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ROZPRAWA DOKTORSKA

Cykl publikacji powiązanych tematycznie

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Spis treści

1. CYKL PRAC STANOWIĄCYCH ROZPRAWĘ DOKTORSKĄ

1. **Świerczyńska K**, Białynicki-Birula R, Szepietowski JC. Chronic Intractable Pruritus in Chronic Kidney Disease Patients: Prevalence, Impact, and Management Challenges - A Narrative Review. *Ther Clin Risk Manag*. 2021;17:1267-1282. Published 2021 Nov 30. doi:10.2147/TCRM.S310550

   IF: 2,775

   Punktacja Ministerialna: 70

2. **Świerczyńska K**, Krajewski P, Reszke R, Krajewska M, Nochaiwong S, Białynicki-Birula R, Szepietowski JC. Uraemic Pruritus in Dialysis Patient (UP-Dial) questionnaire: creation and validation of the Polish language version. Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii. 2022;39(3):538-544. doi:10.5114/ada.2021.107271.

   IF: 1,4

   Punktacja Ministerialna: 70

3. **Świerczyńska K**, Krajewski PK, Nowicka-Suszko D, Białynicki-Birula R, Krajewska M, Szepietowski JC. The Serum Level of IL-31 in Patients with Chronic Kidney Disease-Associated Pruritus: What Can We Expect?. *Toxins (Basel)*. 2022;14(3):197. Published 2022 Mar 7. doi:10.3390/toxins14030197

   IF: 4,2

   Punktacja Ministerialna: 100

4. **Świerczyńska-Mróz K**, Nowicka-Suszko D, Fleszar MG, Fortuna P, Krajewski P, Krajewska M, Białynicki-Birula R, Szepietowski JC, Serum Level of Protein-Bound Uraemic Toxins in Haemodialysis Patients with Chronic Kidney Disease-Associated Pruritus: Myths and Facts. *J Clin Med*. 2023;12(6):2310. Published 2023 Mar 16. doi:10.3390/jcm12062310

   IF: 3,9

   Punktacja Ministerialna: 140

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Sumaryczna Punktacja Ministerialna: ***380 punktów***

2. WYKAZ SKRÓTÓW

CI	Przewlekły świąd (ang. *chronic itch*)
EIC	Chromatogram dla wybranych jonów (ang. *extracted ion chromatograms*)
HD	Hemodializa
IFSI	Międzynarodowe Forum Badań Świądu (ang. *International Forum of Study of Itch*)
IL-13	Interleukina 31
IS	Siarczan indoksylu (ang. *Indoxyl Sulfate*)
ItchyQoL	Kwestionariusz jakości życia specyficzny dla świądu (ang. *Itch-specific quality of life questionnaire*)
NRS	Numeryczna Skala Oceny (ang. *Numerical Rating Scale*)
PBUTs	Toksyny mocznicowe związane z białkami (ang. *Protein Bound Uraemic Toxins*)
PChN	Przewlekła choroba nerek
PCS	Siarczanu p-krezolu (ang. *p-Cresol Sulfate*)
SD	Odchylenie standardowe (ang. *standard deviation*)
UP	Świąd mocznicowy (ang. *uraemic pruritus*)
UP-Dial	14-punktowa skala świądu mocznicowego u chorych dializowanych (ang. Uraemic Pruritus in Dialysis Patient)
4IIQ	Czteropunktowy kwestionariusz oceny świądu (ang. *Four-item itch questionnaire*)

3. OMÓWIENIE ROZPRAWY DOKTORSKIEJ

3.1. Wstęp

Świąd to nieprzyjemne uczucie prowadzące do drapania się. Trwający dłużej niż 6 miesięcy jest klasyfikowany jako świąd przewlekły (CI). Międzynarodowe Forum Badań Świądu (IFSI) wyróżnia sześć kategorii świądu: (I) świąd skórny, (II) świąd układowy, (III) świąd neurologiczny, (IV) świąd psychogenny, (V) świąd mieszany i (VI) świąd o nieznanej etiologii - tym samym podkreślając, iż zjawisko to występuje nie tylko w pierwotnych chorobach skóry, lecz także w licznych schorzeniach ogólnoustrojowych. Świąd mocznicowy występujący u pacjentów z przewlekłą chorobą nerek (PChN) dotyczy 37% osób przewlekle dializowanych, ma negatywny wpływ na jakość życia pacjentów, a także przyczynia się do wzrostu ryzyka śmiertelności w tej grupie chorych. Pomimo toczących się przez ostatnie dekady badań jego pełna etiopatogeneza nie została w pełni poznana, a schorzenie to nadal pozostaje wyzwaniem terapeutycznym dla nefrologów i dermatologów. Przeprowadzone do tej pory liczne badania dotyczące poszukiwania czynników odpowiedzialnych za odczuwanie świądu często dają sprzeczne wyniki.Scharakteryzowanie świądu mocznicowego odgrywa istotną rolę w ocenie jakości życia pacjentów dializowanych. Wśród szerokiej gamy polskojęzycznych narzędzi, którymi posługujemy się w dermatologii, nie występowała do tej pory skala dedykowana bezpośrednio ocenie świądu w przewlekłej chorobie nerek. W 2017 r. Nochaiwong i wsp. stworzyli wielowymiarowy kwestionariusz oceny świądu u pacjentów dializowanych, składający się z 14 pytań. Narzędzie ocenia trzy aspekty świądu: objawy, zaburzenia snu, oraz zaburzenia psychospołeczne. Zwalidowanie polskojęzycznej wersji takiej skali może wpłynąć na podejmowanie decyzji klinicznych, wybór terapii oraz ocenę jej skuteczności. Według obecnej wiedzy najważniejszymi czynnikami patogenetycznymi wpływającymi na odczuwanie świądu u pacjentów dializowanych są: dysfunkcja układu immunologicznego, neuropatia, dysregulacja transmisji opioidów, nagromadzenie toksyn mocznicowych, suchość skóry oraz zaburzenia gospodarki wapniowo-fosforanowej. W wielu dotychczas opublikowanych badaniach wykazano, że wzrost stężenia mediatorów prozapalnych może indukować świąd mocznicowy. IL-31 jest cytokiną o udowodnionym wpływie na obecność i intensywność świądu w wielu dermatozach zapalnych. Tym samym dokładne zbadanie tej ścieżki immunologicznej w patogenezie świądu mocznicowego może przynieść nowe rozwiązania terapeutyczne. Ponadto istnieje również hipoteza mówiąca o tym, iż toksyny mocznicowe zatrzymywane w organizmie pacjentów z zaawansowaną

niewydolnością nerek, mogą negatywnie oddziaływać na funkcje biologiczne organizmu. Poziom toksyn mocznicowych związanych z białkami (PBUTs) w organizmie pacjentów dializowanych koreluje z pogorszeniem funkcji nerek. Niektórzy autorzy widzą możliwy wpływ konkretnych molekuł - siarczanu indoksylu (IS) i siarczanu p-krezolu (PCS) na genezę świądu.

Efektywna terapia tego schorzenia pozostaje wyzwaniem w praktyce klinicznej. Do rekomendowanych metod terapeutycznych zaliczamy fototerapię UVB oraz liczne terapie miejscowe, na przykład z wykorzystaniem inhibitorów kalcyneuryny, mocznika czy emolientów. W terapii ogólnej rejestrację posiada tylko jeden lek – difelikefalina. W praktyce klinicznej zadowalające efekty można również osiągnąć za pomocą leków przeciwpadaczkowych: gabapentyny i pregabaliny. Mimo obecnego wielostopniowego podejścia do terapii świądu mocznicowego, nawracający i utrzymujący się charakter choroby powoduje częste niepowodzenia terapeutyczne. Tendencja ta popiera dalszą konieczność zgłębienia patogenezy świądu co może w przyszłości zaowocować nowymi metodami terapeutycznymi gwarantującymi poprawę kliniczną.

3.2. Cel badań i problemy badawcze

Celem przeprowadzonych w ramach rozprawy doktorskiej badań było stworzenie nowego, zwalidowanego kwestionariusza - Uraemic Pruritus in Dialysis Patient (UP-Dial), służącego do oceny świądu mocznicowego w praktyce klinicznej, a także poszukiwanie nowych czynników patogenetycznych świądu mocznicowego poprzez oznaczenie stężenia interleukiny 31 oraz toksyn mocznicowych związanych z białkami u pacjentów poddawanych hemodializom.

Cele szczegółowe:

3.2.1 Dokonanie przeglądu piśmiennictwa dotyczącego epidemiologii, patogenezy oraz możliwości terapeutycznych świądu mocznicowego.

3.2.2. Tłumaczenie i walidacja na polską wersję językową nowego kwestionariusza - 14-punktowej skali świądu mocznicowego u chorych dializowanych - Uraemic Pruritus in Dialysis Patient (UP-Dial), służącego do scharakteryzowania świądu mocznicowego u pacjentów dializowanych.

3.2.3 Zbadanie stężenia interleukiny 31 w surowicach pacjentów dializowanych oraz w grupie kontrolnej.

3.2.4 Zbadanie stężenia toksyn mocznicowych związanych z białkami (wolnego i całkowitego siarczanu indoksylu i siarczanu p-krezolu) u pacjentów dializowanych oraz w grupie kontrolnej.

3.2.5 Analiza poziomu stężeń badanych substancji między poszczególnymi grupami pacjentów oraz zbadanie korelacji poziomu stężeń badanych substancji z nasileniem świądu mocznicowego oraz jakością życia pacjentów.

3.3. Materiał i metody

Pierwszą pracą z cyklu rozprawy doktorskiej jest przegląd systematyczny piśmiennictwa dotyczący charakterystyki świądu mocznicowego i obejmujący epidemiologię, patogenezę oraz możliwe i poznane do tej pory opcje terapeutyczne w świądzie mocznicowym. Przeglądu dokonano we wrześniu 2021 r. Bazy danych takie jak PubMed, ScienceDirect i Scholar Google zostały przeszukane przy użyciu kluczowych słów: „świąd mocznicowy", „świąd" „przewlekła choroba nerek", „hemodializa". Brano pod uwagę jedynie artykuły w języku angielskim będące artykułami badawczymi. Do dalszej analizy włączono manuskrypty pełnotekstowe dotyczące świądu mocznicowego, jego charakterystyki oraz terapii.

Druga praca z cyklu przedstawia stworzenie polskiej wersji językowej i walidację kwestionariusza Uraemic Pruritus in Dialysis Patient (UP-Dial). Anglojęzyczną wersję kwestionariusza otrzymano od autorów wersji oryginalnej. Wyrazili oni zgodę na tłumaczenie i walidację ankiety. Kwestionariusz został przetłumaczony na język polski zgodnie z międzynarodowymi standardami i sprawdzony przez autorów wersji oryginalnej. Pierwsze tłumaczenie z języka angielskiego na polski zostało wykonane przez dwóch niezależnych tłumaczy. Następnie dwa tłumaczenia zostały przeanalizowane pod kątem spójności i słownictwa przez dwujęzycznego eksperta w dziedzinie UP. Następnie kolejnych dwóch ekspertów, nieznających wersji oryginalnej, wykonało tłumaczenie wsteczne z polskiego na angielski. Obie wersje następnie przesłano autorom wersji oryginalnej kwestionariusza. Dzięki współpracy uzgodniono ostateczną wersję tłumaczonego kwestionariusza. W kolejnym kroku walidacja narzędzia została przeprowadzone na grupie 30 pacjentów przewlekle dializowanych,

odczuwających świąd mocznicowy. Każdy z badanych wypełnił ankietę dwukrotnie z 3-7 dniową przerwą. Dodatkowo pacjenci zostali poproszeni o wypełnienie trzech innych kwestionariuszy: skali NRS, kwestionariusza IchQoL i 4-punktowego kwestionariusza oceny świądu, celem wykonania korelacji instrumentów. Wewnętrzną zgodność instrumentu oceniano za pomocą współczynnika α Cronbacha. Aby ustalić, że kwestionariusz jest wewnętrznie spójny, współczynnik Cronbacha powinien wynosić co najmniej 0,70. Powtarzalność kwestionariusza (rzetelność: test-retest) oceniano za pomocą współczynnika korelacji wewnątrzklasowej (Intraclass Correlation Coefficient, ICC) porównując dwie odpowiedzi każdego pacjenta. Wynik ICC powinien wynosić co najmniej 0,70. Dodatkowo odpowiedzi na każde pytanie z pierwszego i drugiego wypełnienia porównano za pomocą Testu Wilcoxona w celu poszukiwaniu istotnych różnic. Trafność zbieżną oparto na teście korelacji rang Spearmana pomiędzy UP-Dial i innymi użytymi instrumentami (NRS, 4IIQ i ItchyQoL).

W trzeciej i czwartej publikacji cyklu, będącymi oryginalnymi pracami badawczymi, oceniono stężenie interleukiny 31 oraz toksyn mocznicowych związanych z białkami (wolnego i całkowitego siarczanu indoksylu i siarczanu p-krezolu) w surowicy pacjentów dializowanych. Badania przeprowadzono w latach 2020-2023 w dwóch ośrodkach – w Stacji Dializ Uniwersyteckiego Szpitala Klinicznego im. Jana Mikulicza-Radeckiego we Wrocławiu oraz w Stacji Dializ Uniwersyteckiego Szpitala Klinicznego w Opolu. Grupa badana stanowiła pacjentów dorosłych poddawanych hemodializie 2 lub 3 razy w tygodniu przez co najmniej 3 miesiące. Kryteriami wyłączenia z badania były: pierwotne choroby skóry, inne swędzące dermatozy, zaburzenia psychiczne lub problemy z komunikacją, wiek poniżej 18 lat, leczenie przeciwświądowe oraz odmowa pacjentów udziału w badaniu. Wszyscy uczestnicy byli poddani badaniu fizykalnemu i dermatologicznemu. Zebrano od pacjentów podstawowe dane demograficzne w tym płeć, wiek, przyczynę niewydolności nerek, czas trwania HD, rodzaj dostępu naczyniowego i historię dotyczącą wcześniejszego leczenie świądu. Wszyscy pacjenci biorący udział w badaniu po zapoznaniu się z opisem badania podpisali świadomą zgodę. Dokonano analizy statystycznej różnicy stężeń badanych molekuł między poszczególnymi grupami (pacjenci dializowani odczuwający świąd, pacjenci dializowani bez świądu oraz grupa kontrolna osób zdrowych) a także zbadano korelację pomiędzy badanymi substancjami a nasileniem świądu i jakością życia pacjentów.

W pracy trzeciej oceniającej poziomu IL-31 do badania włączono 175 pacjentów. Uczestnicy zostali podzieleni na trzy grupy. Do grupy A włączono 64 pacjentów hemodializowanych z UP, do grupy B włączono 62 pacjentów hemodializowanych nie zgłaszających UP, a do grupy C - 49 osób zdrowych stanowiących grupę kontrolną, które

odpowiadały wiekiem i płcią pacjentom z grupy badanej i nie miały w przeszłości żadnych chorób związanych ze świądem. Przed planową dializoterapią, od każdego pacjenta została pobrana próbka krwi (9ml), którą następnie odwirowano, a surowicę przechowywano w -80°C do czasu wykonania dalszych etapów badania. Poziom IL-31 w surowicy pacjentów oznaczono metodą ELISA przy użyciu zestawu Nori Human IL-31 ELISA Kit (numer katalogowy: GR 111374, GENORISE SCIENTIFIC, Inc., Glen Mills, PA, USA) zgodnie z instrukcją producenta. Absorbancję próbki mierzono przy długości fali 450 nm za pomocą wielopłytkowego czytnika EPOCH (BioTEK® Instruments, Inc., Winooski, VT, USA). IL-31 miała zakres testowy 50–3200 pg/ml i czułość 10 pg/ml.

