduced pruritus associated with mild to moderate psoriasis. However, the study was conducted on a small population and patients with severe psoriasis were excluded, thus further investigations are needed to confirm these observations [37]. In another study, aprepitant was shown to improve refractory chronic pruritus and quality of life in psoriatic patients [38]. Moreover, other possible pathways should be taken into consideration regarding SP. An excellent example is the transient receptor potential A1 (TRPA1), which is an ion channel that enhances SP release. Although it has never been explored in mediating psoriasis-associated itch, in a mouse model it was shown to be a necessary mediator of chronic pruritus [39]. Furthermore, TRPA1 blockade inhibited in mice behaviors associated with itching, such as scratching [40,41]. As these studies were performed on murine models of psoriasis, further investigations on this topic are warranted in human beings.

Reich et al. [10] assessed the relationships between plasma levels of selected neuropeptides, such as SP, VIP, neuropeptide Y (NPY), and calcitonin gene-related peptide (CGRP), and the presence of pruritus and its intensity in patients with psoriasis. Unexpectedly, decreased plasma levels of NPY in patients with pruritus were observed [10]. Later studies performed on mice showed that NPY signaling constitutively suppresses mechanical itch by inhibiting NPY receptor 1-expressing neurons, which are required for mechanical itch transmission in the spinal cord [41]. Based on these findings, it can be speculated that reduced NPY plasma levels in psoriasis patients aggravated mechanical itch by central modulation of this sensation. Another observation was a correlation between higher SP and VIP plasma levels with the lower pruritus intensity [10]. As SP induces itching, one may expect contrary results, i.e., positive correlation between SP levels and itch intensity [12]. However, neuropeptides may be released locally from dermal nerve endings and the reduced plasma concentrations of neuropeptides may not necessarily reflect their skin concentrations, but may result from an increased consumption or degradation of these substances in the plasma—an analogous explanation to that described for histamine. Another hypothesis takes into account the role of central nervous system (CNS) in perception of pruritus and the divergent role of neuropeptides at the periphery and in the CNS. If the level of neuropeptides in plasma corresponds to their level in the CNS rather than to the skin, then plasma and dermal levels of neuropeptides do not need to be interrelated.

Nevertheless, our current understanding of the role of neuropeptides in psoriatic pruritus is far from being complete, and further investigations are needed to be able to better prevent and combat this unwanted ailment in our patients.

### 3.3. Nerve Growth Factor and Innervation

Chronic itch is associated with increased levels of nerve growth factor (NGF)—a molecule that belongs to the neurotrophic factor family [42]. This protein influences an inflammatory reaction by regulating neuropeptides, angiogenesis, cell trafficking molecules and T cell activation. Moreover, NGF exerts its action on the growth, proliferation and survival of peripheral sensory and sympathetic neurons and on a number of brain neurons [43]. Currently there two receptors for this molecule are known: high affinity tropomyosin-receptor kinase A (Trk A) and low affinity receptor p75 [44]. Nakamura et al. reported increased NGF content and increased expression of Trk A in lesional psoriatic skin with pruritus in comparison to non-pruritic skin. Additionally, the expression levels of these proteins correlated positively with the severity of pruritus [7]. Subsequent studies demonstrated that NGF expression was higher also in lesional pruritic skin than in non-lesional skin [42]. A probable consequence of elevated concentration of NGF and Trk A is elongation and branching of epidermal nerve fibers, which results in hyperinnervation. In turn, this hyperinnervation is considered to cause hypersensitivity of itch in psoriasis. However, reports of studies remain contradictory—some investigators observed increased nerve density in psoriatic skin [7], whereas others did not see such correlation [14]. This disparity may be due to different measurement techniques or heterogenous clinical history of lesions taken during biopsies. Therefore, increased nerve fiber density in the epidermis may not be an essential factor for the pathogenesis of psoriatic pruritus and further studies are needed to clarify their exact role.

### 3.4. Interleukins

The role of inflammation in psoriatic-related itch origin is undoubtedly relevant, as it is confirmed by elevated concentration of a number of inflammatory mediators and by an antipruritic effect of anti-inflammatory drugs. Various immune cells secrete cytokines that directly or indirectly may aggravate or even induce itch by increasing the inflammatory response [45]. Nakamura et al. analyzed differences in cytokine expression in the epidermis between pruritic and non-pruritic psoriatic patients. Among the tested cytokines (IFN-ɣ, TNF-α, IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12) only IL-2, a SP-induced cytokine that triggers the maturation of T cells, was significantly increased in pruritic psoriatic skin [7]. Other cytokines, such as IL-4, IL-13, IL-31 and IL-33 play a key role in the pro-inflammatory and anti-inflammatory signaling pathways in patients suffering from inflammatory skin diseases such as psoriasis or atopic dermatitis [19]. In 2020, Badoor et al. published results of a study evaluating the correlation between serum concentration of IL-4, IL-13, IL-31 and IL-33 and intensity of pruritus in psoriasis and atopic dermatitis. In patients with psoriasis, similarly to atopic dermatitis, the levels of IL-4 and IL-31 were significantly elevated in comparison to healthy controls [19]. These findings were compatible with the results of another study in which elevated levels of IL-31 in the skin or serum of patients with psoriasis were demonstrated [46,47]. However, these elevated concentrations did not correlate with the intensity of itch [19]. Interestingly, Narbutt et al. proved significant reduction in both, serum IL-31 levels and severity of pruritus after narrowband ultraviolet B (UVB) phototherapy [47]. Although there are some inaccuracies in the literature, this observation might be proof that IL-31 contributes to the induction of pruritus in psoriasis. Cytokines involved in the pathogenesis of psoriasis such as IL-17, IL-22 or IL-23 are also potential agents to evoke pruritus in psoriasis, but to date data on them in relation to pruritus are limited.

### 3.5. Vessel-Derived Molecules

Vascular abnormalities are frequently observed in psoriatic lesions and have also been suspected to be relevant in the pathogenesis of psoriasis-associated pruritus. This suggestion was supported by the positive correlation between the density of E-selectin-positive venules and the intensity of pruritus in patients with psoriasis [7]. The key role in angiogenesis of psoriatic lesions is played by the vascular endothelial growth factor (VEGF) [48]. Moreover, VEGF was also suggested to play a role in perception of pruritus in psoriasis. Higher VEGF-A expression was found in the epidermis of lesional skin from the psoriatic patients with pruritus than those without pruritus [49]. In addition, Madej et al. showed that serum concentration of vascular adhesion protein-1 (VAP-1), another adhesion molecule, was significantly higher in the group of psoriatic patients with pruritus vs. those without pruritus [50]. Prostaglandin E2 (PGE2), endothelin-1 (ET-1) and endothelial leukocyte adhesion protein 1 (ELAM-1) have also been considered to be good candidates as itch mediators in psoriasis but future studies are required to confirm this hypothesis [45].

### 3.6. Endogenous Opioids

The opioid system is considered to be a modulator of pruritus in psoriasis. It is suggested that activation of μ-opioid receptor (MOR) by a MOR ligand β-endorphin can stimulate itch, while the interaction between κ-opioid receptor (KOR) and its ligand: Dynorphin A, suppresses pruritus [51–53]. Opioids may also induce itch acting in the central nervous system—activation of KOR in the brain may reduce or even alleviate itch [15].

Teneda et al. followed the expression patterns of μ- and κ -opioid systems in pruritic and non-pruritic psoriatic skin as well as in healthy skin. No differences regarding μ-opioid receptor expression and β-endorphin levels in the epidermis of psoriatic patients with or without itch and healthy controls were found. However, the levels of KOR and dynorphin A were significantly decreased in the epidermis of patients with psoriasis, especially those who reported pruritus compared with the control group [14]. In an analogous study, conducted few years later in Poland, compatible results were obtained showing no significant difference in MOR system expression in both lesional and non-lesional psoriatic skin, the same as in the healthy control skin. Regarding the κ-opioid pathway, the KOR system was downregulated in the lesional pruritic psoriatic skin, and its expression was positively correlated with itch sensation [15]. These findings indicate that the imbalance in the cutaneous expression of opioid receptors and their ligands may result in disordered neuroepidermal homeostasis in psoriasis, which could potentiate the transmission of itch. Importantly, in imiquimod-induced psoriasis-like dermatitis in mice, scratching behavior was suppressed by peripheral and a central MOR antagonist or a central KOR agonist [54]. It indicates that the central opioid receptor system is also involved in the regulation of pruritus in psoriasis.

### 3.7. Lipocalin-2

Another molecule which is suspected to play an important role in the pathogenesis of pruritus in psoriasis is lipocalin-2 (LCN2). This protein, also known as 24p3 and neutrophil gelatinase-associated lipocalin (NGAL), is stored in the specific granules of human neutrophils and secreted by activated cells [55,56]. LCN2 has been associated with neurodegeneration, cancer metastasis, insulin resistance, obesity, and inflammatory responses [57,58]. Additionally, LCN2 was found to contribute to the pathogenesis of psoriasis by modulating neutrophil function to enhance T-helper 17-type responses [58]. Aizawa et al. on the group of 59 patients suffering from psoriasis observed that serum LCN2 concentration is significantly higher in this group compared to healthy controls and that plasma LCN2 level positively correlated with the intensity of pruritus [18]. These findings may indicate that LCN2 could be another mediator involved in the aggravation of pruritus in psoriasis.

### *3.8. Future Directions to Identify New Itch Mediators*

Gene expression analyses is possible way to find factors involved in the pathogenesis of pruritus in psoriasis. Nattkemper et al. used RNA sequencing to analyze so called "itchscriptom" and identified several possible "itch-related" genes, including also well-known and inflammatory mediators described above, such as various cytokines (IL-17A, IL-23A, IL-31), which were commonly overexpressed in itchy atopic and psoriatic skin [17]. Nowadays, part of them is a target of biological drugs used in psoriasis therapy, e.g., IL-17A. In addition, overexpression of genes encoding SP and its receptor NK-1R in both atopic and psoriatic lesional skin was observed, a finding that further supports SP's role in the pathogenesis of pruritus in psoriasis. In addition, elevated gene transcript levels of such genes, as phopspolipase A2 IVD and phospholipase C, voltage-gated sodium channel 1.7 (Nav1.7), transient receptor potential vanilloid 1 and 3 (TRPV1, TRPV3), transient receptor potential melastatin 8 (TRPM8) and IL-36 were also observed in itchy psoriatic skin [17]. Products of mentioned genes are potential good candidates as potential targets for new antipruritic drugs.

## 4. Conclusions

On the basis of the performed systematic electronic literature search of the PUBMED, Mendeley and Science Direct databases, several biomarkers involved in the pathogenesis of psoriasis-related pruritus were described. In summary, the molecular basis for psoriatic pruritus is a result of complex interaction between the nervous, neuroendocrine, immune and vascular system and is still not fully understood. As a consequence, there is a lack of effective antipruritic treatment for psoriatic patients. Thus, further studies are urgently needed to provide clarification of the mechanisms involved in the pruritus in psoriasis to develop better medications for psoriatic itch. Medical history plays a pivotal role in determining the pruritus causes also in psoriatic patients and should drive the anti-pruritic therapy. Since pruritus is a significant determinant of patients' quality of life, physicians should be aware that even effective anti-psoriatic therapies may not necessarily control pruritus or the occurrence of pruritus in responders to anti-psoriatic treatment may be a fist symptom of growing secondary unresponsiveness.

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# Characteristics of Pruritus in Various Clinical Variants of Psoriasis: Results of the Multinational, Multicenter, Cross-Sectional Study

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**Abstract:** Psoriasis is a chronic, inflammatory skin disease present in about 3% of the world's population. The clinical symptoms manifest diversely, therefore one can distinguish several subtypes of psoriasis. The majority of patients with psoriasis experience pruritus, which is an unpleasant sensation that decreases patients' quality of life. The knowledge on pruritus in different subtypes of psoriasis is limited. We have performed a cross-sectional, prospective, and multicenter study to evaluate the relationship between clinical subtypes of psoriasis (large-plaque, nummular, guttate, palmoplantar, inverse, erythrodermic, palmoplantar pustular, generalized pustular psoriasis, and psoriasis of the scalp) and the prevalence, intensity, and clinical manifestation of itch. We introduced a questionnaire assessing various aspects of pruritus to a total of 254 patients. Out of these, 42 were excluded. Pruritus was present in 92.9% of the remaining patients and its prevalence did not depend on the clinical subtype. A correlation between the severity of psoriasis and the intensity of itch was explicitly noticeable in palmoplantar pustular psoriasis and scalp psoriasis ($p < 0.05$). The itch sensation was individual and differed among subtypes of psoriasis. In conclusion, pruritus is a frequent phenomenon, and its presentation is different in various subtypes of psoriasis.

**Keywords:** psoriasis; palmoplantar pustulosis; pruritus; itch; itching

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## 1. Introduction

Psoriasis is a chronic, inflammatory skin disease, characterized by a multifactorial and complexed pathogenesis, and with a varied clinical picture. The most representative and common skin lesion is an erythematous plaque covered with silvery scales [1]. However, it is not the only one clinical manifestation of this disease. A less common subtype is pustular psoriasis, characterized by the formation of sterile pustules on an erythematous base [2]. This form may affect the entire body (i.e., generalized pustular psoriasis), or may be limited to the hands and feet (i.e., localized pustular psoriasis) [3]. Nowadays, it

is widely recognized that pruritus is an important subjective symptom of psoriasis that affects up to 90% of patients [4]. This phenomenon is described as the most disturbing symptom of psoriasis, which has a negative impact on patients' quality of life. The intensity of the itch seems to correlate with various psychological aspects including depressive symptoms or anxiety. However, data regarding factors that influence the intensity of pruritus and the presence of other symptoms associated with itching are still sparse. Moreover, the molecular basis of pruritus in psoriasis is still not fully elucidated, albeit a complex interaction between the nervous, neuroendocrine, immune, and vascular systems is suggested. Many mediators were indicated to modulate this sensation in psoriasis, but none has been proven to be a crucial one to date. The knowledge on pruritus in psoriasis is even more limited when considering different clinical subtypes of this disease, as most reports published so far have focused on plaque-type psoriasis. As a consequence, there is a challenge for clinicians to choose the most effective antipruritic treatment for specific subgroups of psoriatic patients [5]. The aim of this study was to evaluate the relationship between clinical subtypes of psoriasis and the prevalence, intensity, and clinical manifestation of itch.