W czwartym z cyklu artykule opisującym badanie dotyczące toksyn mocznicowych związanych z białkami do badania włączono 174 pacjentów. Uczestnicy również zostali podzieleni na trzy grupy. Do grupy A włączono 61 pacjentów hemodializowanych z UP, do grupy B włączono 63 pacjentów hemodializowanych nie zgłaszających UP, a do grupy C 50 osób zdrowych stanowiących grupę kontrolną. Materiał biologiczny - krew była tak samo pobrana i opracowana jak w poprzednim badaniu. Próbki oraz wzorce kalibracyjne poddano tej samej procedurze przygotowania. W skrócie, dla substancji związanych z białkami 100 µL próbki wymieszano z 10 µL mieszaniny wzorców wewnętrznych w metanolu (40µg/ml siarczanu indoksylu -d5 i siarczanu p-krezolu -d7). Następnie poddano odbiałczeniu z wykorzystaniem 400 µL acetonitrylu. Uzyskany supernatant wymieszano w stosunku 1:4 z wodą i poddano analizie LC-MS. Dla wolnych form siarczanu indoksylu oraz siarczanu p-krezolu, 200 µL próbki wymieszano z 20 µL mieszaniny wzorców wewnętrznych w metanolu (40µg/ml siarczanu indoksylu -d5 i siarczanu p-krezolu -d7) a następnie filtrowano przy użyciu filtrów wirówkowych 3000 MWCO (Merck Millipore). Następnie poddano je przygotowaniu i analizie analogicznie do form związanych. Ilościową analizę wolnego i całkowitego siarczanu indoksylu i siarczanu p-krezolu przeprowadzono w systemie LC-QTOF-MS składającym się systemu ultra wysokosprawnego chromatografu cieczowego Acquity Ultra-Performance Liquid Chromatography System (Waters, Milford, MA, USA) sprzężonego z hybrydowym spektrometrem mas typu kwadrupol-analizator czasu przelotu (Xevo G2 Q-TOF MS, Waters, Milford, MA, USA). Widma masowe zbierano w trybie MSe pozwalającym na jednoczesny pomiar jonów prekursorowych i fragmentacyjnych w rampie energii kolizji dla wszystkich analitów. Do analizy ilościowej wykorzystano chromatogram dla wybranych jonów (ang. extracted ion chromatograms (EIC)) wykorzystując następujące stosunki masy do ładunku (m/z): 212.0018 m/z, 187.0065 m/z, 217.0331 m/z and 194.0504 m/z odpowiednio dla siarczanu indoksylu, siarczanu p-krezolu, siarczanu indoksylu -d5 i siarczanu p-krezolu -d7.

W dwóch ostatnich badaniach ocenę świądu przeprowadzono wielowymiarowo, korzystając z dobrze znanych narzędzi oraz nowo zwalidowanego kwestionariusza. Nasilenie świądu oceniano za pomocą skali NRS, powszechnie stosowanego i preferowanego narzędzia do oceny intensywności świądu. Pacjenci wskazali największe natężenie świądu, jakie odczuwali w ciągu ostatnich 3 dni. Wyniki sklasyfikowano w następujący sposób: NRS < 3 – świąd łagodny, NRS ≥ 3 i <7 – świąd umiarkowany, NRS ≥ 7 i <9 – świąd ciężki, NRS ≥ 9 – świąd bardzo silny. Ponadto wykorzystano, zwalidowaną przez nasz zespół polską wersję kwestionariusza UP-Dial.

Dodatkowo w czwartej publikacji oceniającej toksyny mocznicowe w celu oceny wpływu przewlekłego świądu na jakość życia, wypełniono polską wersję kwestionariusza ItchyQoL. Jest to narzędzie składające się z 22 pytań i obejmujące trzy wymiary świądu: objawy, ograniczenia funkcjonalne i emocje. Pytania oceniane są w 5-punktowej skali, a łączny wynik mieszczący się w przedziale od 22 do 110 punktów pozwala oszacować jakość życia pacjenta. W badaniu tym pacjenci wypełnili dodatkowo czteropunktowy kwestionariusz oceny świądu (4IIQ), składający się z 4 pytań dotyczących rozkładu, nasilenia i częstotliwości świądu oraz zaburzeń snu. Możliwy wynik mieści się w przedziale od 3 do 19 punktów.

Do analizy statystycznej dwóch ostatnich badań wykorzystano oprogramowanie IBM SPSS Statistics v. 26 (SPSS Inc., Chicago, IL, USA). Do oceny zmiennych ilościowych wykorzystano test U Manna–Whitneya oraz korelacje Spearmana lub Pearsona. Ocenę wyników jakościowych przeprowadzono za pomocą testu chi-kwadrat. W przypadku różnic w więcej niż dwóch grupach przeprowadzono jednokierunkową analizę wariancji rang Kruskala–Wallisa. Dane wyrażono jako średnią ± SD, medianę, pierwszy i trzeci kwantyl. $P < 0,05$ uznano za istotne statystycznie.

3.4. Podsumowanie wyników

Przygotowana praca poglądowa udowodniła, iż UP to wszechobecny, lecz w rutynowej praktyce bardzo często lekceważony stan u pacjentów poddawanych hemodializom lub cierpiących na PChN, który pogarsza ich jakość życia i zwiększa ryzyko śmiertelności. Pomimo ciągłego zainteresowania naukowców zrozumieniem pełnej etiopatogenezy UP, wyniki wielu przeprowadzonych badań były sprzeczne. Obecna sytuacja wymaga kontynuacji badań w tej dziedzinie i ponownej oceny pewnych teorii, które mogą mieć istotny wpływ na kliniczne decyzje dotyczące pacjentów z UP. Przyszłe badania poszukujące nowych czynników

odpowiedzialnych za UP mogą pomóc w opracowaniu nowych leków, skierowanych na konkretne molekuły biorące udział w patogenezie UP.

W badaniu dotyczącym walidacji kwestionariusza UP-Dial wartość współczynnika alfa Cronbacha dla całkowitej oceny UP-Dial wynosiła 0,90 - co wskazywało na bardzo dobrą wewnętrzną spójność zwalidowanego narzędzia. Ponadto każda z trzech domen kwestionariusza wykazała dobrą lub bardzo dobrą spójność wewnętrzną, uzyskując współczynniki alfa Cronbacha odpowiednio 0,75 dla domeny objawów; 0,93 dla domeny snu oraz 0,75 dla domeny psychospołecznej. Znaleziono istotne statystycznie korelacje między większością wyników uzyskanych dla poszczególnych pytań, a całkowitym wynikiem przetłumaczonego kwestionariusza. Tylko pytania 5, 7 i 14 (odpowiednio: pytanie o drętwienie, suchość skóry oraz problemy seksualne) nie korelowały z całkowitym wynikiem. Współczynnik korelacji wewnątrzklasowej (Intraclass Correlation Coefficient) wykorzystany do oceny powtarzalności kwestionariusza był bardzo wysoki – 0,90. Ocena trafności zbieżnej wykazała silną korelację pomiędzy UP-Dial, a innymi narzędziami oceniającymi nasilenie świądu – NRS ($r = 0,74; p < 0,01$) i 4IIQ ($r = 0,82; p < 0,01$). Podobnie, kwestionariusz UP-Dial silnie korelował z ItchyQoL ($r = 0,88$; $p< 0,01$). Wyniki przedstawione w naszym badaniu potwierdziły bardzo dobrą spójność wewnętrzną, odtwarzalność oraz trafność zbieżną polskiej wersji kwestionariusza UP-Dial. Respondenci zgłosili dobrą zrozumiałość pytań, a proces wypełniania całego narzędzia trwał od 7 do 10 minut.

Wśród badanych poziom IL-31 w surowicy był znacząco wyższy w grupie pacjentów dializowanych zgłaszających świąd ($p < 0,001$) w porównaniu do pacjentów dializowanych nieodczuwających świądu. Ponadto istniała statystycznie istotna różnica ($p < 0,001$) w poziomach IL-31 między pacjentami poddawanymi HD z i bez świądu oraz grupą kontrolną (odpowiednio $p < 0,001$ i $p = 0,019$). Zaobserwowano również marginalną tendencję w kierunku istotności ($r = 0,242$, $p = 0,058$) pomiędzy poziomem IL-31, a nasileniem świądu w ciągu ostatnich 3 dni ocenianym za pomocą skali NRS. Całkowity wynik kwestionariusza UP-Dial silnie korelował z NRS ($r = 0,399$, $p = 0,001$). Dodatkowo każda domena UP-Dial wykazywała istotną korelację z wynikami NRS. Jednakże korelacja pomiędzy poziomem IL-31 w surowicy, a całkowitym wynikiem UP-Dial nie była istotna statystycznie. Średni wynik UP-Dial w badaniu oceniającym poziom IL-31 wyniósł $14,2 \pm 9,8$ punktu. U 58% pacjentów z UP świąd zakłócał sen, a tylko 29% nie zgłaszało wpływu świądu na następujące czynności: pracę lub naukę, interakcje społeczne, nastrój bądź jakąkolwiek aktywność seksualną. Średni wynik NRS wyniósł $4,9 \pm 2,2$ punktu. Według wartości granicznych NRS łagodny świąd

zgłoszono w 14,5% przypadków, umiarkowany w 59,7%, ciężki w 22,6% i bardzo ciężki w 3,2%.

Wyniki etapu dotyczącego toksyn mocznicowych związanych z białkami wykazały, iż stężenia wolnego i całkowitego IS i PCS w surowicy były istotnie wyższe zarówno u pacjentów hemodializowanych ze świądem, jak i u pacjentów hemodializowanych bez świądu w porównaniu ze zdrową grupą kontrolną ($p < 0,001$). Nie zaobserwowano jednak istotnej różnicy w stężeniu wolnego i całkowitego IS oraz PCS w surowicy pomiędzy pacjentami zgłaszającymi UP, a pacjentami bez świądu. Nie stwierdzono również korelacji pomiędzy stężeniem PBUTs w surowicy, a nasileniem świądu ocenianym skalą NRS. Podobnie wyniki innych kwestionariuszy zastosowanych w tym badaniu (Up-Dial, 4IIQ i ItchyQoL) nie wykazały istotnego związku ze stężeniami PBUTs w surowicy. Średnie natężenie świądu oceniane w skali NRS wyniosło 4,87 ± 2,21 punktu. Według wartości odcięcia NRS tutaj również najczęściej zgłaszano umiarkowany świąd – w 60,65% przypadków. Średni wynik kwestionariusz 4IIQ i ItchyQoL w tej grupie wyniosły odpowiednio 8,44 ± 3,64 i 36,84 ± 13,65 punktu.

3.5 Etyka

Projekt badawczy pracy doktorskiej opartej na poniższych publikacjach uzyskał pozytywną opinię Komisji Bioetycznej Uniwersytetu Medycznego we Wrocławiu - Nr KB 253/2023. Badanie przeprowadzono przestrzegając zasad Good Clinical Practice oraz zasad Deklaracji Helsińskiej Światowego Stowarzyszenia Lekarzy przyjętą przez 18 Zgromadzenie Ogólne Światowego Stowarzyszenia Lekarzy (WMA) w Helsinkach w czerwcu 1964 r., a zmienionej przez 64 Zgromadzenie Ogólne WMA w Brazylii w październiku 2013 r. Podczas przeprowadzania badań zachowano anonimowość uzyskiwanych danych.

3.6 Wnioski

3.6.1. Zwiększone stężenie IL-31 w surowicy może przyczyniać się do występowania świądu oraz modulować odczucie świądu u pacjentów dializowanych.

3.6.2. Zaburzenia stężeń toksyn mocznicowych związanych z białkami w surowicy pacjentów dializowanych nie odgrywają roli w genezie świądu mocznicowego.

3.6.3. Stworzenie polskojęzycznej wersji kwestionariusza UP-Dial umożliwia rzetelną ocenę i charakterystykę świądu mocznicowego w codziennej praktyce klinicznej i badaniach naukowych.

3.6.4. Konieczne jest kontynuowanie badań poszukujących nowych czynników odpowiedzialnych za patogenezę świądu mocznicowego w celu opracowania innowacyjnych i skutecznych opcji terapeutycznych w tej jednostce chorobowej.

4. ARTYKUŁ PIERWSZY

Chronic Intractable Pruritus in Chronic Kidney Disease Patients: Prevalence, Impact, and Management Challenges - A Narrative Review.

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REVIEW

Chronic Intractable Pruritus in Chronic Kidney Disease Patients: Prevalence, Impact, and Management Challenges — A Narrative Review

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Abstract: Chronic kidney disease (CKD) is recognized as a leading public health problem and causes numerous health complications. One of the most common and burdensome dermatological symptoms affecting patients undergoing dialysis is CKD-associated pruritus (CKD-aP). This condition not only has a negative impact on sleep, mood, daily activities, and quality of life but also increases the mortality risk of hemodialyzed patients. Despite that, this condition is greatly underestimated in clinical practice. Due to the complex and still not fully understood etiopathogenesis of CKD-aP, the choice of an effective therapy remains a challenge for clinicians. Most common therapeutic algorithms use topical treatment, phototherapy, and various systemic approaches. This review aimed to summarize most recent theories about the pathogenesis, clinical features, and treatment of CKD-aP.

Keywords: chronic kidney disease, chronic kidney disease–associated pruritus, treatment

Introduction

Chronic itch (CI) is an uncomfortable sensation that causes a desire to scratch and lasts >6 weeks. In contrast to acute itch, which is regarded as a defense mechanism, CI occurs in many skin conditions and systemic diseases. The International Forum for the Study of Itch (IFSI) expert group created the classification of CI, basing it on the etiology of pruritus. They distinguished causes of CI as cutaneous (I), systemic (II), neurological (III), psychogenic (IV), mixed (V), and other (VI).[1] Over the whole range of systemic disorders occurring with itch, special attention should be paid to chronic kidney disease (CKD). This condition was defined in 2002 by the National Kidney Foundation as an abnormality of kidney structure or function presenting at least for 3 months and having implications for patients' health.[2] The prevalence of CKD is about 13%, and it is recognized as a leading public health problem.[3,4] CKD has a broad spectrum of complications, of which cutaneous manifestations play a great role. Changes in skin color, elastosis, ecchymoses, xerosis, and uremic frost, as well as perforating disorders, metastatic calcification, or bullous dermatosis, are often observed in end-stage renal disease (ESRD).[5] One of the most common and burdensome dermatological symptoms affecting patients undergoing dialysis, described for the first time in 1932, is CKD-associated pruritus (CKD-aP). The nomenclature of this condition has changed over the years. Originally "uremic pruritus" was a common definition for itch associated with CKD. However, due to a lack of dependence between uremia and this sensation,

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CKD-aP or "CKD-associated itch" are more suitable.[6] This condition not only has a negative impact on sleep, mood, daily activities, and quality of life (QoL) but also increases the mortality risk of hemodialysis (HD) patients.[7,8] Despite this, the condition is often underestimated in clinical practice.[9] Due to the etiopathogenesis of CKD-aP not being fully understood, therapy for this condition remains a challenge for dermatologists and nephrologists.

Prevalence

Over the years, studies on CKD-aP have shown variable prevalence of this condition. From the beginning of dialysis therapy, scientists reported that even 85% of the patients with ESRD may suffer from CI.[10] This number decreased with the development and accessibility of renal replacement therapy. It is difficult to specify a clear cause of this phenomenon, although possible explanations could be revealed through more precisely performed dialysis based on Kt/V or creatinine-clearance measurements.

The usage of more modern and biocompatible dialyzers can also bring about this positive effect.[11] Additionally, by learning about other new factors that may cause uremic pruritus, it is possible to control them. One of the possible explanations is better control of calcium and phosphate metabolism in CKD patients. Pisoni et al[12] in 2006 presented the results of the large international Dialysis Outcomes and Practice Patterns Study (DOPPS). The research assessed CI in 18,801 HD patients from 12 countries for 1996–2004. The first phase of the study focused on 1996–2001 (DOPPS I) and the second 2002–2004 (DOPPS II). Those perceiving moderate–extreme itch came to 45% and 42%, respectively, which confirmed a decreasing tendency of CKD-aP prevalence. A follow-up (2012–2015, DOPPS V), which involved 6,256 patients from 17 countries, showed that the proportion of patients with moderate or severe itch had declined to 37%.[13] Rayner et al[13] also emphasized how strongly underestimated CKD-aP is among nephrologists. Of HD patients in their study, 17% with CI did not report their symptoms to any health-care provider and 18% were not receiving any therapy. Similar results were observed for dialysis outcomes and practice patterns in Japan, where moderate–xtreme pruritus was noted by 44% of HD patients between 1999 and 2004.[14] A German cross-sectional study investigated 860 HD patients and revealed CI prevalence of 25% and 12-month prevalence 27.2%. Approximately 35% of subjects had suffered from CI at least once in their lifetime.[15] A meta-analysis of 42 cross-sectional studies showed that the prevalence of CKD-aP ranged between 18% and 97.8% and the overall prevalence of CKD-aP reached 55%. The analysis did not find any difference in prevalence the sexes. Pooled prevalence in male and female patients was 55%. CI occurred comparably often in patients undergoing peritoneal dialysis (PD) and HD patients (56% and 55%, respectively).[16] However, a South Korean study assessed pruritus in 648 patients with ESRD and showed that not only prevalence (62.5% vs 48.3%) but also intensity of itch measured by a visual analogue scale (VAS) was significantly higher in PD patients than HD patients.[17] On the other hand, Wu et al[18] showed the opposite results. VAS scores were significantly higher in HD patients than PD patients. This notwithstanding, another study showed a lack of significant difference in severity of itching and similar prevalence of CI in HD and PD patients (61.8% and 61.5%, respectively).[19] The research also investigated pruritus in a group of patients with stage 4 or 5 CKD without dialysis therapy, where the prevalence of CI was 43.2%. Another cross-sectional study determined the prevalence of CI in a group of 3,780 non-dialysis patients with CKD stages 3–5. The results showed that the prevalence of moderate–extreme pruritus was 24% and was more likely in older patients, women, and those with stage 5 CKD, lung disease, diabetes, and physician-diagnosed depression.[20] Similar prevalence was found in a cross-sectional study of 402 stage 2–5 CKD patients. On the contrary, the prevalence of CKD-aP did not correlate with CKD stage and reached 18.9%.[21]

CI has been well investigated not only in adult populations but also among pediatric patients. CKD-aP in children occurs less commonly and with a more benign course than in adults.[22] Data from German pediatric dialysis centers showed that only 9.1% of 199 children perceived itch. Reported intensity of pruritus was not severe.[23] A multicenter Polish study found that pruritus affected 20.8% of children with CKD in stages 3–5.[24] This was 18.4% in a group of predialysis patients and 23.5% on dialysis (HD or PD). The severity, duration, and location of pruritus did not statistically vary by method of applied therapy.

Underestimation

Despite the prevalence of CKD-aP — approximately 40% in HD patients — the problem appears to be markedly underestimated by clinicians. In phase V of DOPPS, 65%

of medical directors estimated that <5% of their patients had severe pruritus, and overall they underestimated the prevalence of pruritus in 69% of facilities. Furthermore, as mentioned before, patients tend not to report CI to healthcare providers. This varied from 8% in Italy and 12% in Gulf countries to 21% in Sweden and 33% in the US.[13] This may be due to patients' fear of numerous medical tests and extension of the diagnostic process, which can be burdensome for them. Years after reporting the CKD-aP and not receiving effective therapy, patients may feel resigned. A German cross-sectional survey completed by 204 nephrologists showed that most respondents estimated the prevalence of CI in HD patients to be <30%. This figure is inadequate to compare with international CKD-aP prevalence. The authors of that study presumed that clinicians neglecting this problem may be due to a lack of knowledge of effective therapy for CKD-aP.[25] It is important to emphasize that lack of reporting this burdensome problem very often may be caused by a lack of interest and questions from nephrologists. A lack of available gold-standard therapy that could help patients intensifies this trend.

Pathogenesis

Scientists have developed several hypotheses regarding the development of pruritus in chronic renal failure, but the precise etiopathogenesis of this phenomenon remains elusive. False assumptions about the pathophysiological mechanisms of CKD-aP slow the discovery of better therapy in clinical practice; therefore, deeper research is necessary for breakthroughs in this area. This paper presents the most popular and proven theories as follow.

Xerosis

Characterized by rough and scaly skin, xerosis is a common complication in HD patients, with prevalence of 50%–85% and occurring with greater frequency in PD patients than HD patients.[26] Evaluation of this skin condition among children with CKD was first performed by Wojtowicz-Prus et al.[27] Approximately 68% of children undergoing dialysis presented xerosis. Based on published studies, it can be concluded that xerosis is a risk factor associated with CKD-aP.[28,29] Research has shown that xerosis has an impact on the severity of itch.[30] Morton et al[31] demonstrated not only a correlation between itch and reduced stratum corneum hydration but also the efficacy of emollients in relieving the pruritus. However, not all studies in this area have confirmed these findings. Yosipovitch et al[32] did not find a correlation between xerosis and itch. Similarly, in another cross-sectional study, there was no significant difference in xerosis prevalence between pruritic and nonpruritic patients.[33] Despite these discrepancies, regular use of emollients is widely recommended for patients with CKD-aP and may improve not only dryness of the skin but also itch severity and patients' QoL.[34–36]

CKD-aP as an Inflammatory Disease

Results of a multicenter study showed that inflammation and dysregulation of the immune system play a great role in the pathogenesis of CKD-aP. In research on 13 HD patients with CKD-aP and 13 without CKD-aP serum levels of inflammatory markers, IL6 and C-reactive protein were significantly elevated in patients with pruritus versus those without. This may be explained by augmented T_h1 lymphocyte differentiation in patients suffering from CKD-aP.[36] Fallahzadeh et al[37] supported the theory of T_h 1 overactivity, showing significantly increased levels of the proinflammatory cytokine IL2 in HD patients with itch versus those without it. Two studies confirmed an important role of IL31 in CKD-aP pathophysiology, which may cause itch by stimulating peripheral nerve endings. Serum levels of IL31 were higher in patients reporting uremic itch.[38,39] Despite this fact, a randomized double-blind placebo-controlled study with nemolizumab, a monoclonal antibody against IL31RA, did not find statistically significant reductions of VAS scores in CKD-aP patients.[40] However, further investigation with a bigger, more representative group is required.

Uremic Toxins

CKD prevents proper elimination of various substances resulting from metabolic processes and predispose to its accumulation in the organism. These compounds, which interact negatively with various biological functions, are known as uremic toxins (UTs) and can be distinguished into three subgroups: small solutes, middle molecules, and protein-bound toxins. In 2021, the European Uremic Toxin (EUTox) database[41] listed 130 substances. Low–molecular weight molecules can be readily removed during the process of dialysis. One of the substances belonging to this group — uric acid — not only has an impact on CKD progression and mortality risk but can also cause CKD-aP.[42] According to a study performed by Wang et al[43] on 320 patients with CKD, pruritus was associated with higher levels of uric acid. However, the outcomes of two

other studies were contrary to this.[21,44] The aforementioned research also estimated the role of protein-bound UTs (PBUTs), ie, indoxyl sulfate (IS) and *p*-cresyl sulfate (PCS), in the pathogenesis of pruritus. PBUTs are predominantly excreted by renal tubular secretion, which cannot be replaced by conventional dialysis. Thereby, they are barely eliminated in patients undergoing HD or PD.[45] Patients with CKD-aP have higher total levels of IS and PCS than patients without itch. Total PCS concentration is significantly associated with pruritus severity.[43] Another study investigated the effect of IS, PCS, and uremic sera from CKD patients on PAR2 expression in normal human epidermal keratinocytes. Both PBUTs and CKD induced PAR2 expression and upregulated PAR2 expression in skin samples taken from human and mouse CKD subjects compared to healthy controls.[46] Similarly, Moon et al[47] found significantly higher epidermal PAR2 expression in ESRD patients then in controls. In addition, a positive correlation between PAR2 expression and VAS pruritus scores was found. All these findings and the implication that PAR2 is a histamine-independent pruritic mediator confirmed the possible role of this receptor in CKD-aP etiopathogenesis.[48] Wu et al[49] performed metabolic profiling on 200 uremic patients to find metabolites associated with CKD-aP. They found nine markers likely to play a role in the pathogenesis of CKD-aP. Metabolites associated with severe CKD-aP were LysoPE (20:3 [5Z,8Z,11Z]/0:0), *p*-cresol glucuronide, LysoPC (20:2 [11Z,14Z]), hypotaurine, 4-aminohippuric acid, LysoPC (16:0), phenylacetic acid, kynurenic acid, and androstenedione. It must be noted, however, that it is difficult to draw any direct causal relationship between elevated serum levels of these compounds and CKD-aP occurrence. On the contrary, in their metabolomic analysis of plasma of HD patients with severe pruritus versus mild/no pruritus, Bolanos et al[50] did not find any solutes associated with pruritus.

Calcium and Phosphorus Metabolism in CKD

CKD leads to imbalances in calcium, phosphorus, and vitamin D metabolism. An initial theory of CKD-aP mechanism also included calcium phosphate skin deposits, which arise as a result of imbalance between calcium and phosphorus in HD patients' blood and are able to activate local nerve fibers.[51,52] In 1985 Blachley et al[53] suggested that an increased number of divalent ions found in skin biopsies obtained from patients with CKD-aP may lead to microprecipitation of calcium or magnesium phosphate and be the cause of pruritus. Momose et al[54] found higher deposition of calcium ions in the basal layer of the epidermis in patients with moderate–severe itch versus patients without. Hyperphosphatemia, hypocalcemia, and decreased calcitriol production can all increase parathyroid hormone (PTH) production and consequently cause secondary hyperparathyroidism.[55] PTH has been proposed by some authors as a pruritogenic factor. This conclusion was made based on studies that confirmed reductions in CKD-aP after parathyroidectomy.[56,57] Makhlough et al[58] found a significant difference in CKD-aP intensity between patients with and without hyperparathyroidism (5.71 ±5.39 and 4.93±2.93 points, respectively; P=0.005). PTH levels correlated with severity of pruritus in HD patients.[58] However, other studies did not support the role of PTH as a mediator of CKD-aP.[33,59,60] Intradermal injections of PTH analogues did not induce pruritus or any other cutaneous reaction in dialysis patients or control groups. This hormone was not detected in skin biopsies of HD patients either.[61] Additionally, research performed by Duque et al[62] on 105 HD patients excluded the role of PTH and serum phosphorus in presence or intensity of itch, but demonstrated a positive correlation between CKD-aP and calcium serum concentration. This interdependence was confirmed by several other studies, including DOPPS, which identified other factors associated with pruritus as well: longer period of dialysis, male sex, Kt/V_{urea} (ratio representing fractional urea clearance) <1.5, and lower serum levels of albumin, ferritin, and hemoglobin.[12,55,63]

Mast Cells

Histamine is well known as a classical itch mediator released from mast cells. However, it plays a key role only in certain pruritic diseases, such as mastocytosis or urticaria. Initially, the significance of this potential pruritogen was thoroughly tested in terms of CKD-aP. Various studies showed a positive correlation between serum levels of histamine and CKD-aP,[64,65] whereas others disproved this theory.[66,67] Additionally, according to different reports, mast cells occur in increased numbers, are diffusely spread, and more often degranulated in the skin of patients suffering from CKD-aP than in healthy controls.[68–71] Nonetheless, Mettang et al[72] did not confirm that histamine plasma levels and number of mast cells in the skin correlated with the presence of CKD-aP. Another pruritogenic mediator released from mast cells is tryptase.

Dugas-Breit et al[73] demonstrated a significant correlation between tryptase serum levels and itch severity. Likewise, serum levels of serotonin were higher in patients with CKD-aP than the control group.[74] With the therapeutic use of a $5HT_3$-receptor inhibitor, ondansetron, significant reduction in the severity of pruritus has been observed.[75] Despite these contradictory findings, personal clinical experience affirms a lack of antihistamine effectiveness in CKD-aP therapy.

Opioid System

The opioid system is one of the several components involved in the etiopathogenesis of CKD-aP. Exogenous opioids, eg, morphine, are enabled to induce itch as a side effect. The incidence of opioid-induced pruritus depends on the route of administration and occurs in 10%–50% of intravenous administrations and 20%–100% of neuraxial administrations.[76] This fact inspired scientists to examine if opioid receptors were somehow associated with chronic pruritus. Bergasa et al[77] supported the hypothesis that cholestatic pruritus is modulated by endogenous opioids. They proved the effectiveness of opiate antagonists in alleviating this itch. Thus far, published reports have suggested that activation of μ-opioid receptors can trigger the itch and agonists of κ-opioid receptors are able to reduce the itch by inhibiting histamine and substance P.[78,79] Studies utilizing mouse models have revealed that the activation of central κ-opioid receptors antagonize the central μ-opioid receptor, thereby reducing itch sensation.[80] Wieczorek et al[81] assessed the expression of μ- and κ-opioid receptors in the skin of HD patients with and without uremic pruritus, and concluded that changes in the peripheral opioid system may play an important role in CKD-aP pathogenesis. This study demonstrated a negative correlation between skin expression of κ-opioid receptors and the intensity of CKD-aP. All these observations prompted scientists to experimentally implement opioid agonists and antagonists in the treatment of CKD-aP, which brought diverse outcomes (reviewed in subsequent sections).

Neuropathy

Dysfunction of the central or peripheral nervous system is considered another etiopathogenetic mechanism in CKD-aP. Itch can be caused by centrally acting mediators, defects in the peripheral sensory pathway, cortical hypersensitivity, decreased cortical inhibitory mechanisms, or a defective spinal cord inhibition.[35] A positive correlation between itch severity and occurrence of paresthesia in HD patients has been found. Most pruritic patients also develop peripheral sensorimotor neuropathy and dysautonomia.[82] Johansson et al[83] found altered cutaneous innervation in 12 CKD patients in whom nerve fibers sprouted through the epidermis, in contrast to healthy controls. Another study found a reduction in total number of skin nerve terminals in uremic patients.[84] Additionally, central brain neuropathy has been confirmed in functional magnetic resonance imaging of the brain in 13 patients undergoing HD and suffering from pruritus.[85] Sorour et al[86] aimed to evaluate serum levels of two neurotrophins — BDNF and NT4 — in 60 uremic patients with pruritus, 60 nonpruritic uremic patients, and 60 healthy subjects. The results showed not only significantly increased serum levels of NT4 in uremic patients with pruritus but also revealed a positive correlation between concentrations of NT4 and the severity of CKD-aP. Serum BDNF levels were higher in uremic patients than controls, but the presence of pruritus did not significantly influence the concentration of this neurotrophin. Natriuretic polypeptide B, also known as brain natriuretic peptide (BNP), has been described as a neuropeptide enabled to activate pruriceptive neurons in mice.[87] In a cross-sectional study, serum levels of BNP were found to be frequently elevated in HD patients. As such, the authors suggested BNP as one of many possible causes of daytime CKD-aP.[88]

Other Risk Factors of CKD-aP

According to DOPPS, patients on HD with coexisting hepatitis C infection are 1.29 times more likely to perceive CKD-aP.[12] This viral infection predisposes to development of CI, due to cholestasis, induction of interferon-stimulated gene,s and elevated production of cytokines (eg, IL8) and chemokines (eg, CCL2, CXCL1, and CXCL5).[22,35] Interestingly, hepatitis B does not show a significant association with pruritus, and this has raised the question of whether the pathogenesis of pruritus differs between these two diseases.de Kroes and Smeenk found elevated serum levels of vitamin A in all 35 CKD patients included in their research. However, there was no correlation between vitamin A concentration and the presence of CKD-aP. Two other studies have reported that increased serum levels of aluminum correlate significantly with the occurrence and intensity of CKD-aP.[8922]

Clinical Presentation

Clinical presentation of CKD-aP assessed in studies has varied among studied populations. In general, the sensation of the itch affects large, discontinuous regions of the skin and shows bilateral symmetry. It is very often unceasing, recurrent, and the intensity seems to be worse during the night.[90] Clinically, excoriations, erosions, ulcerations, nodules, or dyspigmentation can be observed, mostly as secondary lesions caused by scratching. Certain factors are known to exacerbate or reduce itching, including heat, dialysis, stress, cold, physical activity, or showering.[91] CKD-aP can be localized or generalized. Weiss at al[92] observed that the most common location of CKD-aP is the legs, back, and scalp. The results were similar to a study conducted by Heisig et al.[93] Overall, 38% of respondents reported a single location of the itch — mostly the back, lower extremities, scalp, upper extremities, and abdomen — and bilateral symmetry was predominant. Generalized itch presented in 26.6% of the patients. On the other hand, a cross-sectional study on Iranian HD patients showed generalized pruritus in 70% of respondents.[33] Ozen et al[94] estimated entire-body pruritus to be present in 35.3% of patients. Another important aspect that is constantly assessed by researchers is the intensity of CI. In a large German study, mean severity of itch measured with a VAS was 4.1±1.7 points, while severity at the time of investigation amounted to 4.2±2.6 points and the worst severity within the last 6 weeks was 6.5±2.5 points.[92] Mathur et al[90] showed that mean worst itching intensity for enrolled patients was 59.9 mm using the 100 mm VAS. Scores were significantly higher for the 12-hour nighttime period than for the 12-hour daytime period, which corresponds with the research on patients undergoing PD conducted by Minato et al.[95] Additionally, in DOPPS, a third of patients were most bothered by itch at night.[13]

Apart from the time of day, there are many other factors that can affect the course of itch. A study on 130 HD patients conducted at our center revealed that the frequency of itching can positively correlate with xerosis. Itch appeared more often (56.2%) in patients with very rough skin than patients with rough (34.5%) or slightly dry skin (27%).[96] According to Ozen et al,[94] dry skin is a risk factor of CKD-aP. In other research skin dryness just after rest was the second–most common exacerbating factor of chronic pruritus in patients undergoing dialysis.[97] Heat, sweat, wool clothing, and stress were aggravating factors, while activity, sleep, hot/cold showers, and cold temperatures were considered ameliorating factors. Surprisingly, dialysis had no significant influence on itch severity.[97] Other studies have revealed a connection between the dialysis process and itching. About 29% of patients in a Polish study reported itch to be the most severe during, at the end, or immediately after dialysis.[93] Rayner et al[13] found that 15% of the patients admitted that the worst itch was perceived during the dialysis session and 9% indicated the period soon after the session. However, for 14%, the itch was the most intense on days without dialysis. Some authors have emphasized the influence of the dialysis membrane on pruritus and hypothesized that some pruritogenic cytokines or substances may be activated after blood contact with membranes. This thesis needs more precise evaluation. A positive significant correlation has been found between HD period and total pruritus score.[96] Interestingly, Rad et al[98] proved that the severity of pruritus was significantly reduced in patients receiving a cool dialysis solution (35.5°C) during three consecutive dialysis sessions.