## 2. Materials and Methods

### *2.1. Study Design*

This was a cross-sectional, prospective study conducted in five Polish (Bydgoszcz, Łódź, Olsztyn, Rzeszów, Wrocław) and one Turkish (Ankara) dermatology clinics. Demographic data, anthropometric measurements, data on comorbidities including psoriatis artritis (PsA), and current treatment as well as clinical characteristics of pruritus were introduced into a questionnaire, which has been used by our group in previous studies [6]. Patients above 16 years old, with the confirmed diagnosis of psoriasis, were considered in the analysis. The exclusions criteria encompassed systemic antipsoriatic treatment within 4 weeks before the assessment, topical antipsoriatic treatment within 2 weeks before the assessment, other concomitant dermatological or systemic disorders that might cause pruritus such as chronic uremia or cholestasis, and usage of medications that could influence the sensation of itch. Disease severity was measured with Body Surface Area (BSA) and Static Physician Global Assessment (sPGA) in all patients, as well as with the Psoriasis Area and Severity Index (PASI) in patients with psoriasis vulgaris [7,8]. Patients with palmoplantar pustular psoriasis (PPPP) were assessed with Palmoplantar Pustulosis Severity Index (PPSI), while those suffering from generalized pustular psoriasis (GPP) were evaluated according to Generalized Pustular Psoriasis Severity Index (GPPSI) [9,10]. The maximal peak pruritus and the average pruritus intensity within the previous 3 days were evaluated with the 11-point Numerous Rating Scale ($NRS_{max}$, and $NRS_{average}$, respectively) from 0 (no pruritus) to 10 (worst imaginable pruritus) [11]. In addition, the 10-item Pruritus Severity Scale (10-PSS) was used as another method of measurement for pruritus intensity [12]. Regarding 10-PSS, the extension, intensity, and duration of pruritus episodes and their influence on concentration and psyche are evaluated, along with scratching as a result of pruritus. The maximal possible result is 20 points, which indicates the most severe itch. The Dermatology Life Quality Index (DLQI) was applied to evaluate the impact of skin lesions on the patient's quality of life [13]. The DLQI scoring ranges from 0 to 30, with a higher score indicating a more impaired quality of life.

### *2.2. Patients*

A total of 254 patients with different clinical subtypes of psoriasis were included. In most subjects, the diagnosis was made according to clinical manifestation, while in doubtful cases, a histopathological assessment of skin biopsies was performed. Forty-two individuals were excluded from further analysis because they were on systemic or topical treatment while data collection was performed. The remaining patients were divided into 9 groups according to the dominant subtype of psoriasis: large-plaque psoriasis ($n$ = 45), nummular psoriasis ($n$ = 27), guttate psoriasis ($n$ = 24), palmoplantar psoriasis ($n$ = 11), psoriasis of the

scalp ($n$ = 23), inverse psoriasis ($n$ = 11), erythrodermic psoriasis ($n$ = 18), PPPP ($n$ = 42), and GPP ($n$ = 11) (Table 1). The mean age of all patients was 45.1 ± 14.9 years (range: 16–77 years). Subjects with guttate psoriasis and scalp psoriasis were slightly younger, while those with pustular forms of psoriasis were slightly older than the rest of the patients, albeit the difference was significant ($p < 0.001$) (Table 1). Out of all studied subjects, 50% were women and 50% were men. However, in the erythrodermic subtype, men predominated (72.2%). On the contrary, the majority of patients with PPPP were women (85.7%; $p < 0.001$). The mean duration of psoriasis was 13.6 ± 12.3 years (range: 0–59 years) and this parameter was similar among all subtypes of psoriasis (Table 1). All patients agreed to take part in this study and signed the written informed consent. The study was approved by the Ethics Committee by Subcarpatian Physician Chamber in Rzeszów and also by the Gazi University Ethics Committee.

### *2.3. Statistical Analysis*

All data were analyzed statistically with Statistica 13.0 (Statsoft, Krakow, Poland). Means, standard deviations (SD), median values, and frequencies were calculated. The differences between the groups of patients were analyzed using the Student's $t$-test for independent variables, Mann–Whitney U test, and analysis of variance (ANOVA), where appropriate. Correlations between analyzed parameters were verified by using Spearman's rank correlation test (ρ—correlation coefficient). $\chi^2$ test was used to determine whether there was a significant difference between the expected and observed frequencies in one or more categories. The results were considered statistically significant if the $p$-value was less than 0.05.

**Table 1.** Characteristics of included patients (* $p$ values according to analysis of variance, ** $p$ values according to $\chi^2$).

| | All Patients | Large-Plaque Psoriasis | Nummular Psoriasis | Guttate Psoriasis | Palmo-Plantar Psoriasis | Psoriasis of the Scalp | Inverse Psoriasis | Erythrodermic Psoriasis | Palmo-Plantar Pustular Psoriasis | Generalized Pustular Psoriasis |
|---|---|---|---|---|---|---|---|---|---|---|
| Number of patients (%) | 212 (100) | 45 (21.2) | 27 (12.7) | 24 (11.3) | 11 (5.2) | 23 (10.8) | 11 (5.2) | 18 (8.5) | 42 (19.8) | 11 (5.2) |
| Age (years, mean ± standard deviation) | 45.1 ± 14.9 | 46.8 ± 16.0 | 41.2 ± 12.4 | 37.4 ± 9.6 | 42.2 ± 12.6 | 34.6 ± 12.9<br>$p < 0.001$ * | 42.1 ± 15.3 | 47.7 ± 16.1 | 53.8 ± 12.8 | 54.1 ± 14.4 |
| Women (%) | 106 (50) | 15 (33.3) | 10 (37) | 10 (41.7) | 5 (45.5) | 13 (56.5) | 5 (45.5) | 5 (27.8) | 36 (85.7) | 6 (54.5) |
| Men (%) | 106 (50) | 30 (66.7) | 17 (63) | 14 (58.3) | 6 (54.5) | 10 (43.5)<br>$p < 0.001$ ** | 6 (54.5) | 13 (72.2) | 6 (14.3) | 5 (45.5) |
| Duration of psoriasis (years) | 13.6 ± 12.3 | 16.4 ± 13.4 | 14.8 ± 11.5 | 12.9 ± 10.2 | 10.2 ± 8.4 | 9.8 ± 8.4<br>$p = 0.06$ * | 11.7 ± 10.2 | 16.3 ± 14.2 | 8.3 ± 11.9 | 14.2 ± 11.5 |

## 3. Results

### *3.1. Prevalence and Intensity of Pruritus*

Pruritus ever in the course of psoriasis (the lifetime prevalence of pruritus) was experienced by the great majority (92.9%) of patients, while 81% reported the presence of this symptom within the 3 days preceding the examination (the point prevalence of pruritus). There were no significant differences between the clinical subtypes of psoriasis and the presence of itch in the course of the disease ($p = 0.48$) and within the last 3 days ($p = 0.9$). In most psoriasis subtypes, pruritus was limited to the lesional skin. Only in erythrodermic psoriasis was generalized pruritus observed with significantly higher frequency as compared to other subtypes ($p = 0.03$). Nonetheless, this result may not be so relevant due to the generalized distribution of skin lesions in the erythrodermic subtype of psoriasis. No significant relationships were found between subtypes of psoriasis and the intensity of pruritus according to NRS or 10-PSS. The detailed results referring to all groups are shown in Table 2.

### *3.2. Disease Severity*

The mean PASI, BSA, sPGA, PPSI, and GPP scores in each subgroup are summarized in Supplementary Table S1. In scalp psoriasis and PPPP, the intensity of pruritus strongly correlated with the severity of psoriasis ($p < 0.05$). Interestingly, in nummular psoriasis, such a relationship was observed only for the 10-PSS score. A significant correlation was also seen between the severity of pruritus and BSA in GPP. In large plaque-type, guttate, palmoplantar, inverse, and erythrodermic psoriasis, no significant correlations were found between the intensity of pruritus and disease severity. Correlations between pruritus intensity and disease severity according to the morphological phenotype of psoriasis are presented in Table 3.

### *3.3. Descriptions of Pruritus*

The perception of itch was quite individual and differed even within the same subtype of psoriasis. Most of these differences did not reach statistical significance. However, in both palmoplantar psoriasis and PPPP, patients more often described pruritus as painful and deep ($p < 0.05$). In addition, a burning or warming feeling accompanied 36% of patients with palmoplantar psoriasis. Furthermore, it seems that in GPP, itching can be experienced as feeling cold ($p < 0.002$). Nonetheless, there was a small population size and only one subject used this term to describe pruritus; thus, this result may be random. The characteristics of pruritus among different subtypes of psoriasis are presented in Supplementary Table S2.

Patients with scalp, erythrodermic, and inverse psoriasis experienced marked emotional irritation due to pruritus ($p < 0.01$). Patients also frequently mentioned that pruritus is quite disturbing (Table 2). We observed that in GPP, the most intense pruritus occurred when the skin lesion extended their size, and this feature was rather unique to this disease subtype. Frequency of pruritus and moment of alleviation of this symptom did not differ significantly between the groups. In each studied population, patients experienced itching every day or at least a few times a week, and pruritus was mostly relieved after the significant improvement or complete disappearance of skin lesions. Subjects with palmoplantar and inverse psoriasis had the most intense pruritus when skin lesions were fully developed (Supplementary Table S2).

### *3.4. Quality of Life*

According to the collective analysis of all psoriatic patients, pruritus correlated positively with impaired quality of life. This correlation was strongly significant in plaque psoriasis and PPPP. In guttate or scalp psoriasis, the impact of itching on quality of life was also observed. Contrarily, such correlation was not observed in nummular, palmoplantar, inverse, erythrodermic psoriasis, and GPP (Table 3).

**Table 2.** Prevalence, intensity, and feelings related to pruritus (NRS—Numerical Rating Scale, 10-PSS—10-item Pruritus Severity Scale, SD—standard deviations, * *p* values according to $\chi^2$ test, ** *p* values according to analysis of variance).

| | All Patients | Large-Plaque Psoriasis | Nummular Psoriasis | Guttate Psoriasis | Palmoplantar Psoriasis | Psoriasis of the Scalp | Inverse Psoriasis | Erythrodermic Psoriasis | Palmo-Plantar Pustular Psoriasis | Generalized Pustular Psoriasis | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pruritus Prevalence | | | | | | | | | | | |
| Pruritus present ever during the disease course: *n* (%) | 197 (92.9) | 43 (95.6) | 26 (96.3) | 22 (91.7) | 10 (90.9) | 23 (100) | 10 (90.9) | 16 (88.9) | 36 (85.7) | 11 (100) | 0.48 * |
| Pruritus present within the last 3 days: *n* (%) | 172 (81.1) | 36 (80) | 23 (85.2) | 19 (79.2) | 9 (81.8) | 21 (91.3) | 9 (81.8) | 15 (83.3) | 31 (73.8) | 9 (81.8) | 0.9 * |
| Pruritus limited to skin lesions: *n* (%) | 159 (80.7) | 35 (81.4) | 23 (88.5) | 21 (95.5) | 8 (80) | 18 (78.3) | 7 (70) | 7 (43.7) | 32 (80.9) | 8 (72.7) | 0.03 * |
| Pruritus also involving non-diseased skin: *n* (%) | 11 (5.6) | 1 (2.3) | 1 (3.8) | 0 (0) | 2 (20) | 2 (8.7) | 0 (0) | 2 (12.5) | 2 (5.6) | 1 (9.1) | |
| Generalized pruritus: *n* (%) | 27 (13.7) | 7 (16.3) | 2 (7.7) | 1 (4.5) | 0 (0) | 3 (13) | 3 (30) | 7 (43.8) | 2 (5.6) | 2 (18.2) | |
| Pruritus Intensity | | | | | | | | | | | |
| $NRS_{average}$ (mean ± SD) | 3.7 ± 2.7 | 4.2 ± 2.9 | 2.9 ± 2.0 | 3.7 ± 2.7 | 3.5 ± 2.9 | 3.6 ± 2.3 | 3.9 ± 3.1 | 4.1 ± 2.9 | 3.8 ± 2.6 | 3.5 ± 3.1 | 0.83 ** |
| $NRS_{max}$ (mean ±SD) | 4.8 ± 2.9 | 5.1 ± 3.2 | 4.2 ± 2.6 | 4.7 ± 2.9 | 4.7 ± 3.4 | 4.8 ± 2.6 | 5.1 ± 3.3 | 4.9 ± 2.9 | 4.8 ± 2.9 | 4.7 ± 3.4 | 0.99 ** |
| 10-PSS (mean ± SD) | 8.5 ± 4.5 | 9.7±4.4 | 7.6 ± 3.3 | 7.8 ± 4.5 | 8.4 ± 4.6 | 8.1 ± 4.1 | 8.0 ± 4.8 | 9.0 ± 5.9 | 8.5 ± 4.7 | 8.6 ± 5.7 | 0.79 ** |
| Feelings Related to Pruritus | | | | | | | | | | | |
| Disturbing: *n* (%) | 120 (60.9) | 28 (65.1) | 15 (57.7) | 13 (59.1) | 7 (70) | 9 (39.1) | 5 (50) | 9 (56.2) | 30 (83.3) | 5 (45.5) | 0.29 |
| Irritating: *n* (%) | 87 (44.2) | 11 (25.6) | 15 (57.7) | 9 (40.9) | 6 (60) | 14 (60.9) | 8 (80) | 10 (62.5) | 11 (30.1) | 3 (27.3) | <0.01 |
| Annoying: *n* (%) | 40 (20.3) | 12 (27.9) | 3 (11.5) | 3 (13.6) | 2 (20) | 3 (13) | 3 (30) | 5 (31.2) | 5 (13.9) | 4 (36.4) | 0.33 |
| Distressing: *n* (%) | 27 (13.7) | 4 (9.3) | 5 (19.2) | 1 (4.5) | 0 (0) | 3 (13) | 1 (10) | 4 (25) | 7 (19.4) | 2 (18.2) | 0.54 |

**Table 3.** Correlations between pruritus intensity and disease severity according to the Spearman rank correlation test (statistically significant values marked in bold; 10-PSS—10-item Pruritus Severity Scale, BSA—Body Surface Area, DLQI—Dermatology Life Quality Index, GPPSI—Generalized Pustular Psoriasis Severity Index, NRS—Numerous Rating Scale, PASI—Psoriasis Area and Severity Index, PPSI—Palmoplantar Pustulosis Severity Index, sPGA—Static Physician Global Assessment).