CKD-aP Assessment

CI should be characterized multidimensionally. Questionnaires, surveys, and similar tools are the best way to evaluate this subjective sensation. The IFSI recommends estimating not only the severity of itch but also its clinical course and consequences.[99] Several scales are widely used to rate the intensity of CI. Numeric rating scales (NRSs) are the most commonly used tool for self-reported pruritus intensity. Visual analogue and verbal rating scales are equally helpful instruments. These quick and undemanding tools should be used together with at least one multidimensional questionnaire assessing frequency, duration, and distribution of the itch, as well as impact on daily activities, sleep, and psychosocial life. Such an extensive assessment of CKD-aP may be of help in evaluation of the effects of applied itch therapy and comparability of studies.[100] Examples of such instruments are the 5-D Itch Scale, four-item Itch Questionnaire, Patient Benefit Index for Pruritus, Skindex 10, and Brief Itching Inventory. Due to the enormous impact of CKD-aP on QoL, assessment of this aspect in patients with CI is significant. The Dermatology Life Quality Index (DLQI) is a popular tool to evaluate QoL in patients with various dermatological diseases. However, ItchyQoL, an instrument dedicated to estimating the influence of CI on QoL, appears to be the best choice. Despite various instruments

describing itch in use, only recently has a specific instrument for CKD-aP — Uremic Pruritus in Dialysis Patients — questionnaire been created.[101] It evaluates three dimensions of UP in patients on dialysis: signs and symptoms, sleep, and psychosocial burden during the last 2 weeks. Besides the original version, only Chinese and Polish versions of this questionnaire have been created and validated.[102,103]

Clinical Outcomes

CKD-aP not only has a negative impact on patients' QoL but also consequently leads to impairment of various patient-oriented outcomes and increased mortality risk. In the first and second part of DOPPS,[12] patients suffering from moderate–extreme pruritus had 2.3–5.2 the odds of feeling drained and 1.3–1.7 times the odds of physician-diagnosed depression than patients not affected by pruritus. uring the QoL results showed that patients strongly bothered by itchy skin had mental and physical composite scores 3.1–8.6 points lower than patients with no or mild pruritus ($P<0.0001$). Likewise, poor sleep quality associated with waking up at night was mentioned by approximately 45% of patients with moderate–severe pruritus. In a group with mild/no pruritus, this amounted to only 29%. A correlation between severity of perceptible itch and mortality risk was also found. Patients with moderate–extreme pruritus had a 17% higher mortality risk than patients not bothered by pruritus.[12] The Japanese DOPPS confirmed these findings: researchers found a 22% higher mortality rate for patients with moderate or extreme pruritus. This condition also induces 1.9–3.7 times the probability of impaired quality of sleep.[14] Interestingly, in an Italian study, pruritus was associated with 8.4 times the adjusted odds of poor sleep.[104] Mathur et al[90] found that intensity of itch measured by VAS was significantly associated with lower health-related QoL in such domains as sleep, mood, and social relationships. Similarly, Szepietowski et al,[9] using a short form scale (SF12) and the DLQI, concluded that not only CKD-aP but also uremic xerosis had a negative impact on patients' QoL and were unfortunately underestimated in clinical practice. Ibrahim et al[105] assessed the QoL of 200 HD patients using the WHOQOL-Bref questionnaire. QoL was impaired markedly in all four domains — physical health, psychological health, social relationships, and environmental health — in a group of patients with CI compared to a control group with no pruritus. All these papers highlight how strongly CKD-aP affects miscellaneous aspects of life and can lead to poor clinical outcomes.

Treatment of CKD-aP

The etiopathogenesis of CKD-aP is particularly complex, and numerous aspects remain to be explored and explained in more detail. As such, successful therapy for this condition often remains a demanding challenge for nephrologists or dermatologists. Considering common comorbidities in this group of patients, every single case ought to be considered individually, and applied therapy must be planned properly. The age of the patient, preexisting diseases, medications, and the quality and intensity of CI should be examined. Most of all, avoiding all exacerbating factors, such as allergenic and irritant substances, stress, hot drinks, alcohol, or hot and spicy food, is crucial.[97] Fundamental antipruritic therapy must include reducing xerosis by moisturizing the skin.

Topical Therapy

Topical therapy is a treatment of first choice in numerous dermatological conditions. Emollients are capable of restoring the skin barrier and retaining water in the stratum corneum, which is crucial in reducing xerosis and thus can be of help in alleviating the itch.[106] To achieve therapeutic effect, an appropriate amount of product and high frequency of application are essential.[22] There are specific ingredients of emollients with proven antipruritic effects. In a randomized, multicenter study performed on 99 patients with uremic xerosis, 15% glycerol and 10% paraffin emulsion, high efficiency was found.[107] The satisfactory treatment response concerned 73% of the patients compared with 44% of patients who responded to a comparator. By day 56 of that trial, patients reported significant relief from the itch (mean VAS score 10.66 ±2.14 mm vs 40.64±3.36 mm at the beginning of the trial). At the end of the study, a significant improvement in patients' QoL, which was measured by the DLQI and SF12 questionnaire, was revealed. In other studies, the application of 10% urea plus dexpanthenol lotion or γ-linolenic acid cream turned out to be effective in alleviating CKD-aP.[108,109] Topical capsaicin has also found the interest of scientists in local therapy. Studies have proved its safety and ability to reduce HD-induced pruritus.[110–112] In Makhlough et al's[112] study on 17 patients with CKD-aP, 0.03% capsaicin was applied for 4 weeks, while 17 patients from control study group received placebo. During the therapy, decrease in pruritus severity was

greater in the study group than the placebo group ($P<0.001$). However, it should be noted that in contrast to emollients, capsaicin may cause irritation of the skin. Therefore, this therapy should be used with great caution, especially in children, where emollients are considered the preferred approach in topical therapy.[22] A prospective Polish study on 21 HD patients using a topical cream containing structured physiological lipids and endogenous cannabinoids twice a day for 3 weeks was conducted. A marked reduction in itch severity was observed after the trial in 38.1% of the patients.[113] This was probably related to the inhibition of mast-cell degranulation and histamine release, as well as the moisturizing effect of the preparation. Studies using calcineurin inhibitors in the treatment of CKD-aP have not shown conclusive results. According to Kuypers et al,[114] treatment with 0.1% and 0.3% tacrolimus ointment for 6 weeks significantly reduced the severity of CKD-aP. This finding was confirmed by Pauli-Magnus et al.[115] On the other hand, in a study carried out by Duque et al,[116] these conclusions were refuted. Likewise, a larger, randomized, double-blind, placebo-controlled study using 1% pimecrolimus demonstrated a lack of efficacy of calcineurin inhibitors for the treatment of HD-related pruritus.[117] Based on clinical experience, good tolerance of topical therapy, and rarity of adverse effects, it is recommended that it be used as a preliminary treatment, especially in patients presenting xerosis.

Phototherapy

Ultraviolet (UV) radiation is widely used in the treatment of various dermatoses. The effectiveness of phototherapy is related to a range of mechanisms, including inhibition of Langerhans cells, decreasing levels of proinflammatory cytokines, strengthening the skin barrier, increasing serum levels of 25-hydroxyvitamin D_3, or stimulating the apoptosis of mastocytes.[22] The use of phototherapy in CKD-aP was first mentioned in the 1970s. Since then, numerous studies have reported beneficial effects after implementation of broadband UVB (290–320 nm wavelength) radiation. Additionally, several studies have proved the effectiveness of narrow-band UVB (NB-UVB) radiation, both in HD and PD patients with CI.[118–121] However, a study comparing NB-UVB (treatment group) and long-wave UVA radiation (control group) in patients with CKD-aP did not show significant differences concerning pruritus intensity between these two groups.[122] A systematic review on this topic defined heliotherapy as a beneficial, efficacious, efficient, safe method of CKD-aP treatment. IT emphasized also that broadband BB-UVB compared to other subtypes is the most effective phototherapy in this condition.[123] NB-UVB may also be considered in children aged >4 years bothered by recurrent CKD-aP thatdoes not respond to topical therapy, although there is still no literature available regarding its potential effectiveness and safety in this particular population.[22] Finally, it must be noted that despite the established role of phototherapy in managing CKD-aP, this method can be troublesome, due to the limited availability and the necessity of frequent irradiation, mostly three to four times a week.

Antihistamines and Mast-Cell Stabilizers

Antihistamines are often the first-line therapy in CI, primarily when it comes to the use of over-the-counter drugs. According to DOPPS data, antihistamines were very widely prescribed for pruritus by doctors who were not skin specialists: 57% of medical directors chose oral antihistamines as an "appropriate" therapy dedicated to CKD-aP.[13] This tendency is not substantiated in light of the research and expert opinions, which emphasize poor or moderate antipruritic effects of histamine-receptor antagonists in CKD-aP.[91,124–129] Additionally, some reviews have suggested that the relief perceived after administration of the antihistamines may be a result of a sedative effect, rather than an antipruritic mechanism. On account of its limited value and risk of oversedation in elderly populations, this group of drugs should be avoided for this condition.[91] Antihistamines are not a recommended modality in CKD-aP, and it is crucial to suppress their overuse in the subtype of CI. On the other hand, several recent studies have proved that the use of mast-cell stabilizers, which preclude histamine release, brings satisfactory effects in the treatment of CKD-aP.[130] Both ketotifen and cromolyn sodium have proved to be effective in reducing itch severity.[67,131] Furthermore, a trial on 60 HD patients in which cromolyn sodium cream 4% was applied twice a day for 4 weeks revealed significantly reduced pruritus severity compared to a placebo.[132]

Antiepileptic Drugs

Gabapentin is an anticonvulsant medication, an analogue of γ-aminobutyric acid, that is widely used in therapy for focal seizures and neuropathic pain. The mechanism of action of gabapentin in the treatment of CKD-aP is not fully known, but due to binding to $\alpha_2\delta$ subunits of calcium channels and suppressing the influx of calcium into nerves,

this drug is able to discontinue itch. A systematic review of randomized controlled trials using gabapentin as a treatment for pruritus in patients undergoing HD established that gabapentin significantly alleviated CKD-aP and was a safe choice. A pooled analysis of seven studies showed reduced VAS scores among HD patients. Furthermore, side effects associated with the therapy were well tolerateds.[133] Another systematic review emphasized that effectiveness of gabapentin in CKD-aP has been evidenced in the greatest number of trials compared to other interventions.[134] Pregabalin, which is another antiepileptic drug with similar mechanism of action to gabapentin, is also advantageous in CKD-aP management and may be effective in patients unable to tolerate the latter.[135] Ravindran et al[136] concluded that pregabalin was associated with fewer side effects than gabapentin. Proven effectiveness of these two antiepileptics makes them the main choice in CKD-aP oral therapy.[136,137]

Opioid-Receptor Agonists and Antagonists

Difelikefalin, a highly selective peripheral agonist of the κ-opioid receptor, can be seen as a new and revolutionary treatment for pruritus in patients undergoing HD.[138] It is the first and only therapy approved by the US Food and Drug Administration for treatment of moderate–severe CKD-aP in adults undergoing HD. Injections of difelikefalin are a real breakthrough in CKD-aP treatment and should be considered as a first-line therapy. In one study, ifelikefalin 0.5, 1.0, or 1.5 μg/kg was administered intravenously three times a week for 8 weeks to HD patients with moderate–severe pruritus. A significant reduction from baseline in itch intensity scores at week 8 favored all difelikefalin doses combined versus placebo (P=0.002). At the end of the trial, 59% of patients receiving difelikefaline reported more than 3-point improvements in mean weekly Worst Itch Intensity NRS (WI-NRS) scores compared to 29% in the placebo group. The study also demonstrated that difelikefalin improved patients' sleep, mood, and social functioning. A significantly larger reduction from baseline in mean Skindex-10 total score in a study group over the control group was observed (−16.4 and −8.2, respectively; P<0.001). Sleep disturbance measured by the Medical Outcomes Study scale in all difelikefalin combined groups had decreased after 8 weeks' therapy (P≤0.006).[139] Similarly, in a double-blind, placebo-controlled, phase III trial, more patients reported at least 3 points of improvement in itch severity measured by the WI-NRS than patients without treatment (49.1% vs 27.9%, P<0.001). The most common adverse events associated with difelikefalin were diarrhea, dizziness, and vomiting. The severity of side effects was generally mild–moderate, and they resolved without evident clinical consequence.[140]

In a systematic review and meta-analysis conducted by Jaiswal et al,[78] nalfurafine, a selective κ-opioid agonist, was mentioned as a potentially effective treatment for CKD-aP. Two studies showed reductions in itch severity in HD patients after 2 weeks of orally applied nalfurafine. In a study on 86 patients who received 5 μg/day nalfurafine and 58 who received placebo, a 50% decrease from initial "worst itching" score assessed by VAS was reported by 36% of patients included in therapy and by only 14% of respondents in the control group.[141] Similarly, in a prospective randomized, placebo-controlled study, Kumagai et al[142] showed that decreases in VAS scores were markedly larger in a group receiving treatment than a placebo group. The most frequent adverse reaction to nalfurafine was insomnia. Four of six patients with this side effect discontinued the therapy. Wikström et al[141] also mentioned headache, vertigo, nausea, and vomiting as common side effects. Both studies emphasized that adverse events were transient and easily resolved, which makes nalfurafine a safe agent for patients who are undergoing routine HD and suffering from CKD-aP.[141,142] However, both studies that evaluated the effectiveness of κ-opioid agonists showed quite high percentages of placebo effectiveness. In a study evaluating difelikefalin, a placebo decreased the intensity of CKD-aP by at least 3 points in WI-NRS score in 27.9% of patients.[140] Wikström et al[141] found that 14% of patients in a placebo group reported a 50% decrease from baseline in "worst itching" VAS scores. According to the authors, subjective improvement in this chronic and burdensome condition can arise from increased attention given to the patients and their confidence in receiving the right therapy. The effectiveness of the μ-receptor antagonist naltrexone in CKD-aP varied between the studies. Naltrexone 50 mg/day received orally for 7 days significantly reduced CKD-aP in a group of 15 HD patients.[143] Notwithstanding, Pauli-Magnus et al[144] established that antipruritic therapy of CKD-aP with naltrexone was ineffective and the frequency of side effects high. Another opioid mediator applied in patients with moderate or severe CKD-aP with a satisfactory effect was nalbuphine. It is a mixed κ-

agonist/μ-antagonist opioid modulator. In a large, multicenter, randomized, double-blind, placebo-controlled trial, 373 HD patients received extended-release nalbuphine tablets (60 or 120 mg) or placebo for 8 weeks. Theere was a significant reduction in itch severity in the group receiving 120 mg in comparison to placebo group. In contrast to placebo, this dose significantly improved sleep disturbances caused by itch.[145]

Toxin Removal

Several studies have examined dialysis efficiency in the context of CKD-aP. Interestingly, researchers found discrepant results concerning the relationship between Kt/V values and the presence of itch in HD patients. Hiroshige et al[146] were the first to reveal that higher dialysis efficacy leads to reductions in prevalence and intensity of pruritus in HD patients. A prospective cohort study of patients receiving maintenance PD[147] found that weekly total Kt/V <1.88 was associated with higher itch intensity. Similarly Ko et al,[148] found Kt/V ≥1.5 and use of a high-flux dialyzer to be factors that may alleviate CKD-aP. Not all results in this topic are equivocal. Duque et al[62] pointed out that increasing the number of months on dialysis, skin dryness, and surprisingly higher Kt/V positively correlated with the intensity of CKD-aP. Even when dialysis is properly optimized, the retention of middle molecules and PBUTs is inevitable However, the removal of IS and PCS may improve health, inhibit CKD progression, and most importantly decrease pruritus.[149]

Originally used to inhibit poison absorption in the intestine, activated charcoal seems to be a promising solution in removing UTs. This alternative to conventional HD and hemodiafiltration was first described by Pederson et al.[150] However, bigger and better-designed studies are necessary to prove this theory. This study showed that 6 g activated charcoal applied once a day for 8 weeks significantly reduced itching compared to placebo and an economical and safe therapy for CKD-aP. Another oral charcoal adsorbent, AST120, has induced reduction in PBUTs. Levels of IS, PCS, and phenyl sulfate were significantly reduced after 2 weeks' usage of 6 g per day in a study group of 20 HD patients.[151] However, this study did not assess the severity of pruritus in patients. On the other hand, cholestyramine, a synthetic resin thatprevents bile reabsorption in the gastrointestinal tract, noticeably improved pruritus in patients undergoing chronic HD.[152] However, study was performed on a very small number of patients, and adverse effects of constipation and nausea were noted. Cupisti et al[149] also emphasized the importance of hemoperfusion and dialysis membranes with activated carbon in itch therapy.

Other Modalities

Parathyroidectomy in patients with ESRD who develop secondary hyperparathyroidism is effective in alleviating CKD-aP.[56,57,153] However, as mentioned before, not all studies have confirmed the pruritogenic nature of PTH. Additionally, hyperparathyroidism is not present in all patients with CKD-aP. Therefore, parathyroidectomy cannot be considered a form of CKD-aP therapy, except in the case of concurrent hyperparathyroidism.[35] In some reports, reduction of itch prevalence after successful renal transplantation has been highlighted.[154,155] The biggest published study on this topic thus far, conducted on 197 renal transplant recipients, showed that in 73.7% of patients the itch disappeared completely after transplantation, while in 23.7% itch had lower intensity and only 2.6% patients did not report any improvement. Nevertheless, 21.3% patients suffered from itch after transplantation, among which in 52.4% cases the itch appeared after renal transplantation.[156] The supplementation of $_3$ fatty acids is not only relevant in the range of diseases coexisting with chronic renal failure but also, according to three studies, can be of help in decreasing itch in comparison to $_6$, $_9$, and placebo supplementation.[157] Nonpharmacological methods taken from alternative medicine have also attracted the attention of researchers in this area. Acupuncture and acupressure have been found to be beneficial in CKD-aP, although some authors underline the high risk of bias in such studies.[158–161] In addition, aromatherapy, stress-reduction techniques, psychotherapy, and physical exercises can be considered support strategies.[162] It is vital to emphasize that in no way can these alternative methods be currently regarded as the basic or only antipruritic modality in the CDK-aP population.

Conclusion

CKD-aP is a pervasive but very often underestimated condition in patients undergoing HD or suffering from CKD, impairs QoL and increases the risk of mortality. Due to its complex etiopathogenesis, the choice of an

effective therapy remains a challenge for clinicians. Future research looking for new factors responsible for CKD-aP can help in the development of novel drugs, specifically targeting particular molecules. Despite continuous research and considerable interest from scientists in understanding the full etiopathogenesis of CKD-aP, the results of many studies have been contradictory. The current situation requires continued research in this area and reevaluation of certain theories that may have a significant impact on the therapeutic management of patients with CKD-aP. Dspite many unknowns, we possess proven therapeutic methods. The proper algorithm in CKD-aP should consist of topical therapy, phototherapy, and systemic therapy. Among the latter, difelikefalin is the first and only therapy to be approved by the US Food and Drug Administration as treatment for moderate–severe CKD-aP. This may result in wide use of this substance as first-line therapy in the near future. Other group of systemic drugs with good effectiveness in this condition are gabapentinoids. Reasonable use of methods with proven effectiveness definitely contributes to improvements in patients' QoL and is crucial in this troublesome condition. It is necessary to underline the recent extensive interest in the role of UTs in CKD-aP. It is hoped that further research in this area will provide more effective and innovative management options in HD patients with CKD-aP.

Author Contributions

All authors made significant contributions to conception and study design, acquisition of data, or analysis and interpretation of data, took part in drafting, revising, and critically reviewing the article, agreed to submit to the current journal, gave final approval to the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

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5. ARTYKUŁ DRUGI

Uraemic Pruritus in Dialysis Patient (UP-Dial) questionnaire: creation and validation of the Polish language version.

Original paper

Uraemic Pruritus in Dialysis Patient (UP-Dial) questionnaire: creation and validation of the Polish language version

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Abstract

Introduction: Uraemic pruritus is a common and burdensome symptom in patients undergoing haemodialysis. Though a significant negative impact of chronic itch on patient's quality of life is proved, this problem is still often underestimated in clinical practice. Various instruments describing itch are in use, however only recently a specific instrument for uraemic itch – Uraemic Pruritus in Dialysis Patient (UP-Dial) – questionnaire has been created.
Aim: To translate and to validate the Polish version of the UP-Dial questionnaire.
Material and methods: Forward and backward translations were conducted according to international standards. The validation was performed on a group of 30 patients undergoing haemodialysis and suffering from uraemic itch. Respondents completed the questionnaire twice with a 3–7 days' interval. Moreover, for convergent validity, the subjects were asked to assess their itch with the Numerical Rating Scale (NRS), 4-Item Itch Questionnaire (4IIQ) as well as ItchyQoL questionnaire.
Results: The Polish version of the UP-Dial questionnaire showed very good internal consistency – Cronbach α coefficient was 0.90 for total score. The reproducibility assessed with the intraclass correlation coefficient (ICC) was also very good – 0.9. Furthermore, UP-Dial correlated strongly with NRS ($r = 0.74$, $p < 0.01$), 4IIQ ($r = 0.82$, $p < 0.01$) and ItchyQoL ($r = 0.88$, $p < 0.01$).
Conclusions: The Polish version of the UP-Dial questionnaire showed high internal reliability, validity and reproducibility and can be widely used both in research and in daily clinical practice.

Key words: pruritus, questionnaire, haemodialysis, quality of life, validation.

Introduction

Chronic kidney disease-associated pruritus (CKD-aP), which for years has been known as uraemic pruritus (UP), is a common and burdensome symptom in patients undergoing dialysis. This condition was first described by Chargin and Keil in 1932 [1]. Despite the long-standing studies in this area, the complex etiopathogenesis of UP is still not fully understood. According to studies published so far, the current prevalence of UP is about 40% [2–5]. UP has a confirmed negative impact on the patient's sleep, daily activities and quality of life (QoL), while it is also responsible for mood disturbances, depression and increased mortality risk [5–8]. Despite many years of trials, therapy of UP is still a challenge for nephrologists and dermatologists.

In clinical practice various instruments have been used to evaluate chronic pruritus. Due to the multifactorial and subjective nature, the International Forum for the Study of Itch (IFSI) recommended an extensive evaluation of chronic pruritus including its intensity, clinical course and consequences [9]. Although several instruments, including the Numerical Rating Scale (NRS), Visual Analogue Scale (VAS), 4-Item Itch Questionnaire (4IIQ),

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5D-Itch Scale, ItchyQoL are available, there has been no specific questionnaire designed to characterize UP in dialysis patients. In 2016, Nochaiwong *et al.* [10] developed a standardized multidimensional 14-item instrument – Uraemic Pruritus in Dialysis Patients (UP-Dial). It evaluates three dimensions of UP in patients on dialysis: signs and symptoms, sleep and psychosocial burden during the last 2 weeks [10].

Aim

The aim of this study was to translate and to validate the Polish version of the UP-Dial questionnaire to enable its use by Polish speaking patients.

Material and methods

The Polish version of the UP-Dial questionnaire was translated and validated according to the international standards. The permission to translate the questionnaire was provided by the copyright holders. The research obtained ethical approval by the Wroclaw Medical University Ethics Committee (Consent no. 26/2021).

Translations and validation

Firstly, the original English version of the UP-Dial questionnaire was translated into the Polish language by two independent translators. Then the translated versions were compared in terms of discrepancies by a third counsellor who is a bilingual expert in the field. The unified version was created. Subsequently, another two independent translators, who were not familiar with the original version of the UP-Dial questionnaire, did the back-translation from Polish to English. Afterwards, the back translations were sent to the members of the team who created the original questionnaire. All raised comments were carefully considered. Finally, the Polish version of the instrument was invented.

After the translation process, the preliminary validation was performed. The questionnaire was completed by a group of 30 patients on maintenance haemodialysis. All of them were suffering from UP. The group consisted of 17 men and 13 women aged 22-83 years (mean age: 63.3 ±14.3 years). The average duration of haemodialysis was 52.5 ±40.5 months (range: 5 weeks–144 months). The patients presented the following aetiology of end stage renal disease: nephrosclerosis (36.7%), diabetes mellitus (30%), polycystic kidney disease (10%) and other causes that occurred only in single cases. The responders were asked to complete the questionnaire twice with an interval of 3–7 days. This period was considered long enough to prevent the patients from remembering previous answers, as well as short enough to prevent any noticeable changes in the characteristics of pruritus. Assessments were supervised by one of the authors of the Polish version of UP-Dial, who controlled the time required to complete the survey. The participants of the study had the opportunity to report any concerns related to the questionnaire. For convergent validity patients were also asked to assess their pruritus with NRS (worst itch intensity during the last 3 days) [11] and 4-Item Itch Questionnaire [12]. Additionally, they filled the Polish version of ItchyQoL [13].

NRS is an easily accessible instrument commonly used to evaluate the intensity of pruritus. On a scale from 0 to 10 points, results over 7 points indicate severe itch [14]. 4IIQ consists of 4 questions which characterize different aspects of itch. First question applies to the extensity of itch, second – to intensity, third – to frequency and fourth – to sleep disturbances caused by itch. The possible score by patients, who experience itch, ranges from 3 to 19 points [12]. ItchyQoL is a validated 22-question instrument, consisting of three dimensions: symptoms, functional limitations and emotions, which estimates influence of chronic itch on QoL [15]. Questions are scored on a 5-point scale (1 – never; 2 – rarely; 3 – sometimes; 4 – often; 5 – all of the time), with the sum forming the total ItchyQoL score with a range of 22–110 [16].

Statistical analysis

All data analyses were carried out using Statistica 13 software (Dell, Inc., Tulsa, USA).

The internal consistency of the instrument was evaluated with Cronbach α coefficient. To establish that the questionnaire is internally consistent, the Cronbach coefficient should reach at least 0.70, while the value above 0.90 indicates very good internal consistency [17].

The questionnaire reproducibility (test-retest reliability) was assessed by using intraclass correlation coefficient (ICC), with results ≥ 0.70 indicating adequate reproducibility [18].

Additionally, responses to each question from the first and the second completion were compared using Wilcoxon test. The correlation between answers from a single completion to each individual question and to the total score was established with Spearman correlation test. Convergent validity was based on the Spearman rank correlation test between UP-Dial and other instruments (NRS, 4IIQ and ItchyQoL). *P*-values less than 0.05 were considered as statistically significant.

Results

Cronbach α coefficient value of UP-Dial total score was 0.90, which indicated very good internal consistency of the validated instrument. Furthermore, each of the three domains presented good or very good internal consistency with Cronbach α coefficient of 0.75 for the signs and symptoms domain, 0.93 for the sleep domain and 0.75 for the psychosocial domain.

Significant correlations between most of the results obtained for each item and the total score of the translated questionnaire were found. Only questions 5, 7 and 14 did not correlate with the total score (Table 1).

Table 1. The correlation coefficients between the answers to each question and between the answers to each question and the total score of the UP-Dial questionnaire

Item	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Q1	1													
Q2	0.614[b]	1												
Q3	0.668[b]	0.668[b]	1											
Q4	0.526[b]	0.545[b]	0.588[b]	1										
Q5	0.236[c]	–0.031[c]	0.228[c]	0.266[c]	1									
Q6	0.146[c]	0.184[c]	0.085[c]	0.250[c]	0.436[a]	1								
Q7	0.362[a]	0.175[c]	0.118[c]	–0.011[c]	0.098[c]	0.116[c]	1							
Q8	0.707[b]	0.609[b]	0.589[b]	0.532[b]	0.117[c]	0.082[c]	0.031[c]	1						
Q9	0.702[b]	0.464[b]	0.518[b]	0.577[b]	0.293[c]	0.408a	0.107[c]	0.621[b]	1					
Q10	0.609[b]	0.495[b]	0.393[a]	0.459[a]	0.254[c]	0.317[c]	0.207[c]	0.736[b]	0.730[b]	1				
Q11	0.682[b]	0.610[b]	0.731[b]	0.652[b]	0.368a	0.413[a]	0.162[c]	0.477[b]	0.747[b]	0.535[b]	1			
Q12	0.566[b]	0.372[a]	0.432a	0.518[b]	0.412[a]	0.513[b]	0.094[c]	0.519[b]	0.687[b]	0.650[b]	0.613[b]	1		
Q13	0.506[b]	0.601[b]	0.627[b]	0.248[c]	0.194[c]	0.356[c]	0.107[c]	0.536[b]	0.502[b]	0.534[b]	0.650[b]	0.412[a]	1	
Q14	0.071[c]	0.035[c]	0.384[a]	0.003[c]	0.178[c]	0.087[c]	-0.059[c]	0.100[c]	0.007[c]	0.016[b]	0.043[c]	0.170[c]	0.211[c]	1
Total	0.823[b]	0.757[b]	0.726[b]	0.629[b]	0.342[c]	0.457[a]	0.333[c]	0.758[b]	0.735[b]	0.754[b]	0.775[b]	0.665[b]	0.716[b]	0.145[c]

[a]p < 0.05; [b]p < 0.01; [c]p > 0.05; Q – question.

The ICC used for the evaluation of the questionnaire reproducibility was very high – 0.90. Moreover, besides only two questions (1 and 2), no statistically significant differences were found for each particular question answered during the first and the second completion (Table 2). Both questions mentioned above belong to the signs and symptoms domain, which also significantly differed between the assessments. A strong positive correlation ($r = 0.93$, $p < 0.001$) was found between the results of the total score from both assessments. Likewise, positive correlations were also found for each particular question (detailed data not shown).

Two of the instruments used for the evaluation of convergent validity in the study assessed the severity of the itch. The score of the worst itch intensity during the last 3 days, estimated by NRS, ranged between 1 and 8 points with the mean of 4.8 ±2.0 points. The results of 4IIQ were in the range from 4 to 18 points. The mean result was 9.2 ±4.1 points. The evaluation of convergent validity showed a strong correlation between UP-Dial and the instruments which assess intensity of the itch – NRS ($r = 0.74$, $p < 0.01$) and 4IIQ ($r = 0.82$, $p < 0.01$). Similarly, the UP-Dial questionnaire strongly correlated with Itchy-QoL ($r = 0.88$, $p < 0.01$) (Figure 1). Additionally, each domain of the survey showed a significant correlation with all the above-mentioned instruments (Table 3).

The results presented in our study proved very good internal consistency, reproducibility and convergent validity of the Polish version of the UP-Dial questionnaire. The respondents reported good comprehensibility of the questions and the process of completing the whole instrument took 7–10 min. None of patients reported any difficulties in understanding the questionnaire items. The Polish validated version of UP-Dial is presented in Appendix 1.

Discussion

UP is one of the most common dermatological symptoms associated with chronic kidney disease [19]. Despite the evolution of dialysis methods during past decades, this problem still bothers about 40% of patients undergoing haemodialysis [5, 20]. The characteristics of UP include intensity, localization and consequences of the itch differ among patients. Nevertheless, a significant negative impact of chronic itch on patients' quality of life has been proved, yet this problem is still often underestimated in clinical practice [21]. In order to characterize UP, a multidimensional instrument is necessary. Although various instruments describing itch are in use, so far there has been no specific tool designed particularly for itch in dialysis patients. UP-Dial seems to be the first instrument ever developed specifically for UP. This questionnaire contains three domains: signs and symptoms, sleep and psychosocial. These domains investigate all important aspects of chronic itch: frequency, intensity, distribution, skin lesions caused by itch, impact on sleep and psychosocial life of the patient. The total score of UP-Dial also enables classifying the severity of itch. Moreover, Nochaiwong *et al.* [22] proposed cut-off points of this instrument, which present as follows: ≤ 12 points indicate mild, 13-21 points moderate and ≥ 22 points severe itch.

Table 2. Reproducibility of results

Item	1st assessment [points]			2st assessment [points]			*P*-value
	Median	1st quartile	3rd quartile	Median	1st quartile	3rd quartile	
Q1	0.00	0.00	2.00	0.00	0.00	1.00	0.021
Q2	2.00	2.00	2.00	2.00	1.00	2.00	0.034
Q3	1.50	1.00	2.00	1.00	1.00	2.00	0.726
Q4	1.00	0.00	2.00	1.00	1.00	2.00	0.469
Q5	0.00	0.00	0.00	0.00	0.00	0.00	0.063
Q6	0.00	0.00	1.00	0.00	0.00	1.00	0.206
Q7	4.00	3.00	4.00	4.00	3.00	4.00	0.942
Q8	1.00	0.00	4.00	0.50	0.00	2.00	0.527
Q9	0.00	0.00	1.00	0.00	0.00	1.00	1
Q10	0.00	0.00	1.00	0.00	0.00	2.00	0.527
Q11	0.00	0.00	2.00	0.00	0.00	2.00	0.102
Q12	0.00	0.00	1.00	0.00	0.00	0.00	0.317
Q13	1.00	0.00	2.00	1.00	0.00	2.00	0.813
Q14	0.00	0.00	0.00	0.00	0.00	0.00	0.317
Signs and symptoms	9.00	7.00	14.00	8.00	6.00	13.00	0.025
Sleep	1.00	0.00	4.00	1.00	0.00	5.00	0.783
Psychosocial	2.00	0.00	4.00	1.50	0.00	4.00	0.248
Total score	11.00	8.00	21.00	10.50	8.00	21.00	0.064

Q – question.