| | | All Patients | Large-Plaque Psoriasis | Nummular Psoriasis | Guttate Psoriasis | Palmo-Plantar Psoriasis | Psoriasis of the Scalp | Inverse Psoriasis | Erythrodermic Psoriasis | Palmoplantar Pustular Psoriasis | Generalized Pustular Psoriasis |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PASI vs. | $NRS_{average}$ | **ρ = 0.22, *p* < 0.01** | ρ = 0.26, *p* = 0.09 | ρ = 0.16, *p* = 0.43 | ρ = 0.31, p = 0.14 | ρ = 0.15, *p* = 0.69 | **ρ = 0.65, *p* < 0.001** | ρ = 0.25, *p* = 0.47 | **ρ = 0.51, *p* = 0.03** | - | - |
| | $NRS_{max}$ | **ρ = 0.17, *p* < 0.03** | ρ = 0.28, *p* = 0.07 | ρ = 0.18, *p* = 0.38 | ρ = 0.15, p = 0.49 | ρ = 0.13, *p* = 0.73 | **ρ = 0.64, *p* < 0.001** | ρ = 0.25, *p* = 0.45 | **ρ = 0.54, *p* = 0.02** | - | - |
| | 10-PSS | **ρ = 0.23 *p*< 0.01** | ρ = 0.19, *p* = 0.24 | **ρ = 0.52, *p* < 0.01** | ρ=0.09, p = 0.7 | ρ = 0.46, *p* = 0.25 | **ρ = 0.74, *p* < 0.001** | ρ = 0.02, *p* = 0.95 | ρ = 0.41, *p* = 0.1 | - | - |
| BSA vs. | $NRS_{average}$ | **ρ = 0.18, *p* = 0.01** | ρ = 0.15, *p* = 0.33 | ρ = 0.28, *p* = 0.16 | ρ = 0.31, *p* = 0.14 | ρ = −0.01, *p* = 0.99 | **ρ = 0.68, *p* < 0.001** | ρ = 0.21, *p* = 0.54 | ρ = −0.04, *p* = 0.88 | **ρ = 0.35, *p* < 0.05** | **ρ = 0.85, *p* < 0.01** |
| | $NRS_{max}$ | **ρ = 0.16, *p* = 0.02** | ρ = 0.17, *p* = 0.28 | ρ = 0.26, p = 0.2 | ρ=0.23, p=0.28 | ρ = −0.1, *p* = 0.78 | **ρ = 0.71, *p* < 0.001** | ρ = 0.22, *p* = 0.52 | ρ = −0.13, *p* = 0.61 | **ρ = 0.38, *p* = 0.03** | **ρ = 0.88, *p* < 0.01** |
| | 10-PSS | **ρ = 0.17, *p* = 0.02** | ρ = 0.08, *p* = 0.60 | **ρ = 0.52, *p* < 0.01** | ρ = 0.13, p = 0.57 | ρ = 0.16, *p* = 0.69 | **ρ = 0.63, *p* = 0.002** | ρ = 0.22, *p* = 0.6 | ρ = −0.14, p=0.6 | ρ = 0.21, *p* = 0.25 | **ρ = 0.75, *p* = 0.03** |
| sPGA vs. | $RS_{average}$ | **ρ = 0.35, *p* < 0.001** | ρ = 0.27, *p* = 0.08 | ρ = 0.17, *p* = 0.4 | ρ=0.22, p = 0.3 | ρ = 0.35, *p* = 0.3 | **ρ = 0.61, *p* = 0.002** | ρ = 0.42, *p* = 0.2 | ρ = 0.32, *p* = 0.19 | **ρ = 0.48, *p* = 0.001** | ρ = 0.4, *p* = 0.22 |
| | $NRS_{max}$ | **ρ = 0.37, *p* < 0.001** | **ρ = 0.31, *p* = 0.04** | ρ = 0.28, *p* = 0.17 | ρ=0.24, p=0.25 | ρ = 0.48, *p* = 0.14 | **ρ = 0.53, *p* < 0.01** | ρ = 0.4, *p* = 0.22 | ρ = 0.39, *p* = 0.1 | **ρ = 0.56, *p* < 0.001** | ρ = 0.59, *p* = 0.06 |
| | 10-PSS | **ρ = 0.4, *p* < 0.001** | ρ = 0.21, *p* = 0.19 | **ρ = 0.63, *p* < 0.001** | ρ=0.11, p = 0.62 | ρ = 0.49, *p* = 0.18 | **ρ = 0.52, *p* = 0.01** | ρ = 0.3, *p* = 0.47 | ρ = 0.36, *p* = 0.15 | **ρ = 0.66, *p* < 0.001** | ρ = 0.34, *p* = 0.31 |
| PPSI vs. | $NRS_{average}$ | - | - | - | - | - | - | - | - | **ρ = 0.46, *p* = 0.002** | - |
| | $NRS_{max}$ | - | - | - | - | - | - | - | - | **ρ = 0.53, *p* < 0.001** | - |
| | 10-PSS | - | - | - | - | - | - | - | - | **ρ = 0.6, *p* < 0.001** | - |
| GPPSI vs. | $NRS_{average}$ | - | - | - | - | - | - | - | - | - | ρ = 0.31, *p* = 0.11 |
| | $NRS_{max}$ | - | - | - | - | - | - | - | - | - | **ρ = 0.63, *p* = 0.04** |
| | 10-PSS | - | - | - | - | - | - | - | - | - | ρ = 0.46, *p* = 0.16 |
| DLQI vs. | $NRS_{average}$ | **ρ = 0.32, *p* < 0.001** | **ρ = 0.51, *p* < 0.001** | ρ = 0.005, *p* = 0.98 | ρ = 0.13, *p* = 0.55 | ρ = 0.16, *p* = 0.64 | **ρ = 0.44, *p* = 0.03** | ρ = 0.12, *p* = 0.72 | ρ = 0.22, *p* = 0.37 | **ρ = 0.48, *p* = 0.001** | ρ = 0.58, *p* = 0.06 |
| | $NRS_{max}$ | **ρ=0.35, *p* < 0.001** | **ρ = 0.56, *p* < 0.001** | ρ = −0.09, *p* = 0.66 | ρ = 0.3, *p* = 0.15 | ρ = 0.19, *p* = 0.58 | ρ = 0.41, *p* = 0.05 | ρ = 0.21, *p* = 0.54 | ρ = 0.25, *p* = 0.31 | **ρ = 0.57, *p* < 0.001** | ρ = 0.38, *p* = 0.25 |
| | 10-PSS | **ρ = 0.47, *p* < 0.001** | **ρ = 0.46, *p* = 0.003** | ρ = 0.17, *p* = 0.41 | **ρ = 0.6, *p* = 0.002** | ρ = 0.39, *p* = 0.3 | **ρ = 0.76, *p* < 0.001** | ρ = 0.47, *p* = 0.24 | ρ = 0.34, *p* = 0.18 | **ρ = 0.58, *p* < 0.001** | ρ = 0.44, *p* = 0.18 |

## 4. Discussion

Pruritus defined as an unpleasant sensation that provokes a desire to scratch was observed in 93% of all patients in our study. In other research, this phenomenon was reported with a frequency of 63–98% [14–19]. These differences may be due to regional features, the clinical characteristics of patients, and the divergent study methodologies used in other centers. To date, pruritus in psoriasis has already been investigated several times, but researchers have not distinguished any clinical subtypes of psoriasis or have mainly been focused on plaque-type psoriasis [20–22]. However, psoriasis manifests with several morphological phenotypes that may differ regarding the intensity and perception of pruritus. In the literature, descriptions of both prevalence and the clinical characteristics of pruritus in psoriasis are limited and contradictory [23–25]. Here, we have presented the results of a multicenter, prospective study analyzing pruritus in various morphological subtypes of psoriasis.

In our study, there was no relationship between the subtypes of psoriasis and the frequency of pruritus. Compatible results were observed by Sung-Min Park with his group, albeit assessment was performed only in guttate and plaque subtypes [16]. Similarly, Szepietowski et al., Yosipovitch et al., and Bahali et al. found that the presence of itch did not depend on the type of psoriasis, although the number of considered clinical subtypes were limited [18,26,27]. In contrast, another research team noticed some differences in the prevalence of pruritus. The most pruritogenic variant according to Sampogna et al. was palmoplantar psoriasis, whereas the least pruritogenic was guttate psoriasis (67.6% and 50.0%, respectively) [14]. On the other hand, two other studies suggested that the presence of pruritus was mostly linked to the pustular subtype [28,29].

Regarding localization of pruritus, we paid attention to whether pruritus was limited to lesional skin or also concerned uninvolved skin. In most psoriasis variants, pruritus was limited to psoriatic lesions. Contrarily, in one previously conducted study, itch was not limited to involved areas [18]. These divergent results may be caused by several limitations of Yosipovith's trial: smaller studied group ($n$ = 101), only three differentiated subtypes (plaque, guttate, erythrodermic), and 45% of subjects receiving antihistamines [18]. In our study, the only exception was erythrodermic psoriasis, in which generalized pruritus was more prevalent. However, it can be easily explained by specific skin involvement in erythrodermic psoriasis, which affects more than 80% of the skin [30].

The data on the interplay between psoriasis severity and itch remains inconclusive–some investigators have shown a positive connection between these factors, while others reported a lack of correlation [6,18,29,31]. However, even if the analysis was based on some different subtypes of psoriasis, the severity of the disease was assessed collectively [18,27]. In our groups of examined patients, we observed that the intensity of pruritus increased along with disease severity, but statistical significance was confirmed only in some disease variants. The most prominent relationship was found between the intensity of pruritus and the severity of the scalp psoriasis and PPPP. In nummular psoriasis, only the 10-PPS score correlated positively with psoriasis severity. However, such correlation was not significant according to the $NRS_{max}$ and $NRS_{average}$ scores. This result can be explained by the complex and multifactorial assessment of pruritus in the 10-PPS scale, which allowed for a more detailed evaluation of the intensity of pruritus along with the extension, duration, and the influence of pruritus on concentration, psyche, and scratching. Furthermore, in GPP, the extension of skin lesion measured by BSA was linked to higher pruritus intensity. The GPP index showed consistent results ($\rho$ ranged from 0.31 to 0.63), albeit probably due to the small studied group, these results were not always statistically significant ($p$ = 0.04–0.16).

It is difficult to uniformly characterize itch; even patients in the same subtypes of psoriasis used various terms to describe their feelings. The most common associated symptoms with large plaque psoriasis were burning and pure itch. Likewise, tingling, pinching, and painful pruritus were commonly used by the patients. Published data regarding individual patients' sensations of itch seems to be limited. In one study, tickling, crawling, and burning were the terms most often used by patients to name pruritus. In

this research, plaque, guttate, and erythrodermic subtypes of psoriasis were taken into consideration; unfortunately authors did not provide a separate analysis for certain types. It is worth mentioning that most of these patients suffered from plaque psoriasis ($n$ = 92), while guttate and erythrodermic subtypes were in the great minority ($n$ = 5 and $n$ = 4, respectively); thus, one can assume that this result is related mostly to plaque psoriasis [18]. In our study, painful itch accompanied mainly palmoplantar types of psoriasis, and it was probably due to a higher density of free nerve endings in this area and the pressure causing additional pain [32]. On the other hand, 27% of responders with GPP also declared painful itch, which could suggest that different factors related to the formation of pustules in psoriasis may be relevant.

In most subtypes, itching occurred during the appearance of skin lesions (10–49%) or when they were fully developed (13–60%). The only exception was GPP, in which the highest intensity of pruritus was during the extension of the skin lesion. It is difficult to compare this data with previous studies as in many cases, no distinction of psoriasis subtypes was provided [6].

It has been well demonstrated that pruritus has a major impact on patients' quality of life [33–35]. In concordance with previous studies, our data indicated that psoriatic patients suffering from intensive pruritus had significantly impaired quality of life [36,37]. Interestingly, in erythrodermic psoriasis, a lower quality of life did not depend on pruritus, which means that pruritus was not the major factor that impacted patients' quality of life. This can be explained by the severe course of this disease subtype.

The pathogenesis of pruritus in psoriasis still remains unclear. Several potential mediators have been proposed, such as substance P, calcitonin gene-related peptide, neuropeptide Y, nerve growth factor and its receptors, lipocalin 2, and interleukin 31; however, data remain controversial and inconclusive [5,15,16,38–40]. Other authors suggested disturbances in the endogenous opioid system homeostasis, but there is still no final proof that indeed the observed abnormalities are a primary phenomenon in psoriasis leading to pruritus [41,42]. Recent data also indicated the role of transient receptor potential (TRP) channels, such as TRPV1, TRPV4, or TRPM8, but further studies are needed to confirm their relevance [43–45].

## 5. Limitations

This study has some limitations. Firstly, the number of patients in this study was not equal in each subtype of psoriasis. Additionally, there were only 11 patients in each of the groups for palmoplantar, inverse, and generalized pustular psoriasis, which makes statistical analysis difficult to interpret.

## 6. Conclusions

This study is unique because it is the first multicenter and prospective study characterizing pruritus in certain clinical variants of psoriasis. A better understanding of this phenomenon according to distinguished subtypes of psoriasis will help to improve communication between physicians and patients, adjust treatment to main complaints, and as a result, improve patients' quality of life. A continuation of this research is needed to increase the sample size and confirm our findings.

**Supplementary Materials:** The following are available online at https://www.mdpi.com/article/10.3390/life11070623/s1, Table S1: Psoriasis severity and quality of life level of analyzed patients. Table S2: Selected features and descriptions of pruritus.

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# The Impact of Pruritus on the Quality of Life and Sleep Disturbances in Patients Suffering from Different Clinical Variants of Psoriasis

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**Abstract:** Background: Quality of life (QoL) and sleep, which are essential for well-being in the mental, physical, and socioeconomic domains, are impaired in psoriatic patients. However, the exact role of the clinical subtype of psoriasis in this aspect remains poorly studied. Objectives: The aim of this study was to investigate differences in QoL impairment and sleeping problems in patients suffering from various clinical subtypes of psoriasis and to evaluate the effects of pruritus on QoL. Methods: This cross-sectional, multicenter study included 295 eligible subjects with diagnosed psoriasis. Each patient was examined with the use of the same questionnaire. Measures included predominant subtype of psoriasis, disease severity, pruritus scores, patients' health-related QoL and the incidence of sleep disturbance. Results: The QoL of most patients was decreased irrespectively of clinical psoriasis subtype, however, the most impaired QoL was in patients with erythrodermic psoriasis. The majority of patients reported sleep disturbances caused by pruritus, albeit there was no relevant differences between analyzed subgroups in this aspect of patients' well-being. Pruritus was an important factor determining QoL and sleeping problems in the studied population. Conclusions: Identifying the most disturbing area of life and recognizing the most bothersome subjective symptoms of psoriasis are pivotal to focusing on the most relevant treatment goal and achieving therapeutic success.

**Keywords:** psoriasis; palmoplantar pustulosis; pruritus; itch; itching; quality of life; quality of sleep; sleep disturbances; sleep disorders

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## 1. Introduction

Psoriasis is a highly prevalent, chronic, inflammatory disease, primarily affecting the skin. The most common skin lesions are erythematous papules and plaques covered with silvery scales, frequently localized on the exposed skin areas as knees, elbows or scalp. Based on clinical presentation, several variants of psoriasis can be distinguished, such as plaque-type psoriasis, small-plaque psoriasis, guttate psoriasis, inverse or flexural psoriasis, psoriasis of the scalp, hands and feet psoriasis, erythrodermic psoriasis, palmoplantar pustular psoriasis (PPPP) and generalized pustular psoriasis (GPP).

Quality of life (QoL), defined as a complex and multidimensional concept and an index of subjective well-being in the mental, physical, and socioeconomic domains as perceived by individuals, is usually decreased in dermatological patients [1]. Health-related QoL is a term that refers to health status and severity of disease. Many factors such as involvement of visible parts of the body, scaling, or subjective symptoms such as pruritus or pain may have a negative impact on patients' QoL. Emotional stress caused by attempts to hide the skin lesions and lowered self-esteem negatively affect interpersonal relationships. The situation may be of particular relevance if skin lesions are located within the anogenital area, as this may affect sexual activity and relationship with the partner. Social awareness of this disease is still low, therefore, psoriatic patients are often stigmatized and excluded by the social and work environment. All these above-mentioned aspects contribute to sadness, depression, anxiety, and suicidal ideation [2]. Moreover, stress and negative emotions are one of the best known factors that exacerbate psoriasis; thus, patients need to be able to manage these symptoms in order to prevent further disease worsening [3].

Sleep is undoubtedly an important aspect of general health. An insufficient amount of high-quality sleep may cause fatigue, irritability, emotional lability and, as a consequence, impaired functioning in the society [4]. Many studies reported sleep disturbances in dermatological diseases including psoriasis [5–7], but data on sleeping problems in different clinical subtypes of psoriasis are limited.

Here, we aimed to investigate and characterize the differences of QoL and sleeping problems in different clinical variants of psoriasis with a special emphasis put on the role of pruritus, as it is the most frequent and the most bothersome subjective symptom of psoriasis [8–10].

## 2. Materials and Methods

### 2.1. Study Design

This cross-sectional study was conducted from June 2020 to November 2021 in six dermatological departments localized in Poland (Rzeszów—$n$ = 102, Bydgoszcz—$n$ = 52, Wrocław—$n$ = 43, Łódź—$n$ = 39, Olsztyn—$n$ = 20) and in Turkey (Ankara—$n$ = 82). The study was approved by the Ethics Committee of the Subcarpatian Physician Chamber in Rzeszow for Poland and by Gazi University Ethics Committee for Turkey. Patients were in details informed about the study aims and signed an informed consent form before initiation of any procedure.

### 2.2. Studied Population

Patients were recruited consecutively from the patients visiting our departments. The inclusion criteria were as follows: each patient had to have an established diagnosis of psoriasis that could be classified to one of the predefined psoriasis subtypes (large plaque psoriasis, small plaque psoriasis, guttate psoriasis, palmoplantar psoriasis, psoriasis of the scalp, inverse psoriasis, erythrodermic psoriasis, PPPP and GPP) and be able to complete the questionnaires. The exclusion criteria included age <16 years, illiteracy, presence of any dermatological or systemic disorder that might cause pruritus, treatment of psoriasis within a period of 2 (for topical agents) or 4 weeks (for systemic therapy or phototherapy) before study inclusion, pregnancy, lactation, and use of drugs with antipruritic potential.

Out of 338 psoriatic patients enrolled primarily in the study, 295 were included for final analysis. The remaining 43 subjects were excluded because of current or recent (within the prior 4 weeks for systemic agents or phototherapy, or within 2 weeks for topical medications) anti-psoriatic treatment or comorbidities of either dermatological or systemic disorders that might cause pruritus.

Patients were divided into nine groups according to the dominant clinical manifestation of psoriasis: large-plaque psoriasis ($n$ = 45), small-plaque psoriasis ($n$ = 32), guttate psoriasis ($n$ = 31), palmoplantar psoriasis ($n$ = 33), psoriasis of the scalp ($n$ = 32), inverse psoriasis ($n$ = 23), erythrodermic psoriasis ($n$ = 33), PPPP ($n$ = 43) and GPP ($n$ = 23) [11]. The majority of the investigated groups were comparable according to gender, age, duration of

psoriasis, BMI and coexistence of psoriatic arthritis. However, some statistically significant discrepancies were observed, which can be explained by particular subtype features (e.g., patients with GPP were older, and patients with plaque-type psoriasis were more obese) (Table 1).

**Table 1.** Comparison of demographic, anthropometric and clinical data in patients with various clinical subtypes of psoriasis (statistically significant differences from other patients ($p < 0.05$) were marked with "*").

| | Number of Subjects (%) | Gender Female (%)/ Male (%) | Age Min–Max (Mean ± SD) | BMI Min–Max (Mean ± SD) | Age at Disease Onset Min–Max (Mean ± SD) | Coexisting Psoriatic Arthritis (%) |
|---|---|---|---|---|---|---|
| **All subjects** | 295 (100) | 148 (50.2)/ 147 (49.8) | 16–77 (45.0 ± 15.3) | 14.5–46.0 (27.5 ± 5.6) | 2–76 (32.9 ± 16.8) | 27 (9.2) |
| **Large plaque psoriasis** | 45 (15.3) | 15 (33.3) 30 (66.7) | 17–77 (46.7 ± 15.9) | 21.4–42.8 (30.2 ± 5.5) $p < 0.001$ * | 6–72 (30.3 ± 17.5) | 5 (11.1) |
| **Small plaque psoriasis** | 32 (10.8) | 11 (34,4) 21 (65.6) | 16–69 (40.6 ± 13.6) | 14.5–37.6 (26.4 ± 5.3) | 3–58 (27.3 ± 15.1) | 2 (6.3) |
| **Guttate psoriasis** | 31 (10.5) | 14 (45.2) 17 (54.8) | 17–73 (37.5 ± 11.6) | 19.5–46.0 (27.5 ± 6.4) | 7–53 (24.0 ± 12.1) | 4 (12.9) |
| **Palmoplantar psoriasis** | 33 (11.2) | 18 (54.6) 15 (45.4) | 16–71 (45.3 ± 14.9) | 18.1–43.4 (28.3 ± 5.7) | 10–69 (36.1 ± 16.5) | 2 (6.1) |
| **Scalp psoriasis** | 32 (10.8) | 19 (59.4) 13 (40.6) | 16–61 (34.9 ± 12.4) | 15.4–34.1 (24.2 ± 4.4) $p < 0.001$ * | 6–50 (23.7 ± 11.7) | 2 (6.3) |
| **Inverse psoriasis** | 23 (7.8) | 12 (52.2) 11 (47.8) | 18–67 (41.5 ± 14.0) | 18.8–41.5 (29.3 ± 5.6) | 13–60 (30.7 ± 14.2) | 2 (8.7) |
| **Erythrodermic psoriasis** | 33 (11.2) | 9 (27.3) 24 (72.7) | 18–71 (47.5 ± 16.6) | 17.6–44.5 (27.8 ± 6.4) | 3–60 (31.9 ± 16.7) | 5 (15.2) |
| **Palmoplantar pustular psoriasis** | 43 (14.6) | 37 (86.1) 6 (13.9) | 28–77 (53.8 ± 12.6) $p < 0.001$ * | 18.8–37.2 (26.4 ± 4.5) | 16–69 (45.7 ± 12.1) $p < 0.001$ * | 1 (2.3) |
| **Generalized pustular psoriasis** | 23 (7.8) | 13 (56.5) 10 (43.5) | 28–76 (54.9 ± 14.3) $p < 0.001$ * | 17.2–39.3 (27.0 ± 4.8) | 2–76 (45.5 ± 19.1) $p < 0.001$ * | 4 (17.4) |

### *2.3. Psychometric and Clinical Assessments*

QoL was assessed with the Dermatology Life Quality Index (DLQI), which contains ten questions covering different topics related to skin disease such as symptoms, change in habits, hobbies, clothing style, leisure and social activities [12–14]. Because of its simplicity and reliable grading, DLQI is widely used in numerous clinical and non-clinical studies. The minimum and the maximum scores vary between 0 and 30, and the higher the score the higher the QoL impairment. Sleeping problems were evaluated using 3 simple questions about problems in falling asleep, frequent awakenings and using sleeping medication.

The 11-point Numerical Rating Scale ranging from 0 (no pruritus) to 10 (worst imaginable pruritus) was used to assess the maximal (NRSmax) and average (NRSaverage) intensity of pruritus during the last three days [15]. The other method of pruritus intensity measurement was the 10-item Pruritus Severity Scale (10-PSS) [16]. In this scale, questions about the severity of pruritus (two questions), duration of itch episodes (one question), localization of pruritus (one question), influence on patient's concentration and psyche (four questions), and scratching behaviors in response to itching (two questions) were included. 10-PSS scoring ranges from 3 to 20 with a higher score indicating more intense pruritus.

Disease severity was measured with the Body Surface Area (BSA), and the Static Physician Global Assessment (sPGA) in all patients as well as with the Psoriasis Area and Severity Index (PASI) in patients with large-plaque psoriasis, small-plaque psoriasis, guttate psoriasis, palmoplantar psoriasis, psoriasis of the scalp, inverse psoriasis and erythrodermic psoriasis [17,18]. Patients with PPPP were assessed with the Palmoplantar Pustulosis Severity Index (PPSI), while those suffering from GPP according to the Generalized Pustular Psoriasis Severity Index (GPPSI) [19,20].

### 2.4. Statistical Analyses

The Statistica 13.0 (Statsoft, Krakow, Poland) software was employed for statistical analysis. Means, standard deviations (SD), maximum, minimum, median values, and frequencies were calculated. The differences between the comparted groups of patients were verified with the analysis of variance (ANOVA) and with a regression analysis. Correlations between analyzed parameters were verified by using the Spearman's rank correlation test. X2 was used to analyze the frequency differences. The results were considered statistically significant if the $p$-value was less than 0.05.

## 3. Results

### 3.1. Quality of Life and Sleep Disturbances in Psoriasis

The QoL of almost all patients was impaired. The mean DLQI in the entire population was 12.7 ± 7.9 points. Based on DLQI scoring, the majority of patients demonstrated a very large effect ($n$ = 108; 36.7%) or extremely large effect ($n$ = 69; 26.5%) of psoriasis on QoL. Only 22 subjects (7.5%) reported no influence (DLQI scoring: 0 or 1) and 44 (15.0%) reported a small effect (DLQI: 2–5 points) of psoriasis on QoL. Comparison of DLQI scoring between different clinical psoriasis subtypes revealed the highest impact on QoL in the erythrodermic psoriasis variant (mean DLQI: 18.1 ± 6.9; $p < 0.001$ compared to other subtypes; Figure 1). There were no significant differences in the remaining psoriasis subgroups regarding QoL (Figure 1). The degree of the impact of psoriasis on QoL in different clinical variants according to DLQI score were summarized on Figure 2.

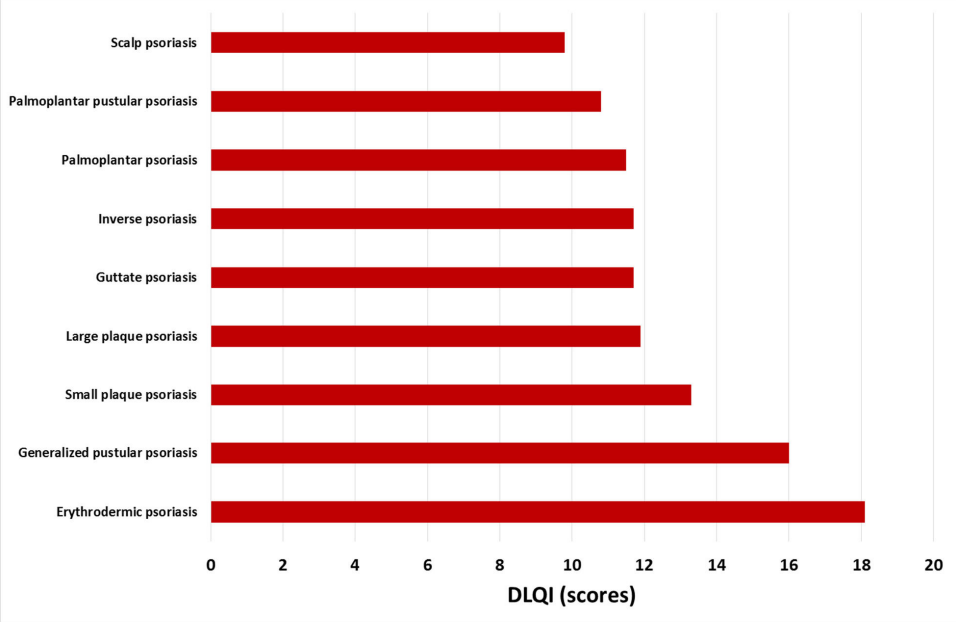


**Figure 1.** Mean Dermatology Life Quality Index score by clinical subtypes of psoriasis.

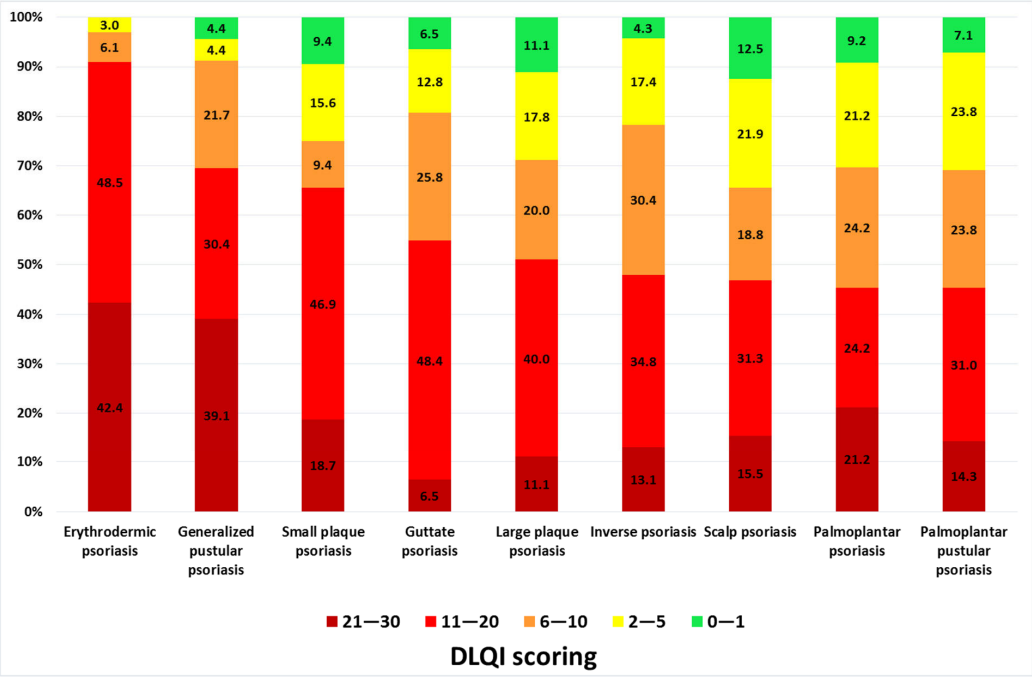


**Figure 2.** Degree of psoriasis impact on quality of life based on Dermatology Life Quality Index (DLQI) scoring in various clinical variants of psoriasis (0–1—no effect, 2–5—small effect, 6–10—moderate effect, 11–20—very large effect, 21–30—extremely large effect on patient's life).

Regarding sleeping problems, 39.3% ($n$ = 116) of patients reported occasional difficulties in falling asleep, and 22.7% of them ($n$ = 67) had such problems almost every day. Moreover, 20.3% ($n$ = 60) woke up during sleep almost every night, and a further 33.6% ($n$ = 99) reported such problem sporadically. However, the majority of participants (79.0%) did not take any sleeping medications. We did not find any differences regarding sleeping problems and clinical variants of psoriasis (data not shown).

### *3.2. Factors Influencing Quality of Life*

The statistical analysis between skin lesion severity indices (PASI, BSA, sPGA, PPSI, GPPSI) and the DLQI indicated that patients with more severe psoriasis had more impaired QoL (Table 2). Higher DLQI scoring indicating a more impaired QoL was also observed in patients suffering from pruritus within previous three days compared to subjects without pruritus (DLQI in the group with pruritus: 13.5 ± 7.5 points vs. DLQI in the group without pruritus: 8.0 ± 8.0 points; $p < 0.001$), with the highest DLQI scoring observed in patients with generalized pruritus (mean DLQI: 16.9 ± 7.6 points). As shown in Table 2, DLQI correlated with all pruritus intensity measurements (NRSmax, NRSaverage, 10-PSS). Interestingly, a low, albeit significant, correlation was also observed between DLQI and BMI (Body Mass Index: $\rho = 0.17$, $p = 0.004$). However, DLQI scoring was independent of gender (females: 12.4 ± 7.7 points vs. males: 12.8 ± 8.1 points, $p = 0.66$), age ($\rho = 0.03$, $p = 0.61$), psoriasis duration ($\rho = 0.03$, $p = 0.6$) and the coexistence of psoriatic arthritis (with psoriatic arthritis: 13.4 ± 8.7 points vs. without psoriatic arthritis: 12.6 ± 7.8 points, $p = 0.59$).