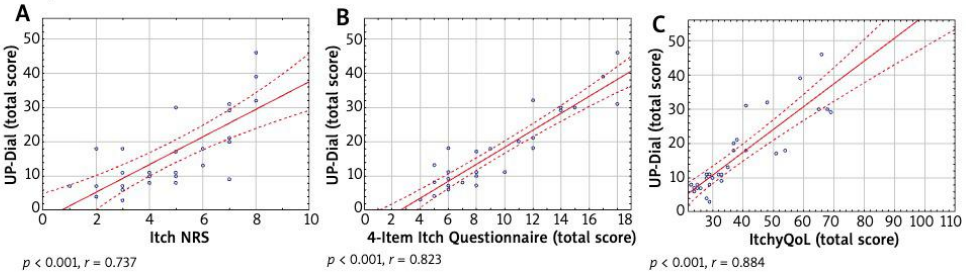

Figure 1. The correlations between UP-Dial and Itch NRS (**A**), 4-Item Itch Questionnaire (**B**) and ItchyQoL (**C**)

This study describes the process of development and validation of the Polish language version of the UP-Dial questionnaire. The translated Polish version showed very good internal consistency with Cronbach α value of 0.90 for the total score and 0.75–0.93 for the three domains. These results are similar to those obtained by the authors of the original version of the questionnaire (Cronbach α 0.90 for total score, for domains: 0.76–0.83). To the best of our knowledge, only the Chinese version of UP-Dial has been validated up till now. Li *et al.* [23], similarly to us proved a good internal consistency of the instrument with Cronbach α coefficient value of 0.75, 0.71, 0.85 of the three subscales (signs and symptoms, sleep and psychosocial) and 0.89 of the whole scale. Three items of UP-Dial did not show correlation with the total score. Responses to questions 5, 7 and 14 showed a lack of variety. Despite significant diversity of final assessment of the itch, the vast majority of the respondents

Table 3. Correlation coefficients between each domain of UP-Dial and other instruments

	Signs and symptoms	Sleep	Psychosocial
NRS	0.705	0.608	0.652
4IIQ	0.831	0.738	0.684
ItchyQoL	0.765	0.806	0.880

NRS – Numerical Rating Scale, 4IIQ – 4-Item Itch Questionnaire.

did not report numbness (question 5) and confirmed constant dryness of the skin (question 7).

Similarly, almost every patient denied any sexual difficulties caused by pruritus (question 14). This may be a result of intimate nature of the question and perceiving sexuality as taboo.

In our study very good reproducibility was achieved with the value of ICC of 0.90 for the whole survey, which was close to the original version (ICC = 0.95). Two questions (1 and 2) and the signs and symptoms domain differed between both measurements, most likely due to subjective perception and variability of the itch.

The evaluation of convergent validity showed a strong correlation between UP-Dial and the other instruments employed for this purpose. The authors of the original paper, similarly to our analysis, proved that UP-Dial is strongly related to other tools. Nochaiwong *et al.* [10] used, for convergent validity procedure, the Visual Analogue Scale ($r = 0.76$, $p < 0.001$) which as well as NRS, applied in our study, describes intensity of the itch. At the time of creation of the original version, ItchyQoL – the tool which estimates influence of chronic itch on QoL, has not been used widely. Therefore, to assess convergent validity of UP-Dial in terms of patients' quality of life the authors employed the Dermatology Life Quality Index ($r = 0.78$, $p < 0.001$) [10].

We are aware of some limitations of our study. This research was a one centre study. Moreover, the preliminary validation was performed on a limited number of patients suffering from UP. Future studies will be helpful to confirm our current findings.

Having a Polish language version of this multidimensional instrument will enable its use in daily clinical practice to characterize UP in Polish speaking patients on maintenance dialysis and can be of help in evaluation of the effects of applied itch therapy. Creation and validation of new language versions of this questionnaire may help in the future to better understand the issue of uraemic pruritus in dialysis patients in different populations.

Conflict of interest

The authors declare no conflict of interest.

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Appendix

14-punktowa skala świądu mocznicowego u chorych dializowanych

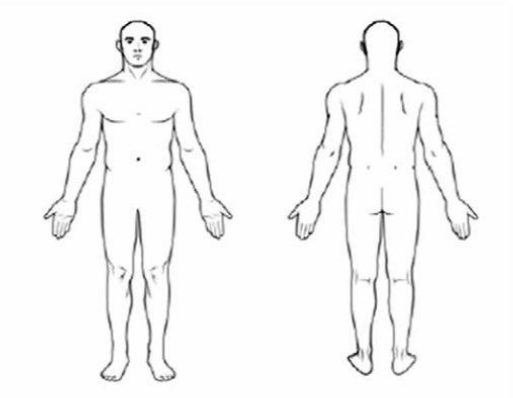
1. W ciągu ostatnich 2 tygodni ile godzin średnio w ciągu danej doby odczuwał (odczuwała) Pan (Pani) świąd?

- ❒ Mniej niż 6 godzin na dobę [0]
- ❒ 6–12 godzin na dobę [1]
- ❒ 12–18 godzin na dobę [2]
- ❒ 18–23 godzin na dobę [3]
- ❒ Całą dobę [4]

2. W okresie ostatnich 2 tygodni, jak bardzo nasilony był świąd, jaki Pan (Pani) odczuwał (odczuwała)?

- ❒ Nie odczuwałem (nie odczuwałam) świądu [0]
- ❒ Łagodny [1]
- ❒ Umiarkowany [2]
- ❒ Ciężki [3]
- ❒ Nie do zniesienia [4]

3. W ciągu ostatnich 2 tygodni, których okolic ciała dotyczył świąd? Proszę zacieniować te obszary.



- ❒ 0% powierzchni ciała [0]
- ❒ 1–25% powierzchni ciała [1]
- ❒ 26–50% powierzchni ciała [2]
- ❒ 51–75% powierzchni ciała [3]
- ❒ 76–100% powierzchni ciała [4]

Proszę ocenić częstość występowania poniższych objawów związanych ze świądem w okresie ostatnich 2 tygodni.

	Brak [0]	Sporadycznie [1]	Czasami [2]	Często [3]	Zawsze [4]
4. Zmiany skórne powstałe w wyniku drapania	.....	.....	.....	.....	.....
5. Uczucie drętwienia	.....	.....	.....	.....	.....
6. Uczucie pełzania mrówek lub owadów	.....	.....	.....	.....	.....
7. Sucha skóra	.....	.....	.....	.....	.....

Jak często świąd zakłócał Pana (Pani) sen?

	Wcale [0]	1–2 razy w tygodniu [1]	3–4 razy w tygodniu [2]	4–6 razy w tygodniu [3]	Codziennie [4]
8. Trudności z zasypianiem (więcej niż 30 minut)	.....	.....	.....	.....	.....
9. Budzenie się w nocy	.....	.....	.....	.....	.....
10. Zakłócenie jakości snu	.....	.....	.....	.....	.....

Proszę ocenić wpływ świądu na następujące aktywności lub domeny w ciągu ostatnich 2 tygodni.

	Brak [0]	Łagodny [1]	Umiarkowany [2]	Silny [3]	Bardzo silny [4]
11. Praca lub nauka	.....	.....	.....	.....	.....
12. Relacje społeczne	.....	.....	.....	.....	.....
13. Nastrój	.....	.....	.....	.....	.....
14. Wszelkie problemy seksualne	.....	.....	.....	.....	.....

6. ARTYKUŁ TRZECI

The Serum Level of IL-31 in Patients with Chronic Kidney Disease-Associated Pruritus: What Can We Expect?

toxins

MDPI

Article

The Serum Level of IL-31 in Patients with Chronic Kidney Disease-Associated Pruritus: What Can We Expect?

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Abstract: Chronic-kidney-disease-associated pruritus (CKD-aP) is one of the most common and burdensome dermatological symptoms affecting patients undergoing dialysis, and its etiopathogenesis has still not been fully discovered. This study was designed to investigate the possible contribution of interleukin-31 (IL-31) to the pathogenesis of itch in patients undergoing maintenance hemodialysis (HD). We evaluated the serum level of IL-31 in HD patients with pruritus, in HD patients without pruritus and in healthy controls, as well as its correlation to the severity of itch. The study enrolled 175 adult subjects. The participants were divided into three groups. Group A included 64 patients on maintenance HD with CKD-aP, Group B included 62 patients on maintenance HD not reporting CKD-aP and Group C included 49 healthy controls. Pruritus severity was assessed using the Numerical Rating Scale (NRS), and the serum levels of IL-31 were measured. The results showed that the IL-31 serum level was significantly higher in the itchy group ($p < 0.001$) in comparison to the patients free from pruritus. Moreover, a marginal trend towards significance ($r = 0.242$, $p = 0.058$) was observed between the IL-31 serum level and itch intensity. Our study supports earlier findings on the extended role of IL-31 in the development of CKD-aP.

Keywords: interleukin-31; chronic-kidney-disease-associated pruritus; hemodialysis patients; renal failure

Key Contribution: Elevated serum interleukin-31 (IL-31) levels were found in patients suffering from CKD-aP in comparison to both non-itchy hemodialysis patients and healthy controls. Therefore, this study points out the possible contribution of IL-31 to the pathogenesis of itch in patients undergoing maintenance hemodialysis.

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1. Introduction

Chronic-kidney-disease-associated pruritus (CKD-aP) is one of the most common and burdensome dermatological symptoms affecting patients undergoing dialysis. The prevalence of CKD-aP has been very variable over the years, yet according to the most comprehensive observational study of hemodialysis (HD) that included patients from 12 different countries, approximately 40% of patients with end-stage renal disease (ESRD) report moderate-to-severe pruritus [1]. So far, conducted studies have unequivocally proven that this condition not only has a negative impact on sleep, mood, daily activities and quality of life (QoL), but it also increases the mortality risk of HD patients [2,3]. Despite the high international prevalence, this problem seems to be markedly underestimated in clinical practice. The reason for this trend may be the lack of knowledge regarding effective therapies for CKD-aP [4]. Despite the long-standing studies and many suggested theories,

the complex etiopathogenesis of CKD-aP has still not been fully discovered. Among the most important factors contributing to the development of CKD-aP, the following ones can be mentioned: uremic toxins (UTs), immune dysfunction, altered opioid transmission, skin dryness (xerosis), neuropathy, dialysis modality and its parameters [5]. Thereby, gold-standard therapy in this condition remains unclearly defined, and determining an effective clinical approach is still a challenge for dermatologists and nephrologists. CKD-aP is often recurrent and does not respond to available therapeutic methods. Further research in the field of the pathophysiology of CKD-aP may lead to a revolution in the therapeutic management of HD patients suffering from pruritus.

Reduced renal function in patients with chronic kidney disease (CKD) precludes the proper elimination of various metabolites, which are known as UTs. Recently, more and more studies indicate the key role of UTs in the progression of CKD and its wide range of severe complications. In the list of medium molecules classified as UTs, a few interleukins can be found, namely interleukin-10, -18, -1β and -6 [6]. Therefore, the role of the immune system seems to play a vital role in CKD-aP. Some studies point out a deranged balance of T helper (TH) cell differentiation towards Th1 predominance in patients with CKD-aP, which allows one to consider this condition as a systemic inflammatory phenomenon. This hypothesis was supported by the elevated serum levels of the C-reactive protein (CRP) and the inflammatory cytokines interleukin (IL)-2 and IL-6 in HD patients with pruritus versus those free from pruritus [7,8].

Interleukin-31 (IL-31) is a T-cell-derived cytokine that takes part in the symptomatology of pruritus, and both IL-31 and its receptor have become potential therapeutic targets for a range of pruritic disorders [9]. It was found that IL-31 signaling through a heterodimeric receptor complex composed of an IL-31Rα subunit and an oncostatin M receptor β subunit (OSMRβ), expressing on the keratinocytes and the epithelial cells, induces severe dermatitis and pruritus in transgenic mice [10]. Moreover, the serum level of IL-31 was elevated in patients with atopic dermatitis. Performed studies revealed a positive correlation between the IL-31 serum level and the Scoring Atopic Dermatitis Index (SCORAD) and also between IL-31 levels and the severity of pruritus-[11–13]. Similar findings were reported in clinical studies concerning other pruritic dermatological diseases, such as prurigo nodularis and psoriasis [14,15]. Although the majority of so-far published studies reported an increased serum IL-31 level in patients suffering from CKD-aP, the correlation between IL-31 and itch intensity is still not clear [16–19]. Therefore, this study was designed to investigate the possible contribution of IL-31 to the pathogenesis of itch in patients undergoing maintenance HD. We aimed not only to evaluate the serum level of IL-31 in HD patients with pruritus, in HD patients without pruritus and in healthy controls, but also to correlate the serum level of IL-31 with itch severity. To evaluate the characteristics and the intensity of the itch, the Numerical Rating Scale (NRS) and a new instrument—the Uraemic Pruritus in Dialysis Patient (UP-Dial) questionnaire—were used.

2. Results

In the group of HD patients suffering from CKD-aP, 50% were males, and the average age was 61.1 $\pm$ 15.9 years. The mean NRS score was 4.9 $\pm$ 2.2 points. According to the NRS cut-offs, mild pruritus was reported in 14.5% of the cases, moderate in 59.7%, severe in 22.6% and very severe in 3.2%. The mean UP-Dial score was 14.2 $\pm$ 9.8 points. In 58% of the CKD-aP patients, itch interfered with their sleep, and only 29% did not report the influence of itch on the following activities: work or study, social interaction, mood or any sexual activities. The mean serum level of IL-31 was 679.9 $\pm$ 1112.3 pg/mL in a group of HD patients reporting CKD-aP, 176.1 $\pm$ 290.7 pg/mL in a group of HD patients not suffering from CKD-aP and 57.3 $\pm$ 65.1 pg/mL in a group of healthy controls (Figure 1). The IL-31 serum level was significantly higher in the itchy group ($p < 0.001$) in comparison to the patients free from pruritus. Moreover, there was a significant difference ($p < 0.001$) in IL-31 serum levels between HD patients with and without pruritus and healthy controls ($p < 0.001$ and $p = 0.019$, respectively).

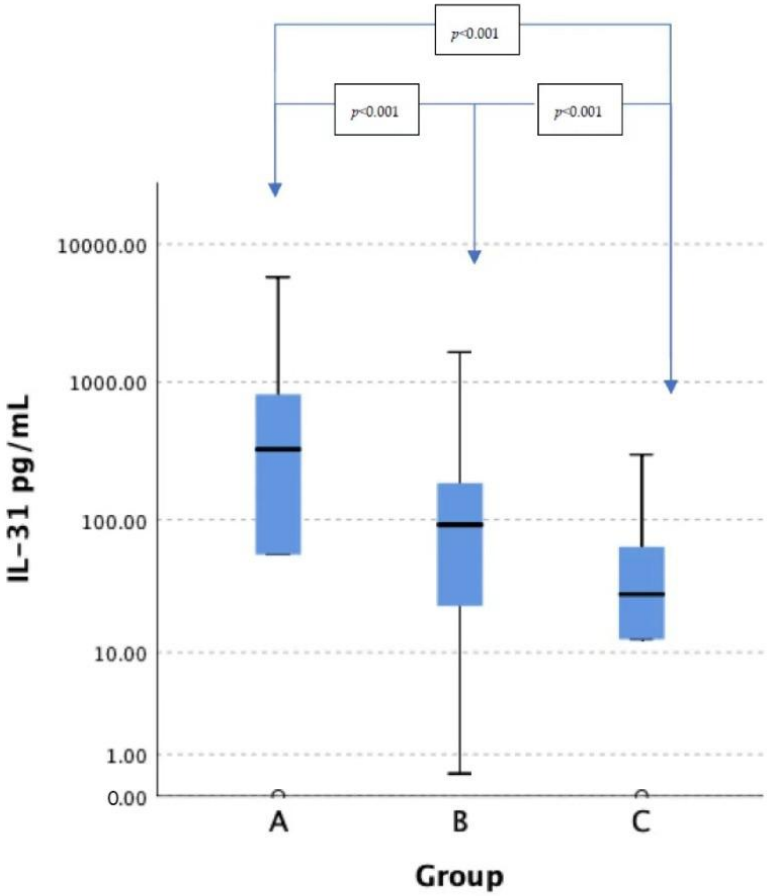

Figure 1. Serum level of IL-31 in study groups. IL-31—interleukin-31, Group A—patients with ESRD on maintenance HD reporting CKD-aP, Group B—patients with ESRD on maintenance HD not reporting CKD-aP, Group C—healthy controls.