**Table 2.** Correlations between Dermatology Life Quality Index (DLQI) and indices of psoriasis severity and pruritus intensity according to Spearman rank correlation test (10-PSS—10-item Pruritus Severity Scale, BSA—Body Surface Area, GPPSI—Generalized Pustular Psoriasis Severity Index, $NRS_{average}$—average Numerical Rating Scale, $NRS_{max}$—maximal Numerical Rating Scale, PASI—Psoriasis Area and Severity Index, PPSI—Palmoplantar Pustulosis Severity Index, sPGA—static Physician Global Assessment).

| | DLQI | | |
|---|---|---|---|
| | ***n*** | **Spearman Rank Correlation Coefficient (ρ)** | ***p*** |
| **PASI** | 209 | 0.41 | <0.001 |
| **BSA** | 281 | 0.38 | <0.001 |
| **sPGA** | 293 | 0.37 | <0.001 |
| **GPPSI** | 23 | 0.34 | 0.12 |
| **PPSI** | 42 | 0.52 | <0.001 |
| **$NRS_{max}$** | 274 | 0.39 | <0.001 |
| **$NRS_{average}$** | 274 | 0.34 | <0.001 |
| **10-PSS** | 263 | 0.51 | <0.001 |

The marked influence of pruritus intensity on QoL may be, at least partially, explained by sleeping problems caused by pruritus. Difficulties in falling asleep, occurring even rarely, similarly to awakenings during the sleep, meaningfully impacted the QoL (Table 3). Patients using sleeping pills also had more reduced QoL than those who did not (Table 3).

**Table 3.** Comparison of quality of life in relation to the sleeping problems (DLQI—Dermatology Life Quality Index).

| | | ***n*** | **Mean DLQI Scoring** | ***p*** |
|---|---|---|---|---|
| Problems in falling asleep | Almost always | 67 | 17.3 ± 7.1 | <0.001 |
| | Rarely | 115 | 13.5 ± 7.0 | |
| | Never | 111 | 9.0 ± 7.5 | |
| Awakenings during the night | Almost every night | 60 | 17.4 ± 7.0 | <0.001 |
| | Rarely | 98 | 13.9 ± 7.5 | |
| | Never | 135 | 9.7 ± 7.2 | |
| Use of sleeping medication | Almost every day | 10 | 18.4 ± 7.0 | <0.001 |
| | Rarely | 51 | 15.5 ± 7.0 | |
| | Never | 232 | 11.8 ± 7.9 | |

The multiple regression analysis considering all above-mentioned parameters indicated that the involvement of body area by psoriasis (BSA), intensity of pruritus measured with 10-PSS and the occurrence and frequency of awakenings during the night caused by itching are all independent factors determining QoL in psoriatic patients.

### *3.3. Relationship between Pruritus and Sleep Disturbance*

The sleeping problems reported were linked with pruritus intensity. Patients who had more severe pruritus measured with 10-PSS, NRSmax, and NRSaverage more commonly reported difficulties in falling asleep, awakenings from sleep and the need to use sleeping pills (Table 4). All differences between compared groups were significant ($p < 0.001$ for all comparisons in-between the subgroups).

**Table 4.** Comparison of pruritus intensity in relation to the sleeping problems (10-PSS—10-item Pruritus Severity Scale, $NRS_{average}$—average Numerical Rating Scale, $NRS_{max}$—maximal Numerical Rating Scale).

| | | Mean $NRS_{max}$ | *p* | Mean $NRS_{average}$ | *p* | Mean 10-PSS | *p* |
|---|---|---|---|---|---|---|---|
| Problems in falling asleep | Almost always | 7.3 ± 2.2 | <0.001 | 6.0 ± 2.5 | <0.001 | 13.5 ± 3.5 | <0.001 |
| | Rarely | 5.5 ± 2.2 | | 4.1 ± 2.1 | | 9.4 ± 3.1 | |
| | Never | 3.3 ± 2.7 | | 2.6 ± 2.5 | | 5.8 ± 3.8 | |
| Awakenings during the night | Almost every night | 7.3 ± 2.3 | <0.001 | 6.1 ± 2.6 | <0.001 | 13.3 ± 3.4 | <0.001 |
| | Rarely | 5.6 ± 2.3 | | 4.2 ± 2.2 | | 9.7 ± 3.6 | |
| | Never | 3.8 ± 2.7 | | 2.8 ± 2.4 | | 6.5 ± 3.9 | |
| Use of sleeping medication | Almost every day | 8.2 ± 1.7 | <0.001 | 7.4 ± 2.5 | <0.001 | 15.1 ± 3.0 | <0.001 |
| | Rarely | 6.4 ± 2.5 | | 4.8 ± 2.3 | | 10.7 ± 3.5 | |
| | Never | 4.7 ± 2.8 | | 3.6 ± 2.6 | | 8.3 ± 4.5 | |

### *3.4. Correlation between Severity of Pruritus and Quality of Life and Sleep Disturbances in Different Clinical Subtypes of Psoriasis*

The intensity of pruritus was correlated with impairment of the QoL and the QoL impairment in patients with psoriasis of the scalp and palmoplantar pustular psoriasis. Surprisingly, QoL of patients suffering from erythrodermic and small-plaque psoriasis did not depend on the severity of itching (Table 5).

**Table 5.** Correlations between pruritus intensity and quality of life according to the Spearman rank correlation test in different subtypes of psoriasis (10-PSS—10-item Pruritus Severity Scale, DLQI—Dermatology Life Quality Index, $NRS_{average}$—average Numerical Rating Scale, $NRS_{max}$—maximal Numerical Rating Scale).

| | | Large-Plaque Psoriasis | Small-Plaque Psoriasis | Guttate Psoriasis | Palmo-Plantar Psoriasis | Psoriasis of the Scalp | Inverse Psoriasis | Erythrodermic Psoriasis | Palmoplantar Pustular Psoriasis | Generalized Pustular Psoriasis |
|---|---|---|---|---|---|---|---|---|---|---|
| DLQI vs. | $NRS_{average}$ | **ρ = 0.51, *p* < 0.001** | ρ = 0.17, *p* = 0.37 | ρ = 0.18, *p* = 0.35 | ρ = 0.27, *p* = 0.12 | **ρ =0.52, *p* = 0.003** | ρ = 0.17, *p* = 0.44 | ρ = 0.15, *p* = 0.41 | **ρ = 0.43, *p* = 0.004** | **ρ = 0.48, *p* = 0.02** |
| | $NRS_{max}$ | **ρ = 0.56, *p* < 0.001** | ρ = 0.07, *p* = 0.71 | ρ = 0.3 *p* = 0.11 | ρ = 0.29, *p* = 0.11 | **ρ = 0.43, *p* = 0.01** | **ρ = 0.42, *p* < 0.05** | ρ = 0.25, *p* = 0.15 | **ρ = 0.53, *p* < 0.001** | ρ = 0.34, *p* = 0.11 |
| | 10-PSS | ρ = 0.16, *p* = 0.29 | ρ = 0.14, *p* = 0.43 | **ρ = 0.54, *p* = 0.002** | **ρ = 0.51, *p* = 0.003** | **ρ = 0.64, *p* < 0.001** | ρ = 0.38, *p* = 0.08 | ρ = 0.18, *p* = 0.32 | **ρ = 0.56, *p* < 0.001** | **ρ = 0.41, *p* < 0.05** |

The clinical subtype of psoriasis was not related to difficulties with falling asleep ($p = 0.83$), awakenings during the night ($p = 0.84$), or the need to use the sleeping pills ($p = 0.34$).

## 4. Discussion

Our cross-sectional, binational study, including a wide spectrum of clinical subtypes of psoriasis, demonstrated the influence of the disease severity on the QoL, irrespective of the particular psoriasis variant. The mean DLQI scoring in our cohort of patients was 12.7 points, indicating on average a large effect of psoriasis on patients' QoL. In the past, many researchers also investigated the QoL of psoriasis patients and obtained similar results demonstrating that psoriasis is a chronic dermatosis which exerts a profound effect on patients' well-being [21–25]. However, in other studies, physicians were focused on various factors that might play a crucial role in lowering the QoL such as the presence of pruritus, occupation of the anogenital area by the disease or visibility of skin lesions [24–27]. Data comparing QoL in different clinical subtypes of psoriasis are quite limited, as the previously published reports are predominated by the patients suffering from plaque-type

psoriasis, which is the most common one. Here, we aimed to analyze whether the level of QoL impairment may differ between various psoriasis variants. We also compared included participants with various psoriasis subtypes regarding sleeping problems.

As presented above, patients with erythrodermic psoriasis had a lower QoL than subjects with other disease subtypes. Systemic symptoms such as chills and fever together with malaise and weakness may be a good explanation for the low QoL in erythrodermic patients, but other factors may also play a role. Pruritus is one of the most relevant clinical parameters that may determine the degree of QoL impairment. In concordance with previous studies [27–32], our data confirmed that pruritus in psoriasis is very frequent, reaching the prevalence of up to 100% in some psoriasis variants, e.g., small-plaque-type psoriasis, scalp psoriasis, and generalized pustular psoriasis [9]. The severity of pruritus correlated with the impairment of QoL, particularly in scalp psoriasis and palmoplantar pustular psoriasis. This observation is slightly surprising as these subtypes were characterized by the lowest mean DLQI scoring (9.8 and 10.8, respectively) among all analyzed subgroups.

QoL was decreased in patients with sleeping disorders. The importance of good sleep for overall well-being is well documented and an insufficient amount of high-quality sleep affects many aspects of life [4]. In our study, the most frequent complaint was difficulty with falling asleep, signaled by 70% of patients. Additionally, more than half of them had to wake up from sleep during the night. In the majority of participants, sleeping problems usually did not appear to be strong enough to result in it being necessary to use sleeping pills. As found in our study, itching can directly affect sleep and patients with more severe pruritus had more difficulties in falling asleep, more frequently report awakenings during the night and more commonly needed to use the sleeping pills. Jensen et al. obtained similar results, and identified the intensity of pruritus as the major predictor of sleep impairment [33]. Hawro et al. [5] also noted that the difficulty in falling asleep was related to itching and explained this by the coexistence of negative emotions such as irritation and discomfort accompanying the pruritus. However, in this study, pruritus intensity did not appear to be sufficiently strong to result in awakenings during the night, which was contrary to our results.

Our study had some limitations. At first, only the DLQI was used to assess QoL, without a QoL-specific instrument for psoriasis. However, DLQI is a widely used method of QoL assessment and in many studies it is the major way how QoL impairment is assessed. Furthermore, sleeping disorders were diagnosed on the basis of three simple questions instead of a validated questionnaire, such as Athens Insomia Scale or Pittsburgh Sleep Quality Index [34,35]; however, we have used them successfully in our previous studies in patients suffering from pruritus [9,36,37] and they were used also by other authors [38,39].

## 5. Conclusions

QoL and the sleep quality of patients suffering from different subtypes of psoriasis are markedly decreased. The healthcare systems should aim to holistically manage psoriatic patients. To make it possible there is a need to focus not only on the objective severity of the disease but also on its impact on the QoL and sleep, as well as on subjective symptoms. Identifying the most disturbed area of life and recognizing the most bothersome symptoms of psoriasis are pivotal to choose the right treatment and achieve a therapeutic success. Pruritus should always be considered as one of key factors determining QoL, and its reduction should always be an important therapeutic goal.

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**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** Data is contained within the article.

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ORIGINAL ARTICLE

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# Characteristics of pruritus in various clinical variants of psoriasis: Final report of the binational, multicentre, cross-sectional study

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**Abstract**

**Background:** Pruritus, which is the most frequent subjective symptom of psoriasis, may cause significant discomfort, embarrassment and even interfere with patients normal daily activities. However, the perception of itch in various psoriasis subtypes remains unknown.

**Objectives:** The aim of this study was to investigate and to characterize pruritus in different clinical variants of psoriasis.

**Methods:** This cross-sectional, binational, multicentre study included 295 subjects suffering from nine different clinical subtypes of psoriasis: large-plaque psoriasis ($n$ = 45), nummular psoriasis ($n$ = 32), guttate psoriasis ($n$ = 31), scalp psoriasis ($n$ = 32), inverse psoriasis ($n$ = 23), erythrodermic psoriasis ($n$ = 33), palmoplantar psoriasis vulgaris ($n$ = 33), palmoplantar pustular psoriasis ($n$ = 42) and generalized pustular psoriasis ($n$ = 23). Measures included sociodemographic and anthropometric data, detailed pruritus characteristics including but not limited to pruritus intensity, frequency and extend, as well as psoriasis severity.

**Results:** The lifetime prevalence of pruritus in each clinical variant of psoriasis was similar and quite high, reaching up to 100% in some disease subtypes (i.e., nummular psoriasis, scalp psoriasis and generalized pustular psoriasis). Psoriasis severity correlated with pruritus intensity in scalp psoriasis, palmoplantar pustular psoriasis and generalized pustular psoriasis. The age, duration of psoriasis and BMI did not interfere with the intensity of itch.

**Conclusions:** Pruritus is highly prevalent in each clinical variant of psoriasis. However, the sensation of itch is very individual, difficult to universally describe even in the same subtype.

## INTRODUCTION

Psoriasis is one of the most common chronic dermatoses, affecting at least 100,000,000 individuals worldwide, which constitutes about 3% of the general population.[1,2] Based on clinical presentation, psoriasis can be categorized into various subtypes such as plaque-type psoriasis, inverse or flexural psoriasis, nummular psoriasis, guttate psoriasis, scalp psoriasis, palmoplantar psoriasis, erythrodermic psoriasis and pustular psoriasis including palmoplantar pustular psoriasis (PPPP) and generalized pustular psoriasis (GPP). The letter subtypes are characterized by the formation of sterile pustules on an erythematous base resulting from massive epidermal neutrophil infiltration.[3,4]

Irrespectively of clinical variant, skin lesions in psoriasis are often accompanied by subjective symptoms, which may cause significant discomfort and embarrassment and their intensity and constant presence can significantly interfere

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with normal daily activities.[5] However, in the past, according to the classic textbook description, psoriasis did not itch. As recently as the mid-1980s, pruritus was considered an occasional rather than a major complain of psoriatic patients. Nowadays, pruritus, defined as an unpleasant sensation that provokes a desire to scratch, is often found in psoriasis and for many patients it is often the most important, the most frequent and the most bothersome subjective sensation.[6] However, itch sensation may be experienced differently among patients with various skin conditions.[7] Compared with other pruritic dermatoses, it was shown that patients with atopic dermatitis experienced pruritus more frequently and more intensely, while patients with psoriasis reported greater embarrassment associated with itch.[7] Similarly, Chernyshow observed higher itch scoring in atopic dermatitis patients than in psoriasis subjects, and itch in atopic dermatitis resulted in greater negative impact on quality of life.[8] Comparing lichen planus with psoriasis showed that pruritus was highly prevalent in both conditions. Patients with lichen planus experienced significantly more intense pruritus than those with psoriasis but excoriations were more frequently observed in psoriasis.[9] Although pruritus in psoriasis may not be as intense as in other pruritic conditions, it is still considered by many patients to be the most bothersome disease symptom.[10]

However, it is important to be able to effectively control itching to prevent scratching-induced worsening of skin lesions (Koebner's phenomenon[6]) and to improve patients' quality of life and sleep. The molecular basis of this symptom in psoriasis is still not fully elucidated, albeit a complex interaction between the nervous, neuroendocrine, immune and vascular systems is suggested. Histamine and mast cells, substance P and other neuropeptides, nerve growth factor (NGF) and innervation abnormalities, vascular endothelial growth factor (VEGF), interleukins (e.g., IL-2, IL-4, IL-31), endogenous opioids and lipocalin-2 can modulate pruritus associated with psoriasis but to date no single mediator has been proven to be a key one.[11]

While searching the PubMed or other databases, several reports characterizing pruritus in psoriasis can be found. However, most of them only refer to plaque psoriasis. Recently preliminary results of the study on itching in various clinical variants of psoriasis were published by our group.[12] Now, we would like to present the final report of a multinational, cross-sectional study conducted by our group from June 1st, 2020, till November 30th, 2021, in which we describe the characteristics of pruritus in different clinical variants of psoriasis.