Despite the above-mentioned results, a marginal trend towards significance (r = 0.242, $p = 0.058$) was observed between the IL-31 serum level and the worst itch intensity during the last 3 days as assessed by the NRS (Figure 2).

The UP-Dial questionnaire total score strongly correlated with the NRS (r = 0.399, $p = 0.001$). Additionally, each domain of the UP-Dial showed a significant correlation with the NRS scores (detailed data not shown). However, the correlation between the serum level of the IL-31 and the UP-Dial total score was not statistically significant.

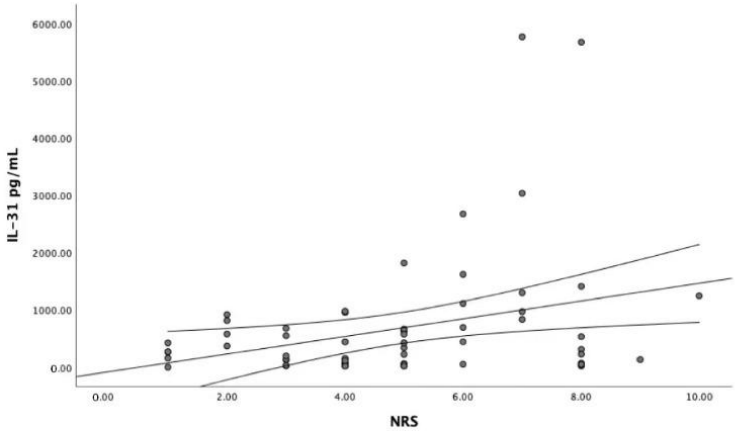

Figure 2. Dependence between IL-31 serum levels and NRS score (r = 0.242, p = 0.058). NRS—Numerical Rating Scale, IL-31—interleukin-31, circles—the serum level of interleukin-31.

3. Discussion

CKD-aP is a prevalent and very burdensome comorbidity associated with CKD, and its pathogenesis is not fully understood. A steering committee of patients, caregivers, researchers and clinicians in Canada that is assembling a list of the top-10 research priorities for kidney disease agreed that determining the causes, effective treatments and preventative measures for CKD-aP is essential for the holistic management of HD patients [20]. This study underlined that pruritus is a relevant symptom from which patients with CKD suffer, and that its effective identification and treatment still causes many clinical issues [21]. Therefore, the importance of further research in the field of the pathogenesis of CKD-aP is undeniable, and their results may provide more effective and innovative management options for HD patients with this condition.

So far, only a few studies evaluating the contribution of IL-31 in the pathogenesis of CKD-aP have been published, and their results were ambiguous. In this study, which aimed to deepen the immune aspect of CKD-aP pathogenesis, the results showed a significant elevation of IL-31 in patients reporting CKD-aP compared to HD patients without pruritus. These findings correspond with Ko et al.'s [16] study, which pointed to an extended role of IL-31 in pruritic skin disease by showing that IL-31 levels were significantly higher in patients with pruritus symptoms than in those without. Moreover, in a cross-sectional study on 65 HD patients and 49 healthy controls, Oweis et al. [17] showed similar findings to ours. The IL-31 serum level was significantly higher in the HD patients than in the control group, while the differences between the levels of IL-13 and IL-33 in these groups were not statistically significant. Interestingly, a study performed by Haggag et al. [18] showed an apparently increased level of IL-31 in CKD-aP patients; however, the difference between the itchy and non-itchy group did not reach statistical significance. Finally, a study performed on 145 participants, which consisted of HD patients, peritoneal dialysis (PD) patients, kidney transplant patients and healthy controls, showed no significant differences in serum IL-31 levels among the study groups [19,22]. Notwithstanding, they concluded that IL-31 might play a role in the development of longitudinal nail ridges by revealing significantly higher IL-31 levels in a group of patients with this nail condition.

Otherwise, Ko et al. [16] additionally demonstrated a positive relationship between IL-31 levels and the Visual Analogue Scale (VAS) score of pruritus intensity. This result is not fully analogous to our research, as we did not prove a significant correlation between the IL-31 serum levels and the pruritus intensity assessed with the NRS. Nevertheless, this dependency reached a borderline level of statistical significance (p = 0.058). The reason

of 18 kDa is classified as a middle molecule, and its clearance using high-flux membranes is low [33]. Therefore, the measurement of the IL-31 levels after the hemodialysis session and the comparison of this result with itch intensity may lead to an interesting outcome.

4. Conclusions

CKD-aP is a pervasive and multifactorial condition strongly affecting patients' quality of life. Its etiopathogenesis involves multiple mediators and remains not fully understood. This study revealed a significantly higher serum level of IL-31 in HD patients with CKD-aP versus HD patients without CKD-aP. This tendency supports earlier findings about the extended role of this interleukin in the development of CKD-aP. It is hoped that further research targeting this cytokine may bring more information about the immunological aspect of CKD-aP etiopathogenesis and possible effective and innovative management options for HD patients with CKD-aP.

5. Material and Methods

5.1. Study Population

This study enrolled 175 adult subjects of which 85 (48.6%) were females and 90 (51.4%) were males. The mean age of the study population was 58.46 ± 15.8 years. The participants were divided into three groups. Group A included 64 patients with ESRD on maintenance HD with CKD-aP, Group B included 62 patients with ESRD on maintenance HD not reporting CKD-aP and Group C included 49 healthy controls who corresponded with age and gender to the patients from the study group and had no history of any pruritic or systemic diseases. The exclusion criteria for this study was as follows: primary skin disorders, other itchy skin diseases, psychiatric disorder or communication problems, age under 18 years, antipruritic therapy and patients' refusal. All participants underwent a physical and dermatological examination. Medical history, including cause of renal failure, duration of HD and previous treatment of pruritus was taken. Most of the patients received dialysis 3 times a week; only 8 of them received dialysis 2 times a week. The average dialysis vintage was 48.8 ± 51.9 months, and the hemodialysis was performed using bicarbonate dialysate. All individuals were undergoing hemodialysis using high-flux polysulfone membrane dialyzers. The single pool Kt/V accessing the dialysis adequacy for the whole study population was 1.28 (SD ± 0.39). In a group of patients reporting CKD-aP, it was 1.21 (SD ± 0.31), and in a group of patients not reporting CKD-aP, it was 1.34 (SD ± 0.43). The difference between these two groups was not statistically significant. Therefore, the level of hemodialysis adequacy did not have an impact on itch sensation.

The most common cause of end-stage renal disease in the entire study cohort was glomerulonephritis (19.8%); in Group A it was diabetic kidney disease (17.7%) and in Group B it was also glomerulonephritis (26.6%). Substantively, the most frequent cause of kidney disease in the general population is diabetic nephropathy. However, currently published studies emphasize that the cause of kidney failure does not determine CKD-aP [34,35].

The average dialysis vintage was 48.8 ± 51.9 months. More than half of the HD patients underwent dialysis through an arterio-venous fistulae (65.1%) and the rest through a tunneled internal jugular central venous catheter. Table 1 summarizes the baseline characteristics of the participants.

Table 1. Baseline characteristics for hemodialysis patients and controls.

Variable	Group A, N (%)	Group B, N (%)	Group C, N (%)
Age, mean (±SD)	61.1(SD ± 15.9)	63.9 (SD ± 15.6)	48.0 (SD ± 10.24)
Gender: Male	31 (50.0%)	30 (46.9%)	24 (48.9%)
Female	31(50.0%)	34 (53.1%)	25(51.0%)

Group A—patients with ESRD on maintenance HD reporting CKD-aP. Group B—patients with ESRD on maintenance HD not reporting CKD-aP, Group C—healthy controls.

This research obtained ethical approval by the Wroclaw Medical University Ethics Committee (Consent no. 26/202, date: 29 January 2021). Patients were included in the research after obtaining their informed consent.

5.2. Pruritus Assessment

Pruritus severity was assessed using the NRS, which is an easily accessible instrument commonly used to evaluate the intensity of pruritus. On a scale from 0 to 10 points, participants indicated the worst itch intensity they experienced during the last 3 days. Patients were classified according to the severity of pruritus as follows: NRS < 3—mild pruritus, NRS > 3 and < 7—moderate pruritus, NRS > 7 and < 9—severe pruritus and NRS > 9—very severe pruritus [36]. Moreover, subjects completed a Polish, validated version of the UP-Dial questionnaire [37]. This 14-item instrument was designed to characterize itch in dialysis patients. It evaluates three dimensions of CKD-aP: signs and symptoms, sleep and psychosocial burden during the last 2 weeks. These domains investigate all of the important aspects of chronic itch: frequency, intensity, distribution, skin lesions caused by itch, impact on sleep and the psychosocial status of the patient [38]. The total score of the UP-Dial also enables one to classify the severity of the itch.

5.3. Samples and Interleukin-31 Serum Level Measurement

Blood samples of 9 mL were collected from all of the participants. Blood was drawn during the routine drawing-of-blood from an arterio-venous fistula or from a permanent HD catheter just before starting a dialysis session in dialysis patients. Subsequently, the samples were centrifuged at 3000× *g* rpm for 15 min. The received serum was stored at—80 °C until the next laboratory steps were performed. The serum level of IL-31 was subsequently measured by the ELISA (enzyme-linked immunosorbent assay) technique using the Nori Human IL-31 ELISA Kit (catalog number: GR 111374, GENORISE SCIENTIFIC, Inc., Glen Mills, PA, USA), according to the manufacturer's instructions. The absorbance of the sample was measured at 450 nm using the EPOCH (BioTEK® Instruments, Inc., Winooski, VT, USA) adjustable microplate reader. IL-31 had a test range of 50–3200 pg/mL and a sensitivity of 10 pg/mL.

5.4. Statistical Analysis

A statistical analysis of the obtained results was performed with the use of the IBM SPSS Statistics v. 26 (SPSS Inc., Chicago, IL, USA) software. All data were assessed for normal or abnormal distribution. The minimum, maximum, mean and standard deviation were calculated. Quantitative variables were evaluated using the Mann–Whitney U test and Spearman's or Pearson's correlations. For the qualitative data, the chi-squared test was used. For differences in more than two groups, the Kruskal–Wallis one-way analysis of variance on ranks was performed. A two-sided p of a value lower than 0.05 was considered significant.

Author Contributions: Conceptualization: K.Ś., P.K.K., R.B.-B., M.K. and J.C.S.; methodology: K.Ś., P.K.K., D.N.-S., R.B.-B., M.K. and J.C.S.; formal analysis: K.Ś., P.K.K., D.N.-S., R.B.-B., M.K. and J.C.S.; investigation: K.Ś., P.K.K., D.N.-S., R.B.-B., M.K. and J.C.S.; writing—original draft preparation: K.Ś., R.B.-B. and J.C.S.; writing—review and editing, K.Ś., P.K.K., R.B.-B., M.K. and J.C.S.; visualization: K.Ś., P.K.K.; supervision: K.Ś., P.K.K., R.B.-B., M.K. and J.C.S.; All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Wroclaw Medical University Ethics Committee (Consent No. 26/202, date: 29 January 2021).

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

Data Availability Statement: The datasets generated and analyzed in the current study are available from the corresponding author on reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

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7. ARTYKUŁ CZWARTY

Serum Level of Protein-Bound Uraemic Toxins in Haemodialysis Patients with Chronic Kidney Disease-Associated Pruritus: Myths and Facts.

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Serum Level of Protein-Bound Uraemic Toxins in Haemodialysis Patients with Chronic Kidney Disease-Associated Pruritus: Myths and Facts

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Abstract: Recent studies place great importance on Protein-Bound Uraemic Toxins (PBUT) in the context of etiopathogenesis of chronic kidney disease-associated pruritus (CKD-aP). This study aimed to investigate the possible contribution of free and total Indoxyl Sulfate (IS) and p-Cresol Sulfate (PCS) to the cause of CKD-aP. Group A included 64 patients on maintenance haemodialysis (HD) with CKD-aP. Group B included 62 patients on maintenance HD that did not report CKD-aP, and group C included 50 healthy controls. Pruritus severity was assessed using a Numerical Rating Scale (NRS). Moreover, other tools like UP-Dial, ItchyQoL, and the 4-Item Itch Questionnaire evaluating CKD-aP were completed by the patients. The serum levels of free and total IS and PCS concentrations were measured using the Ultra Performance Liquid Chromatography System. No significant difference in the serum level of free and total IS, or PCS, was observed between the patients who reported CKD-aP and those without pruritus. Moreover, there was no correlation between serum IS or PCS levels and the severity of the itch. Our study does not support earlier findings about higher levels of IS and PCS in patients reporting CKD-aP. Further studies will be needed to investigate these discrepancies as well as to understand the cause of CKD-aP.

Keywords: protein-bound uraemic toxins; indoxyl sulfate; p-Cresol sulfate; chronic-kidney-disease-associated pruritus; haemodialysis patients

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1. Introduction

Chronic itch (CI) is defined as itching lasting 6 weeks or more. It is commonly associated with many dermatological and systemic diseases, such as diabetes mellitus, hypothyroidism, chronic hepatobiliary conditions, malignancies, and end-stage renal disease (ESRD) [1,2]. The term "uraemic pruritus" is widely used in the literature. However, in accordance with the latest research and a lack of clear dependence between uraemia and itch sensation, world experts in this field proposed "chronic kidney disease-associated pruritus" (CKD-aP) as a more precise nomenclature [3]. CKD-aP affects approximately 40% of patients undergoing maintenance haemodialysis (HD) [4]. It is considered a burdensome, frequent dermatological symptom in patients with ESRD and negatively impacts patients' quality of life [5]. Researchers around the world have proven that this condition has a negative influence on sleep and daily activities, aggravates the symptoms of depression, and increases the risks of mortality and hospitalization in HD patients [6,7]. Surprisingly, in relation to the importance of the problem, there is a noticeable underestimation of CKD-aP in clinical practice. The reason for this may be the lack of knowledge on effective therapies leading to the neglect of this issue [8,9]. The effective treatment of CKD-aP is

very often intractable and remains a challenge for dermatologists and nephrologists. This is due to this recurring and complex condition's multifactorial and not fully understood causes [10]. However, an increasing number of ongoing studies and discoveries in the context of pruritus etiopathogenesis may bring revolutionary therapeutic possibilities. The most common theories explaining the development of CKD-aP include immune dysregulation, neuronal dysregulation, xerosis, disbalance in calcium and phosphorous metabolism, hyperparathyroidism, altered opioid transmission, and uraemic toxins (UTs) [11]. UTs are substances that are retained in the organism by patients with advanced kidney failure and can negatively interact with the biological functions of the organism [12]. In 2021, the European Uremic Toxin (EUTox) database listed 130 substances [13]. UTs can be divided into three groups: free water-soluble low molecular weight molecules (LMWM) (<0.5 kDa), middle molecules (0.5–60 kDa), and protein-bound UTs (PBUT). The latter mentioned have been in the spotlight lately in the context of interfering with the biochemical functions of individuals suffering from advanced stages of chronic kidney disease [14]. PBUT are molecules that circulate in the blood in free solute form and protein bound form and are barely removed during the process of HD [15,16]. Certain compounds belonging to PBUT, like indoxyl sulfate (IS) and p-Cresol sulfate (pCS), have been widely investigated regarding chronic kidney disease and its complications. So far, published studies emphasize the key role of the intestinal microbiome in the generation of UTs [17]. Both p-Cresol sulfate and indoxyl sulfate arise from bacterial protein fermentation in the large intestine [15]. However, their chemical structures differ—indoxyl sulfate belongs to the indole group, and p-Cresol sulfate belongs to phenols [12]. Most of these two substances circulate noncovalently bound to albumin and compete for the same albumin-binding sites (Sudlow site II) [15]. The study estimated the correlation between PBUT concentrations and renal dysfunction and revealed that both indoxyl sulfate and p-Cresol sulfate levels increased when renal function declined [18]. Moreover, the role of these compounds in the context of CKD complications has been extensively estimated in the last decade. IS may play a significant role in vascular diseases and higher mortality in CKD patients [19]. Similarly, free serum levels of p-Cresol are associated with worsened outcomes and may be considered a novel cardiovascular risk factor in haemodialysis patients [20,21]. The data on the potential contribution of PBUT in CKD-aP is very limited; however, this theory has recently been notoriously raised by experts in the field. The research conducted on 320 CKD patients proved not only significantly higher serum levels of total IS ($p = 0.008$) and PCS ($p < 0.0001$) among participants reporting CKD-aP but also a correlation between itch severity and total PCS concentration ($p = 0.002$) [22]. Nonetheless, other investigators did not confirm these findings, and showed no significant association between the 5D score and PBUTs serum concentrations [23]. Another interesting hypothesis assumes that UTs may affect protease-activated receptor-2 (PAR-2) expression in the skin of CKD subjects and thus may lead to the development of CKD-aP [24]. These studies are discussed in more detail in the discussion paragraph. We decided to perform this detailed study to verify earlier ambiguous and limited findings on this topic. Therefore, the aim was to investigate the possible contribution of free and total indoxyl sulfate and p-Cresol sulfate to the pathogenesis of itch in patients undergoing maintenance haemodialysis.