## MATERIALS AND METHODS

### Study design

This research was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee by Subcarpathian Physician Chamber in Rzeszow and by Gazi University Ethics Committee. All subjects or their legal representatives signed an informed consent form before initiation of the study. Participants did not receive any financial compensation for study participation.

A total of 338 participants with psoriasis diagnosed based on the clinical manifestation and/or histopathological assessment of skin biopsies were enrolled into this study. A total of six dermatology centres were involved in the patients' recruitment – five from Poland: Bydgoszcz ($n$ = 52), Łódź ($n$ = 39), Olsztyn ($n$ = 20), Rzeszów ($n$ = 102), Wrocław ($n$ = 43) and one from Ankara in Turkey ($n$ = 82). Patients undergoing antipsoriatic treatment and those who had been treated for psoriasis with systemic agents or phototherapy within the prior 4 weeks or with topical antipsoriatic treatment within 2 weeks before the assessment were considered as not eligible. Other concomitant dermatological or systemic disorders that might cause pruritus such as, for example urticaria, chronic uraemia or cholestasis, and use of medications that could influence the sensation of itch were also exclusive. Thus, 43 individuals were excluded from further analysis due to above mentioned exclusion criteria. Two hundred ninety-five remaining patients were divided into nine groups according to the dominant subtype of psoriasis: large-plaque psoriasis ($n$ = 45), nummular psoriasis ($n$ = 32), guttate psoriasis ($n$ = 31), palmoplantar psoriasis ($n$ = 33), psoriasis of the scalp ($n$ = 32), inverse psoriasis ($n$ = 23), erythrodermic psoriasis ($n$ = 33), PPPP ($n$ = 42) and GPP ($n$ = 23). Detailed characteristics of the study participants was presented in Table 1.

In each site the same standardized questionnaire was used.[12] The first part of the survey included demographic data (gender, age), anthropometric measurements (weight, growth), history and dominant subtype of psoriasis, as well as comorbidities and concurrent treatment. The second part was focused on psoriatic pruritus and the disease severity. Participants were asked to answer short questions about lifetime prevalence of pruritus as well as questions about its duration, localization (within lesional skin, within non-lesional skin or involving all of the body) and frequency of itching. Patients were also requested to choose from the predefined list of terms that best described their feelings of pruritus. Individuals who experienced pruritus within the last 3 days before the examination evaluated its maximal and average intensity with the 11-point Numerous Rating Scale ($NRS_{max}$ and $NRS_{average}$, respectively) from 0 (no pruritus) to 10 (worst imaginable pruritus).[13] The 10-item Pruritus Severity Scale (10-PSS) was used as another method of pruritus intensity measurement in order to make this study more objective and reliable.[14]

Disease severity was assessed in all patients according to the Body Surface Area (BSA) and Static Physician Global Assessment (sPGA).[15] Severity of large-plaque psoriasis, nummular psoriasis, guttate psoriasis, palmoplantar psoriasis, psoriasis of the scalp, inverse psoriasis and erythrodermic psoriasis was measured with Psoriasis Area and Severity Index (PASI).[16] Patients with PPPP were assessed according to Palmoplantar Pustulosis Severity Index (PPSI),[17] while

**TABLE 1** Comparison of demographic, anthropometric and clinical data in patients with various clinical subtypes of psoriasis

| | Plaque-type psoriasis | Nummular psoriasis | Guttate psoriasis | Palmoplantar psoriasis | Scalp psoriasis | Inverse psoriasis | Erythrodermic psoriasis | Palmoplantar pustular psoriasis | Generalized pustular psoriasis | *p* |
|---|---|---|---|---|---|---|---|---|---|---|
| Number of patients (%) | 45 (15.3) | 32 (10.8) | 31 (10.5) | 33 (11.2) | 32 (10.8) | 23 (7.8) | 33 (11.2) | 43 (14.6) | 23 (7.8) | - |
| Female (%) | 15 (33.3) | 11 (34.4) | 14 (45.2) | 18 (54.6) | 19 (59.4) | 12 (52.2) | 9 (27.3) | 37 (86.1) | 13 (56.5) | <0.001 |
| Male (%) | 30 (66.7) | 21 (65.6) | 17 (54.8) | 15 (45.4) | 13 (40.6) | 11 (47.8) | 24 (72.7) | 6 (13.9) | 10 (43.5) | |
| Age (mean ± SD) | 46.7 ± 15.9 | 40.6 ± 13.6 | 37.5 ± 11.6 | 45.3 ± 14.9 | 34.9 ± 12.4 | 41.5 ± 14.0 | 47.5 ± 16.6 | 53.8 ± 12.6 | 54.9 ± 14.3 | <0.001 |
| Min–Max (years) | 17–77 | 16–69 | 17–73 | 16–71 | 16–61 | 18–67 | 18–71 | 28–77 | 28–76 | |
| BMI (mean ± SD) | 30.2 ± 5.5 | 26.4 ± 5.3 | 27.5 ± 6.4 | 28.3 ± 5.7 | 24.2 ± 4.4 | 29.3 ± 5.6 | 27.8 ± 6.4 | 26.4 ± 4.5 | 27.0 ± 4.8 | <0.001 |
| Min–Max (kg/m$^2$) | 21.4–42.8 | 14.5–37.6 | 19.5–46.0 | 18.1–43.4 | 15.4–34.1 | 18.8–41.5 | 17.6–44.5 | 18.8–37.2 | 17.2–39.3 | |
| Age at disease onset (mean ± SD) | 30.3 ± 17.5 | 27.3 ± 15.1 | 24.0 ± 12.1 | 36.1 ± 16.5 | 23.7 ± 11.7 | 30.7 ± 14.2 | 31.9 ± 16.7 | 45.7 ± 12.1 | 45.5 ± 19.1 | <0.001 |
| Min–Max (years) | 6–72 | 3–58 | 7–53 | 10–69 | 6–50 | 13–60 | 3–60 | 16–69 | 2–76 | |
| Coexisting psoriatic arthritis (%) | 5 (11.1) | 2 (6.3) | 4 (12.9) | 2 (6.1) | 2 (6.3) | 2 (8.7) | 5 (15.2) | 1 (2.3) | 4 (17.4) | 0.49 |
| PASI/GPPSI/PPSI* (mean ± SD) | 14.1 ± 10.0 | 13.8 ± 8.4 | 11.4 ± 5.5 | 4.3 ± 2.2 | 2.5 ± 1.8 | 6.5 ± 4.3 | 35.3 ± 10.2 | 7.0 ± 1.9 | 4.8 ± 1.7 | - |
| Min–Max | 0.6–37.6 | 1.6–45.2 | 3.2–22.2 | 0.6–10.0 | 0.3–8.0 | 0.9–14.6 | 17.8–55.6 | 4–11 | 1–8 | |
| BSA (mean ± SD) | 28.7 ± 21.4 | 21.5 ± 10.4 | 20.1 ± 10.3 | 4.7 ± 2.3 | 4.8 ± 4.2 | 6.7 ± 4.2 | 86.7 ± 7.4 | 2.8 ± 1.2 | 29.8 ± 18.4 | - |
| Min–Max | 2–89 | 4–50.5 | 7–41 | 1–9 | 1–21 | 0.9–20 | 70–100 | 0.5–5 | 2–70 | |
| sPGA (mean ± SD) | 3.3 ± 1.2 | 3.1 ± 0.9 | 3.1 ± 0.7 | 2.8 ± 0.8 | 2.9 ± 0.8 | 2.7 ± 0.9 | 4.2 ± 0.8 | 3.3 ± 0.9 | 3.6 ± 1.0 | - |
| Min–Max | 1–5 | 2–5 | 2–5 | 2–4 | 2–4 | 1–4 | 3–5 | 2–5 | 1–5 | |

Abbreviations: BMI, body mass index; BSA, body surface area; GPPSI, generalized pustular psoriasis severity index; Max, maximum; Min, minimum; PASI, psoriasis area and severity index; PPSI, palmoplantar pustulosis severity index; SD, standard deviation.

*Disease severity was assessed with GPPSI in case of generalized pustular psoriasis, with PPSI in palmoplantar pustular psoriasis, and with PASI in all other types of psoriasis.

GPP involvement was evaluated according to Generalized Pustular Psoriasis Severity Index (GPPSI).[18]

## Statistical analysis

Statistical analysis was performed using Statistica® 13.0 (Statsoft). Means, standard deviations (SD), median values and frequencies were calculated. The differences between the groups of patients were analysed using the Student's *t*-test for independent variables, Mann–Whitney *U*-test and analysis of variance (ANOVA), where appropriate. Spearman's rank correlation test was used to verify correlations between analysed parameters. To determine whether there was a significant difference between the expected and observed frequencies in one or more categories $X^2$ test was used. $p$-values < 0.05 were considered significant.

# RESULTS

## Prevalence, severity, localization and factors influencing pruritus

Our study showed that in various psoriasis subtypes the lifetime prevalence of pruritus was high and ranged between 86.1% and 100% ($p = 0.12$). The point prevalence of pruritus (the presence of this symptom within the 3 days preceding the examination) was also high (74.4%–93.8%). The intensity of pruritus ranged from no pruritus (0 points) to the worst imaginable pruritus (10 points) and was lowest in inverse and nummular psoriasis and highest in erythrodermic psoriasis. Interestingly, the intensity of pruritus did not significantly differ between various psoriasis subtypes. Moreover, both the age of the patients and duration of psoriasis did not interfere with the acuteness of the itch. Similarly, there was a lack of relationship between BMI and NRS average or NRS max, or 10-PSS. The sensation of itch was generally limited to the skin lesions. Only some individuals experienced pruritus also in non-lesional skin or suffered from generalized pruritus. The one exception was erythrodermic psoriasis where majority of patients reported itching of the entire body (Figure 1).

## Individual itching sensation

The most common terms used to describe pruritus in all investigated subtypes of psoriasis were burning, pinching and tingling. Interestingly, patients with both papulosquamous and pustular forms of palmoplantar psoriasis significantly more often reported their itch as deep (21.2% and 2.6%, respectively), stinging (21.2% and 18.6%, respectively) and painful (36.4% and 34.9%, respectively) ($p < 0.05$ for all comparisons). Painful and stinging pruritus was more frequently noted by patients suffering from generalized pustular psoriasis (34.8% and 26.1%, respectively). These patients alike those with erythrodermic psoriasis stated their itch also as biting (26.1% and 18.2%) ($p < 0.05$). More than 20% of patients suffering from large-plaque psoriasis characterized itch as painful while the same number of participants with inverse psoriasis named their itch as point itch. Patients with scalp and erythrodermic psoriasis quite often reported pruritus like walking ants. A unique observation in both pustular variants of this disease was the sensation of warming feeling present in more than one-fifth of patients.

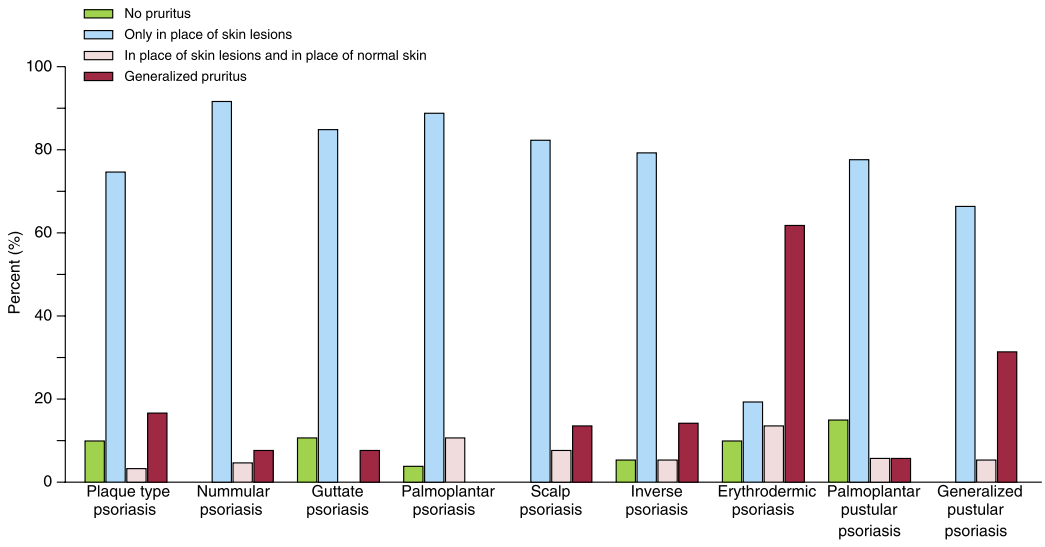


**FIGURE 1** Localization of pruritus in various psoriasis subtypes.

Frequency of terms describing pruritus, used by the subjects, according to each subtype of psoriasis was presented on Figure 2.

Nummular, guttate, palmoplantar, inverse, erythrodermic psoriasis, psoriasis of the scalp and palmoplantar pustular psoriasis mainly described pruritus as 'disturbing' and 'irritating'. In generalized pustular psoriasis, patients equally often used the adjective 'distressing' and 'annoying'. In large-plaque psoriasis, subjects also choose the term 'disturbing'. Nevertheless, one-fourth of them defined pruritus

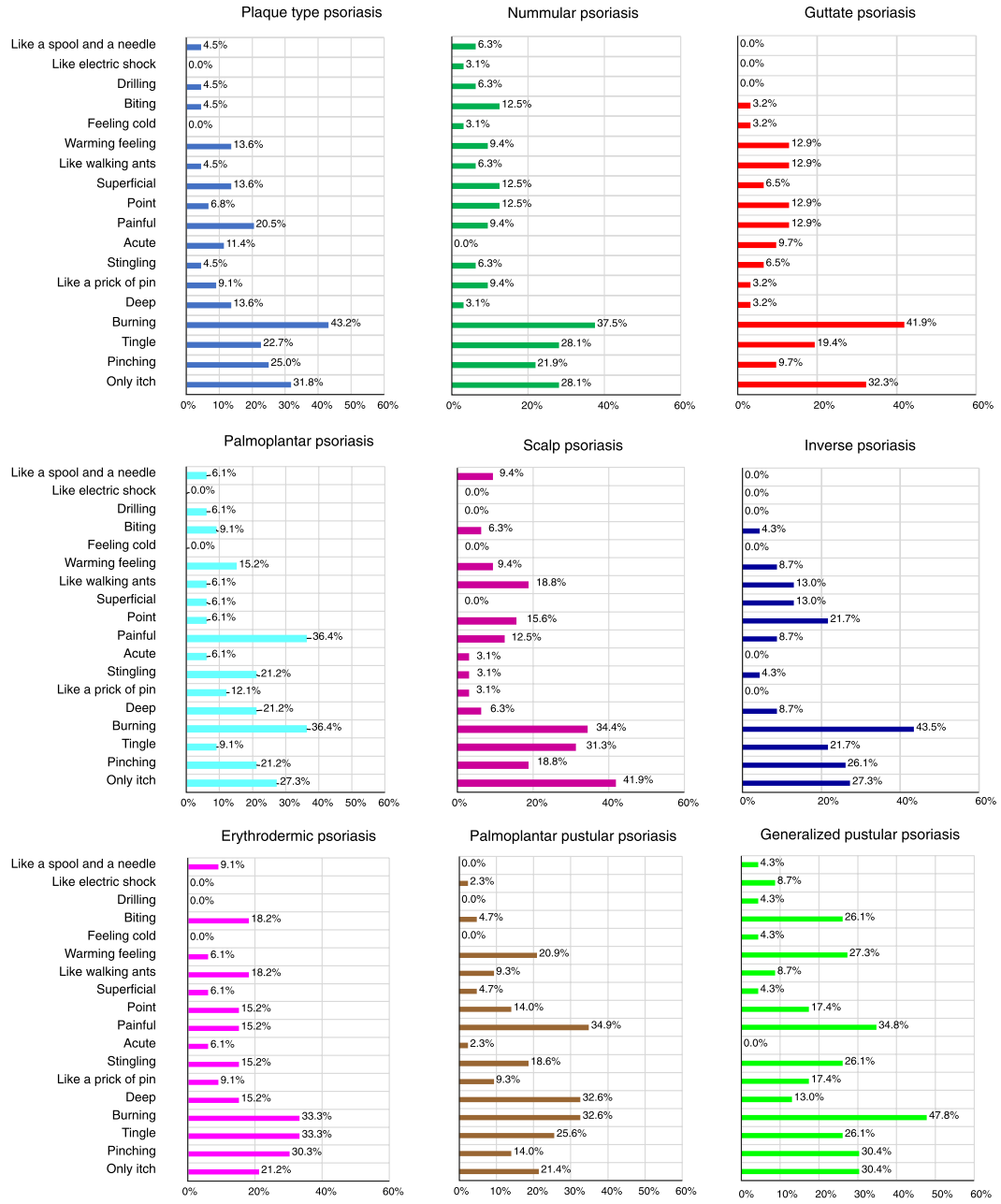


**FIGURE 2** Terms describing pruritus in various subtypes of psoriasis.

as 'irritating' and 'annoying'. However, only regarding the term 'irritating', the differences between the studied groups were statistically significant (Figure 3).

## Frequency, appearance and relief of pruritus

Great majority of patients reported pruritus every day (45.5%–78.8%) or a few times a week (21%–36.4%) in each subpopulation ($p = 0.42$). However, in erythrodermic psoriasis, 78.8% of responders complained of everyday itch, which was the highest prevalence in our study. Contrarily, within the group of inverse psoriasis, only 45.5% of patients suffer from everyday pruritus. Participants were also asked when the sensation of pruritus is the most intense. Possible answers were during the evolution of skin lesions, when skin lesions are fully developed, when skin lesion extend their size, or they could answer that the severity of itch has nothing to do with the appearance of skin lesions. Some differences were observed across all the groups; however, they were not statistically significant. Patients usually answered that the most intense itch accompanies appearance of new skin lesions or occurs when they are fully developed. It is worth noting that half of the patients with scalp psoriasis felt itch during the formation of psoriatic lesions. In palmoplantar psoriasis, more than half of responders (54.5%) reported the greatest pruritus when skin lesions were fully developed. The only one exception, where the most intense pruritus was most often associated with the extension of skin lesions, stated the group of generalized pustular psoriasis (45.5%). Apart from scalp psoriasis, pruritus discontinued predominantly after significant clinical improvement of skin lesions in each clinical variant of psoriasis. Interestingly, 34.4% of patients with scalp psoriasis declared that the itch stopes when the skin lesions disappear entirely and this was the most common answer in this population. An intriguing fact was the persistence of pruritus despite vanishing skin lesions in 18.2% cases with erythrodermic psoriasis. Differences in relief of pruritus were also not statistically significant ($p = 0.35$).

## Correlations between intensity of pruritus and disease severity

In psoriasis of the scalp, palmoplantar pustular psoriasis and generalized pustular psoriasis, a statically significant, positive correlation between disease severity and pruritus intensity was observed. In nummular psoriasis and palmoplantar psoriasis, such correlation was noted when pruritus was measured according to the 10-PSS index. Surprisingly, in large plaque, guttate, inverse and erythrodermic psoriasis, there was no correlation between pruritus and disease severity. The detailed analysis conducted by our group was presented in Table 2.

# DISCUSSION

The current study aims to show the differences in perception of pruritus between each subtype of psoriasis. That is why we focused on the analysis of each group and the investigation of disparities between them. The subtypes of psoriasis were distinguished according to the specific distribution and type of skin lesions. From the definition, surface of affected area

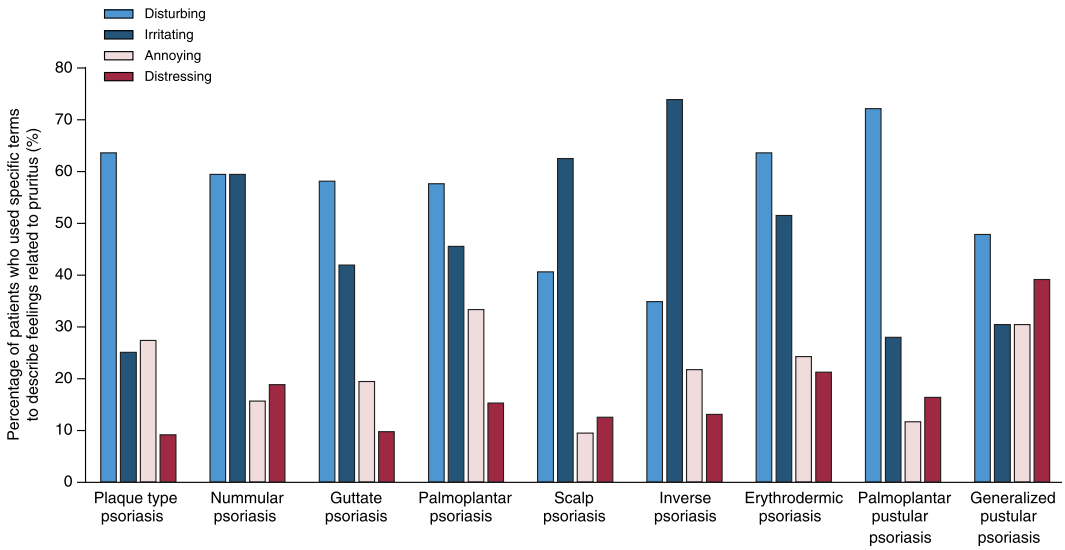


**FIGURE 3** Feelings related to pruritus in patients suffering from various psoriasis subtypes.

**TABLE 2** Correlations between pruritus intensity and disease severity according to the Spearman rank correlation test

| | Large-plaque psoriasis | Nummular psoriasis | Guttate psoriasis | Palmoplantar psoriasis | Psoriasis of the scalp | Inverse psoriasis | Erythrodermic psoriasis | Palmoplantar pustular psoriasis | Generalized pustular psoriasis |
|---|---|---|---|---|---|---|---|---|---|
| PASI versus | | | | | | | | | |
| $NRS_{average}$ | $\rho = 0.2$ | $\rho = 0.35$ | $\rho = 0.35$ | $\rho = 0.19$ | $\rho = 0.6$ | $\rho = 0.19$ | $\rho = 0.14$ | - | - |
| | $p = 0.25$ | $p = 0.06$ | $p = 0.06$ | $p = 0.3$ | $p < 0.001$ | $p = 0.4$ | $p = 0.44$ | | |
| $NRS_{max}$ | $\rho = 0.22$ | $\rho = 0.3$ | $\rho = 0.27$ | $\rho = 0.18$ | $\rho = 0.7$ | $\rho = 0.24$ | $\rho = 0.08$ | - | - |
| | $p = 0.21$ | $p = 0.11$ | $p = 0.16$ | $p = 0.32$ | $p < 0.001$ | $p = 0.3$ | $p = 0.66$ | | |
| 10-PSS | $\rho = -0.1$ | $\rho = 0.69$ | $\rho = 0.05$ | $\rho = 0.53$ | $\rho = 0.61$ | $\rho = 0.09$ | $\rho = 0.19$ | - | - |
| | $p = 0.58$ | $p < 0.001$ | $p = 0.78$ | $p = 0.002$ | $p < 0.001$ | $p = 0.71$ | $p = 0.3$ | | |
| BSA versus | | | | | | | | | |
| $NRS_{average}$ | $\rho = 0.15$ | $\rho = 0.33$ | $\rho = 0.28$ | $\rho = -0.07$ | $\rho = 0.69$ | $\rho = 0.33$ | $\rho = -0.18$ | $\rho = 0.36$ | $\rho = 0.6$ |
| | $p = 0.33$ | $p = 0.07$ | $p = 0.12$ | $p = 0.68$ | $p < 0.001$ | $p = 0.12$ | $p = 0.31$ | $p < 0.05$ | $p = 0.004$ |
| $NRS_{max}$ | $\rho = 0.17$ | $\rho = 0.3$ | $\rho = 0.19$ | $\rho = -0.11$ | $\rho = 0.72$ | $\rho = 0.36$ | $\rho = -0.29$ | $\rho = 0.37$ | $\rho = 0.68$ |
| | $p = 0.28$ | $p = 0.1$ | $p = 0.3$ | $p = 0.55$ | $p < 0.001$ | $p = 0.09$ | $p = 0.1$ | $p = 0.03$ | $p = 0.001$ |
| 10-PSS | $\rho = -0.12$ | $\rho = 0.51$ | $\rho = 0.12$ | $\rho = 0.45$ | $\rho = 0.46$ | $\rho = 0.32$ | $\rho = -0.11$ | $\rho = 0.21$ | $\rho = 0.73$ |
| | $p = 0.42$ | $p = 0.003$ | $p = 0.52$ | $p < 0.01$ | $p < 0.01$ | $p = 0.13$ | $p = 0.55$ | $p = 0.24$ | $p < 0.001$ |
| sPGA versus | | | | | | | | | |
| $NRS_{average}$ | $\rho = 0.27$ | $\rho = 0.29$ | $\rho = 0.27$ | $\rho = 0.59$ | $\rho = 0.6$ | $\rho = 0.37$ | $\rho = 0.3$ | $\rho = 0.44$ | $\rho = 0.5$ |
| | $p = 0.08$ | $p = 0.11$ | $p = 0.14$ | $p < 0.001$ | $p < 0.001$ | $p = 0.22$ | $p = 0.1$ | $p = 0.003$ | $p = 0.01$ |
| $NRS_{max}$ | $\rho = 0.31$ | $\rho = 0.37$ | $\rho = 0.27$ | $\rho = 0.57$ | $\rho = 0.54$ | $\rho = 0.29$ | $\rho = 0.27$ | $\rho = 0.53$ | $\rho = 0.61$ |
| | $p = 0.04$ | $p = 0.04$ | $p = 0.13$ | $p < 0.001$ | $p = 0.001$ | $p = 0.19$ | $p = 0.13$ | $p < 0.001$ | $p = 0.002$ |
| 10-PSS | $\rho = 0.01$ | $\rho = 0.58$ | $\rho = 0.11$ | $\rho = 0.56$ | $\rho = 0.5$ | $\rho = 0.03$ | $\rho = 0.17$ | $\rho = 0.65$ | $\rho = 0.47$ |
| | $p = 0.94$ | $p < 0.001$ | $p = 0.55$ | $p < 0.001$ | $p = 0.004$ | $p = 0.88$ | $p = 0.34$ | $p < 0.001$ | $p = 0.02$ |
| PPSI versus | | | | | | | | | |
| $NRS_{average}$ | - | - | - | - | - | - | - | $\rho = 0.46$ | - |
| | | | | | | | | $p = 0.002$ | |
| $NRS_{max}$ | - | - | - | - | - | - | - | $\rho = 0.53$ | - |
| | | | | | | | | $p < 0.001$ | |
| 10-PSS | - | - | - | - | - | - | - | $\rho = 0.6$ | - |
| | | | | | | | | $p < 0.001$ | |
| GPPSI versus | | | | | | | | | |
| $NRS_{average}$ | - | - | - | - | - | - | - | - | $\rho = 0.54$ |
| | | | | | | | | | $p < 0.01$ |
| $NRS_{max}$ | - | - | - | - | - | - | - | - | $\rho = 0.65$ |
| | | | | | | | | | $p < 0.001$ |
| 10-PSS | - | - | - | - | - | - | - | - | $\rho = 0.56$ |
| | | | | | | | | | $p = 0.006$ |

Abbreviations: 10-PSS, 10-item Pruritus Severity Scale; BSA, body surface area; DLQI, dermatology life quality index; GPPSI, generalized pustular psoriasis severity index; NRS, Numerous Rating Scale; PASI, psoriasis area and severity index; PPSI, palmoplantar pustulosis severity index; sPGA, static physician global assessment.

in psoriasis of the scalp cannot be more than 9% or 10%, so the severity of psoriasis of the scalp may be high; however, its severity would not be reflected in PASI score. That's why also comparison of the severity between the subtypes would be pointless and was not presented in the article.

Across the literature, the pruritus in psoriatic patients was found to be frequent phenomenon, which is consistent with our results.[19,20] However, there is minority of studies describing the exact prevalence of pruritus in different subtypes and the investigated groups, except plaque-type psoriasis, were not abundant. In our study, all patients with nummular psoriasis, scalp psoriasis and generalized pustular psoriasis suffered from pruritus, whereas in other groups the prevalence ranged between 86.1% and 97.0%. While in case of scalp psoriasis, it can be explained by the high concentration of free nerve endings in the scalp, in the remaining groups there is a need of further investigation to confirm it.

Most subjects with erythrodermic psoriasis complained about generalized pruritus. In the study conducted by André et al., the cowhage-induced pruritus was more intensive in inflamed skin than non-inflamed skin.[21] In case of erythrodermic psoriasis extensiveness of skin lesions may even lead to elevation of systemic inflammatory factors, which may explain distribution of pruritus in this cohort. Furthermore, involvement of the entire body surface area may also be crucial.

Interestingly, while being asked about occurrence of pruritus within the last 3 days before the survey, it was found that part of responders answered negatively. The discrepancies between the studied cohorts were not statistically significant; however, the group of palmoplantar pustular psoriasis was conspicuous and reported life and point pruritus slightly less frequent than other population.

## LIMITATIONS

The most significant limitation of this study was the relatively small sample size, which may not fully reflect the correlation between pruritus and the specific subtype of psoriasis. Although the project was a multicentre one, the studied population was predominantly uniform in the race. The great majority of patients required hospitalization and systemic treatment due to the severity of psoriasis. That is why the results of this study mainly refer to moderate or severe psoriasis.

## CONCLUSIONS

In conclusion, there is a lack of exact and comprehensive description of the sensation of pruritus in particular clinical variants of psoriasis. The current study provides first hints about prevalence, intensity and clinical presentation of pruritus in various variants of psoriasis. Our study showed that the sensation of pruritus is individual, and it is difficult to distinguish the most pruritogenic psoriasis subtype. However, some important observations were demonstrated above. Unfortunately, it is difficult to compare our results to other studies because such a detailed analysis of this topic was not performed before. There is a great need of continuation of investigation on this topic. A better understanding of pruritus in specific clinical subtypes of psoriasis will help to personalize treatment and better manage this phenomenon, which is often the most troublesome symptom of psoriasis.

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### CONFLICT OF INTEREST

K.J. has been a subinvestigator in clinical trials sponsored by AbbVie, Corbus, Kymab Limited, Leo Pharma, Novartis, Galderma, Pfizer and VielaBio. A.R. has been a consultant or speaker for AbbVie, Bioderma, Bristol-Myers Squibb, Celgene, Chema Elektromet, Eli Lilly, Galderma, Janssen, Leo Pharma, Medac, Menlo Therapeutics, Novartis, Pierre-Fabre, Sandoz and Trevi; principal investigator or subinvestigator in clinical trials sponsored by AbbVie, Argenx, Corbus, Drug Delivery Solutions Ltd, Eli Lilly, Galderma, Genentech, Janssen, Kymab Limited, Leo Pharma, Menlo Therapeutics, MetrioPharm, MSD, Novartis, Pfizer, Trevi and VielaBio. The other authors have no disclosures.

### DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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## Rozdział 10. Streszczenie w języku polskim

Łuszczyca jest przewlekłą, zapalną chorobą skóry dotyczącą ponad 100 mln ludzi na całym świecie [1]. Charakteryzuje się wzmożoną proliferacją keratynocytów i licznymi zaburzeniami immunologicznymi, a swój udział w jej patogenezie mają również czynniki genetyczne i środowiskowe [2]. Z uwagi na różnorodną morfologię pojedynczych wykwitów oraz ich lokalizację wyróżnić można kilka podtypów klinicznych łuszczycy: plackowatą wielkoogniskową, pieniążkowatą, grudkową, erytrodermiczną, skóry owłosionej głowy, dłoni i podeszew, odwróconą (wyprzeniową), krostkową uogólnioną oraz łuszczycę krostkową dłoni i podeszew. Jednym z najczęściej zgłaszanych objawów subiektywnych, towarzyszących łuszczycy, jest świąd skóry. Bagatelizowanie tego problemu przez klinicystów, czy też niepowodzenia terapeutyczne w aspekcie leczenia świądu, skutkują frustracją pacjentów, których jakość życia oraz jakość snu jest znacznie obniżona. Wiedza na temat patogenezy świądu w łuszczycy, a także obrazu klinicznego tego uporczywego objawu jest ograniczona. Jeszcze mniejszą ilością informacji dysponujemy w odniesieniu do poszczególnych podtypów klinicznych tej jednostki chorobowej.

Celem rozprawy doktorskiej była charakterystyka świądu łuszczycowego oraz ocena jego wpływu na jakość życia i zaburzenia snu, w odniesieniu do poszczególnych wariantów klinicznych łuszczycy.

Na podstawie analizy 13 oryginalnych prac znalezionych w bazach danych PubMed, Mendeley lub Science Direct wyróżniono mediatory świądu łuszczycowego takie jak histamina, substancja P, czynnik wzrostu nerwów (NGF), naczyniowo-śródbłonkowy czynnik wzrostu (VEGF), interleukiny (IL-2, IL-4, IL-31), endogenne opioidy, czy lipokalina-2. Zaburzenia w unerwieniu i unaczynieniu skóry również okazały się być istotne, niemniej jednak stwierdzono, że patogeneza świądu łuszczycowego jest złożona i wciąż nie do końca poznana, przez co wymaga dalszych badań.

Celem dokonania charakterystyki świądu w różnych wariantach klinicznych łuszczycy, przeprowadzono wieloośrodkowe badanie ankietowe na grupie 295 chorych na łuszczycę (45 plackowatą wielkoogniskową, 32 pieniążkowatą, 31 grudkową, 32 owłosionej skóry głowy, 33 klasyczną dłoni i stóp, 23 wyprzeniową, 33 erytrodermiczną,

23 krostkową uogólnioną i 42 krostkową dłoni i stóp). W ankiecie oceniono m.in. obecność, nasilenie oraz obraz kliniczny świądu, a także nasilenie zmian skórnych, jakość życia i zaburzenia snu występujące u chorych. Niezależnie od podtypu klinicznego łuszczycy stwierdzono, iż świąd jest bardzo częstym jej objawem, raportowanym przez 86,1% – 100% pacjentów. Dominujący rodzaj zmian skórnych, wiek pacjentów i czas jaki upłynął od zachorowania nie wpływały na jego nasilenie. Świąd dotyczył głównie obszarów skóry zajętych przez wykwity łuszczycowe. W przypadku chorych na łuszczycę pieniążkowatą, owłosionej skóry głowy, dłoni i stóp, krostkową uogólnioną i krostkową dłoni i stóp większe nasilenie zmian skórnych korelowało z bardziej intensywnym świądem. Jakość życia zdecydowanej większości badanych była znacznie obniżona, przy czym pacjenci z łuszczycą erytrodermiczną charakteryzowali się istotnie bardziej upośledzoną jakością życia niż pozostali. Wykazano, iż spośród czynników determinujących jakość życia istotne jest nasilenie zmian skórnych, obecność, rozległość oraz intensywność świądu, a także występowanie zaburzeń snu. Stwierdzono, że z uwagi na częste nasilenie świądu wieczorami i w nocy, nierzadko, bo u 50-66% osób, powodował on trudności z zasypianiem lub wybudzenia nocy.

Dalsze badania nad patogenezą i obrazem klinicznym świądu w łuszczycy są konieczne, ponieważ wciąż istnieje wiele niejasności w tej tematyce. Z klinicznego punktu widzenia, jest to istotne, ponieważ lepsze poznanie świądu, a następnie opanowanie umiejętności jego kontrolowania przyczyniłyby się do poprawy jakości życia pacjentów.

## Rozdział 11. Streszczenie w języku angielskim

Psoriasis is a chronic inflammatory skin disease affecting more than 100 million people worldwide [1]. It is characterised by increased keratinocyte proliferation and multiple immune abnormalities, and genetic and environmental factors also play a role in its pathogenesis [2]. Due to the varied morphology of individual lesions and their localisation, several clinical subtypes of psoriasis can be distinguished: large plaque psoriasis, nummular psoriasis, papular psoriasis, erythrodermic psoriasis, scalp psoriasis, hand and sole psoriasis, inverse psoriasis, generalised pustular psoriasis and pustular psoriasis of the hands and soles. One of the most frequently reported subjective symptoms accompanying psoriasis is pruritus. Underestimation of this problem by clinicians, or therapeutic failures in terms of pruritus treatment, result in frustrated patients whose quality of life and quality of sleep is significantly reduced. Knowledge of the pathogenesis of pruritus in psoriasis, as well as the clinical presentation of this persistent symptom, is limited. Even less information is available regarding the different clinical subtypes of this disease entity.

The aim of this dissertation was to characterise psoriatic pruritus and assess its impact on quality of life and sleep disturbance, in relation to the different clinical variants of psoriasis.

Based on an analysis of 13 original papers found in PubMed, Mendeley or Science Direct databases, mediators of psoriatic pruritus such as histamine, substance P, nerve growth factor (NGF), vascular endothelial growth factor (VEGF), interleukins (IL-2, IL-4, IL-31), endogenous opioids, or lipocalin-2 were distinguished. Abnormalities in the innervation and vascularisation of the skin also appeared to be important; nevertheless, the pathogenesis of psoriatic pruritus was found to be complex and still not fully understood, thus requiring further research.

In order to characterise pruritus in the different clinical variants of psoriasis, a multicentre questionnaire study was conducted on a group of 295 patients with psoriasis (45 large plaque psoriasis, 32 nummular psoriasis, 31 papular psoriasis, 32 scalp psoriasis, 33 classic palmoplantar psoriasis, 23 inverse psoriasis, 33 erythrodermic psoriasis, 23 generalised pustular psoriasis and 42 pustular hand and foot psoriasis). The questionnaire assessed, among other things, the presence, severity and clinical

presentation of pruritus, as well as the severity of skin lesions, quality of life and sleep disturbances experienced by the patients. Regardless of the clinical subtype of psoriasis, pruritus was found to be a very common symptom of psoriasis, reported by 86.1 % - 100 % of patients. The predominant type of skin lesion, the age of the patients and the time elapsed since the onset of the disease did not affect its severity. Pruritus mainly affected skin areas occupied by psoriatic lesions. In patients with nummular psoriasis, psoriasis of the scalp, palmoplantar psoriasis, generalised pustular psoriasis and pustular psoriasis of the hands and feet, higher severity of skin lesions correlated with more intense pruritus. Quality of life was significantly impaired in the vast majority of subjects, with patients with erythrodermic psoriasis having significantly more impaired quality of life than others. The severity of skin lesions, the presence, extent and intensity of pruritus, and sleep disturbances were found to be important determinants of quality of life. It was found that due to the frequent severity of pruritus in the evenings and at night, not infrequently (in 50-66% of subjects) itch caused difficulties falling asleep or waking up at night.

Further research into the pathogenesis and clinical presentation of pruritus in psoriasis is necessary, as there is still much ambiguity on this topic. From a clinical point of view, this is important, as a better understanding of pruritus and subsequent mastery of the skills to control it would contribute to an improved quality of life for patients.

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## Rozdział 13. Oświadczenia współautorów

lek. Joanna Muda-Urban

Klinika Dermatologii w Rzeszowie

Rzeszów, 28.11.2022 r.

# OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w pracy:

- Jaworecka K, Muda-Urban J, Rzepko M, Reich A. *Molecular Aspects of Pruritus Pathogenesis in Psoriasis.* International Journal of Molecular Sciences, 2021;22(2):858;

mój wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie prac w formie publikacji to:

- udział w zbieraniu danych

- korekta i akceptacja finalnej wersji manuskryptu.

Jednocześnie wyrażam zgodę na przedłożenie powyższej pracy przez lek. Kamilę Jaworecką, jako część rozprawy doktorskiej na temat patogenezy i obrazu klinicznego świądu w różnych postaciach łuszczycy, w formie spójnego tematycznie zbioru artykułów naukowych opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wskazuje na indywidualny wkład lek. Kamili Jaworeckiej polegający na opracowaniu koncepcji pracy, koordynowaniu zbierania danych, udziale w zbieraniu danych, opracowaniu i interpretacji wyników analizy oraz przygotowaniu manuskryptu do druku.

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Podpis

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Rzeszów, 28.11.2022 r.

# OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w pracach:

- Jaworecka K, Muda-Urban J, Rzepko M, Reich A. *Molecular Aspects of Pruritus Pathogenesis in Psoriasis.* International Journal of Molecular Sciences, 2021;22(2):858;
- Jaworecka K, Rzepko M, Marek-Józefowicz L, Tamer F, Stefaniak AA, Szczegielniak M, Chojnacka-Purpurowicz J, Gulekon A, Szepietowski JC, Narbutt J, Owczarczyk-Saczonek A, Reich A. *The Impact of Pruritus on the Quality of Life and Sleep Disturbances in Patients Suffering from Different Clinical Variants of Psoriasis.* Journal of Clinical Medicine, 2022;11(19):5553;

mój wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie prac w formie publikacji to:

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.....

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Klinika Dermatologii
Uniwersytet Rzeszowski

Rzeszów, 28.11.2022 r.

# OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w pracach:

- Jaworecka K, Muda-Urban J, Rzepko M, Reich A. *Molecular Aspects of Pruritus Pathogenesis in Psoriasis.*International Journal of Molecular Sciences, 2021;22(2):858;

- Jaworecka K, Kwiatkowska D, Marek L, Tamer F, Stefaniak A, Szczegielniak M, Chojnacka-Purpurowicz J, Matławska M, Gulekon A, Szepietowski JC, Narbutt J, Owczarczyk-Saczonek A, Reich A. *Characteristics of Pruritus in Various Clinical Variants of Psoriasis: Results of the Multinational, Multicenter, Cross-Sectional Study.* Life (Basel, Switzerland), 2021;11(7):623;

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Prof. dr hab. n. med. Adam Reich
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Podpis

dr n. med. Dominika Kwiatkowska

Klinika Dermatologii

Uniwersytet Rzeszowski

Rzeszów, 17.12.2022 r.

# OŚWIADCZENIE WSPÓŁAUTORA

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.....

Podpis

dr n. med. Luiza Marek-Józefowicz

Klinika Dermatologii i Wenerologii

Uniwersytet Mikołaja Kopernika w Toruniu

Bydgoszcz, 14.12.2022 r.

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Luiza Marek-Józefowicz

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Podpis

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Stefaniak Aleksandra

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Podpis

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Klinika Dermatologii, Deratologii Dziecięcej i Onkologicznej

Uniwersytet Medyczny w Łodzi

Łódź, 14.12.2022 r.

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Magdalena Szczegielniak

Klinika Dermatologii, Chorób Przenoszonych Drogą Płciową i Immunologii Klinicznej, MSW w Olsztynie

Olsztyn, 17.11.2022 r.

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Joanna Chojnacka-Purpurowicz

lek. Monika Matławska

Wrocław, 08.12.2022 r.

# OŚWIADCZENIE WSPÓŁAUTORA

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Matławska Monika

Podpis

Prof. dr hab. n. med. Jacek Szepietowski

Klinika Dermatologii, Wenerologii i Alergologii

Uniwersytet Medyczny we Wrocławiu

Wrocław, 08.12.2022 r.

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Podpis

Joanna Narbutt

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Podpis

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mój wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie prac w formie publikacji to:

- udział w zbieraniu danych

- korekta i akceptacja finalnej wersji manuskryptu.

Jednocześnie wyrażam zgodę na przedłożenie powyższych prac przez lek. Kamilę Jaworecką, jako część rozprawy doktorskiej na temat patogenezy i obrazu klinicznego świądu w różnych postaciach łuszczycy, w formie spójnego tematycznie zbioru artykułów naukowych opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. prac wskazuje na indywidualny wkład lek. Kamili Jaworeckiej polegający na opracowaniu koncepcji badania, koordynowaniu zbierania danych, udziału w zbieraniu danych, opracowaniu i interpretacji wyników badania oraz przygotowaniu wszystkich trzech manuskryptów do druku.

A. Owczarczyk-Saczonek

Podpis