2. Materials and Methods

2.1. Study Population

This study enrolled 174 adult subjects. The study groups were formed depending on itch sensations reported by the CKD patients. Group A included 61 patients on maintenance HD with CKD-aP. Group B included 63 patients on maintenance HD that did not report CKD-aP, and group C included 50 healthy controls. The control group corresponded in age and gender to the patients from the study group and had no history of any pruritic or systemic diseases. The study group included patients over 18 years of age receiving haemodialysis 3 times a week for at least 3 months, who signed the patient's informed consent. The following exclusion criteria were respected: primary disorders causing

itch, psychiatric disorders or communication problems, antipruritic therapy, and lack of informed consent. All participants underwent a physical and dermatological examination. Basic demographic and medical data, including the cause of renal failure, duration of HD, type of vascular access, and previous treatment of pruritus, were collected. This research obtained ethical approval from the Wroclaw Medical University Ethics Committee (Consent no. 26/202, date: 29 January 2021). All patients provided their written informed consent to participate in this study.

2.2. Laboratory Tests

Quantitative analysis of Indoxyl Sulfate and p-Cresol Sulfates was carried out on an LC-QTOF-MS system consisting of an Acquity Ultra-Performance Liquid Chromatography System (Waters, Milford, MA, USA) and quadrupole time-of-flight mass spectrometer (Xevo G2 Q-TOF MS, Waters, Milford, MA, USA). At inclusion to the study, blood samples of 9 mL were taken immediately before the dialysis session from all the participants.

2.2.1. Chemicals

Indoxyl sulfate potassium salt, Indoxyl sulfate potassium salt-d5, and p-Cresol sulfate potassium salt were procured from Cayman Chemicals (Ann Arbor, MI, USA). p-Cresol sulfate potassium salt-d7 was obtained from Cambridge Isotope Laboratories (Tewksbury, MA, USA). Methanol, acetonitrile (ACN), water, ammonium formate, and formic acid (FA) were acquired from Merck Millipore (Warsaw, Poland).

2.2.2. Sample and Calibration Standards Preparation and LC-MS Analysis

Indoxyl Sulfate and p-Cresol Sulfate sample quantitative UHPLC-ESI-QTOF-MS analysis. Samples and calibration standards for quantitative analysis of Indoxyl Sulfate and p-Cresol sulfate were procured in the same manner. Briefly, 100 µL of calibration standards or serum samples were placed into 2.0 mL polypropylene tubes with 10 µL of internal standard solution in methanol (40 µg/mL of Indoxyl Sulfate-d5 and p-Cresol sulfate-d7) then after a minute of mixing samples were deproteinized with 400 µL of acetonitrile at 25 °C for 10 min and centrifuged at 12,000 RCF for 7 min at 4 °C. The 100 µL of obtained supernatant was diluted with 400 µL of water and transferred into autosampler glass vials. For free non-bind with protein–forms, 200 µL of calibration standards or serum samples were placed into 2.0 mL polypropylene tubes with 20 µL of internal standard solution in methanol (40 µg/mL of Indoxyl Sulfate-d5 and p-Cresol sulfate-d7) then after a minute of mixing samples were transferred and centrifuged for 50 min at 10,000× *g* at 20 °C with a 3000 MWCO filter (Merck Millipore, Burlington, MA, USA). Subsequently, samples were prepared in the same way as the total form. Quantitative analysis of Indoxyl Sulfate and p-Cresol Sulfates was carried out on an LC-QTOF-MS system consisting of an Acquity UPLC system (Waters, Milford, MA, USA) and quadrupole time-of-flight mass spectrometer (Xevo G2 Q-TOF MS, Waters, Milford, MA, USA). Analytes were separated using Waters HSS T3 chromatographic column (1.0 × 50 mm, 1.75 µm) with a linear gradient from 3% to 95% of mobile phase B in 9.5 min with a total flow rate of 180 µL/min. The mobile phases of 0.1% FA in water (A) and 0.1% FA in acetonitrile (B) were used. Data acquisition was carried out with an electrospray ionization (ESI) ion source operated in negative mode. Source parameters were as follows: nebulizing and drying gas (nitrogen): 700 L/h and 30 L/h, respectively; spray voltage: 2.5 kV; source temperature: 120 °C; and desolvation temperature: 350 °C. The scan range was 105–800 m/z for all acquisition events. The target metabolites were quantified based on their extracted ion chromatograms (EIC)—212.0018 m/z, 187.0065 m/z, 217.0331 m/z, and 194.0504 m/z for Indoxyl Sulfate, p-Cresol sulfate, Indoxyl Sulfate-d5, and p-Cresol sulfate-d7, respectively.

2.3. Pruritus Assessment

The evaluation of pruritus was carried out multidimensionally by using well-known tools as well as some newly validated questionnaires. Itch intensity was assessed using the

NRS, a widely used and preferred instrument to evaluate the intensity of pruritus. Patients indicated, on the eleven-point scale, the worst itch intensity they perceived during the last 3 days. The severity of pruritus was classified as follows: NRS < 3—mild pruritus, NRS ≥ 3 and <7—moderate pruritus, NRS ≥ 7 and <9—severe pruritus, and finally, NRS ≥ 9—very severe pruritus [25]. Another tool used in the study was 4IIQ, which consists of 4 questions concerning the distribution, intensity, and frequency of the itch and sleep disturbances reported by the patients. The possible score ranges from 3 to 19 points [26]. Moreover, a Polish, recently validated version of the UP-Dial questionnaire was employed. UP-Dial characterizes itch, especially in dialysis patients, and consists of 14 multidimensional questions. Three domains of this questionnaire precisely analyze all aspects of chronic itch: frequency, intensity, distribution, skin lesions caused by itch, sleep disorders, and the psychosocial status of the patient [27]. Finally, to evaluate the influence of chronic itch on QoL, a Polish version of the ItchyQoL questionnaire was filled out. It is a validated 22-question instrument with three dimensions: symptoms, functional limitations, and emotions. Questions are scored on a 5-point scale, and the total score ranging between 22 and 110 points estimates QoL [28].

2.4. Statistical Analysis

The IBM SPSS Statistics v. 26 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. All data were checked for normal or abnormal distribution. For quantitative data analysis, the Mann–Whitney U test and Spearman's correlations were used. Assessment of qualitative results was evaluated with the use of the chi-squared test. Data were expressed as mean ± SD, median, first and third quantiles, with $p < 0.05$ considered statistically significant.

3. Results

3.1. Baseline Characteristics of the Subjects

In this cross-sectional study, 174 subjects were included. Females constituted 47% (n = 82) of the study population and males 53% (n = 92). The mean age of the participants was 57.46 ± 16.24 years. All HD patients were undergoing haemodialysis using high-flux polysulfone membrane dialyzers. The average dialysis vintage was 49.58 ± 51.9 months, and the haemodialysis was performed using bicarbonate dialysate. The single pool Kt/V accessing the dialysis adequacy for the whole study population was 1.25 (SD ± 0.40). In a group of patients reporting CKD-aP, it was 1.13 (SD ± 0.32); in a group of patients not reporting CKD-aP, it was 1.34 (SD ± 0.44). We noted no statistically significant difference between these two groups. Thus, the Kt/V level did not play any important role in perceiving pruritus in our study group. Only 35% of HD patients underwent dialysis through a tunneled internal jugular central venous catheter and the rest through an artery-venous fistula. The dominant causes of renal failure in the study group were glomerulonephritis (n = 24, 19.4%) and diabetic nephropathy (n = 24, 19.4%). Moreover, statistical analysis of individual groups showed no significant differences in terms of gender, age, dialysis vintage, and cause of renal failure.

3.2. Serum Levels of Free and Total Indoxyl Sulfate and p-Cresol Sulfate

The results showed that free and total IS and PCS serum levels were significantly higher both in HD patients with pruritus and HD patients without pruritus compared to the healthy controls ($p < 0.001$). However, no significant difference in the serum level of free and total IS, or PCS, was observed between the patients who reported CKD-aP and those without pruritus. The comparison of free and total Indoxyl Sulfate and p-Cresol Sulfate serum level in three study groups is presented in Table 1.

Table 1. Concentrations of free and total Indoxyl Sulfate and p-Cresol Sulfate in HD patients reporting pruritus (group A), not reporting pruritus (group B), and healthy controls (group C).

Parameter (μg/mL)	All HD Patients (n = 124)	Group A—Reporting Itch (n = 61)	Group B—Not Reporting Itch (n = 63)	Group C—Healthy Controls (n = 50)	*p*-Value Group A vs. Group B	*p*-Value Group A vs. Group C	*p*-Value Group B vs. Group C
	Median (Q1; Q3)						
Indoxyl sulfate total	24.1 (11.7; 33.8)	26.7 (12.3; 36.3)	23.8 (10.3; 33.2)	0.9 (0.5; 1.1)	NS	$p < 0.001$	$p < 0.001$
Indoxyl sulfate free	2.6 (1.3; 3.9)	2.8 (1.4; 4.1)	2.4 (1.1; 3.8)	0.1 (0.06; 0.2)	NS	$p < 0.001$	$p < 0.001$
Cresol sulfate total	28.6 (15.1; 38.9)	28.5 (14.0; 40.3)	28.7 (16.5; 36.9)	1.9 (1.0; 3.2)	NS	$p < 0.001$	$p < 0.001$
Cresol sulfate free	3.2 (1.5; 4.9)	3.1 (1.6; 5.4)	3.3 (1.7; 4.7)	0.2 (0.1; 0.3)	NS	$p < 0.001$	$p < 0.001$

NS—not statistically significant, SD—standard deviation.

3.3. Pruritus Assessment and Serum Levels of PBUT

The mean intensity of pruritus assessed by the Numerical Rating Scale (NRS) in patients undergoing maintenance haemodialysis was 4.87 ± 2.21 points. According to the NRS cut-offs, moderate pruritus was reported most frequently—in 60.65% of the cases. Mild pruritus was experienced by 14.75%, severe by 21.31%, and very severe only by 3.27% of the study population. The mean Uraemic Pruritus in Dialysis Patients (UP-Dial) total score in the itchy group was 14.31 ± 9.85 points. Additionally, the mean score of the 4-Item Itch Questionnaire (4IIQ) and ItchyQoL in this group was assessed as 8.44 ± 3.64 points and 36.84 ± 13.65 points, respectively. More detailed data are presented in Table 2.

Table 2. Pruritus Assessment in hemodialysis patients.

Tool	Mean, SD	Minimum Score (Points)	Maximum Score (Points)	Amount of Patients according to Itch Severity *
NRS	4.87 ± 2.21	1	10	mild: n = 9 moderate: n = 37 severe: n = 13 very severe: n = 2
ItchyQoL	36.84 ± 13.65	22	80	
4IIQ	8.44 ± 3.64	4	18	
UP-Dial	14.31 ± 9.85	2	54	

NRS—Numerical Rating Scale, 4IIQ—4-Item Itch Questionnaire, Up-Dial—Uraemic Pruritus in Dialysis Patients, * Severity of pruritus was classified as follows: NRS < 3—Mild pruritus, NRS ≥ 3 and <7—Moderate pruritus, NRS ≥ 7 and <9—Severe pruritus, finally NRS ≥ 9—Very severe pruritus.

However, no correlation was found between the serum level of PBUT and the severity of itch assessed by NRS. Likewise, the total scores of other instruments used in this study (Up-Dial, 4IIQ, and ItchyQoL) also did not reveal significant relationships with serum concentrations of studied PBUT (Table 3).

Table 3. Relationship between the serum level of PBUT and total scores of itch questionnaires.

Parameter	NRS	ItchyQoL	4IIQ	UP-Dial
Indoxyl sulfate total	r = −0.0148 p = 0.254	r = −0.081 p = 0.535	r = 0.005 p = 0.97	r = −0.128 p = 0.324
Indoxyl sulfate free	r = −0.25 p = 0.846	r = −0.005 p = 0.969	r = 0.096 p = 0.464	r = −0.011 p = 0.932
Cresol sulfate total	r = 0.18 p = 0.164	r = 0.125 p = 0.336	r = 0.098 p = 0.454	r = 0.057 p = 664
Cresol sulfate free	r = 0.213 p = 0.099	r = 0.212 p = 0.1	r = 0.201 p = 0.121	r = 0.183 p = 0.159

NRS—Numerical Rating Scale, 4IIQ—4-Item Itch Questionnaire, Up-Dial—Uraemic Pruritus in Dialysis Patients, p—p-Value, r—Correlation coefficient.

4. Discussion

In recent decades, the negative impact of PBUT on the proper functioning of the organism and the relationship between their serum level and patients' clinical outcomes were highlighted in a large number of studies [18–21,29–31]. Due to their strong tendency to bind with albumins, the process of elimination during standard haemodialysis is very restrained. Toxin accumulation may lead to various side effects, including higher mortality risk, cardiovascular complications, and infections [18]. IS has proved to have a multifactorial nephrotoxic impact. Firstly, by enhancing the expression of transforming growth factor-β1 (TGF-β1), tissue inhibitor of metalloproteinase-1 (TIMP-1) and pro-α-1(I)-collagen and stimulating both tubulointerstitial fibrosis and glomerular sclerosis [32]. Moreover, it may induce renal hypoxia by stimulating oxidative stress, which is followed by endothelial senescence [33]. Additionally, one cannot fail to mention the pro-inflammatory effects of IS [34]. The toxicity of PCS also comes from stimulating the generation of reactive oxygen species and intensifying cytotoxic effects on renal tubular cells [14]. Similarly to IS, PCS increases the production of inflammatory cytokines (TGF-β1, TIMP-1, pro-α-1(I)-collagen), causing renal fibrosis [35]. What is more interesting, Lin et al. suggested p-Cresol sulfate levels as a valuable marker in the prediction of cardiovascular disease and kidney function deterioration in CKD patients without dialysis (stage 3–5) [36]. Analysis showed that a serum level of p-Cresol sulfate > 6 mg/L was significantly related to these complications during a 3-year follow-up [36]. In summation, the conducted studies definitely proved that the influence of IS and PCS on the course of CKD is indisputable. So far, published studies have emphasized that systemic inflammation may contribute to the pathogenesis of CKD-aP. Therefore, the possible proinflammatory role of PBUT may play a role in its pathogenesis. On the other hand, the impact of these toxins on chronic pruritus may be doubtful; only a few research groups have explored this issue so far, with ambiguous results.

Proteinase-activated receptor-2 (PAR-2) was first associated with a novel non-histaminergic pruritic pathway in research performed on patients suffering from atopic dermatitis (AD). Steinhoff et al. revealed not only an enhanced level of this receptor in skin biopsies of AD patients but also proved itch sensations appearing after intracutaneous injection of endogenous PAR-2 agonist [37]. Subsequently, a pilot study conducted on 12 ESRD patients with pruritus, four ESRD patients without pruritus, and six healthy controls documented higher serine protease activity in skin samples taken from pruritic patients. Moreover, a positive correlation was observed between PAR-2 expression and itch intensity assessed with Visual Analogue Scale (VAS) [38]. Finally, Kim et al. performed a detailed study investigating the effect of PBUT on the PAR-2 expression in the skin [24]. Results showed that indoxyl sulfate, p-cresol, and sera from CKD patients significantly induced PAR-2 mRNA and protein expression in the cultures of normal human epidermal keratinocytes (NHEK). Moreover, skin samples from patients with CKD and from mice with CKD presented increased PAR-2 expression compared to healthy controls. These findings support the potential contribution of uraemic solutes in the pathogenesis of CKD-aP. Another study

associating PBUT and CKD-aP, performed on 320 CKD (stage 1–5) participants, reported significantly higher serum concentrations of total IS ($p = 0.008$) and PCS ($p < 0.0001$) among patients with pruritus symptoms [22]. After further adjustments with anthropometric variables, fasting glucose, total cholesterol, glutamic pyruvic transaminase, uric acid, albumin, WBC count, and hs-CRP, the PCS concentration was still significantly associated with pruritus. On the contrary to IS serum levels, in this case, the relationship between pruritus disappeared after adjustments for glutamic pyruvic transaminase and uric acid concentrations. Moreover, Wang et al. also found a correlation between total PCS level and itch severity ($p = 0.0002$) [22]. Authors emphasized the possible proinflammatory role of PCS, which through systemic inflammation, could contribute to the pathogenesis of CKD-aP. Unfortunately, Yamamoto et al. did not support these results and showed no significant associations between the 5D score and serum concentrations of the various PBUTs (IS, PCS, phenyl sulfate, and hippuric acid) [23].

Our study thoroughly estimated total and free concentrations of PBUT in patients undergoing haemodialysis. A major part of both IS and PCS are bound with albumins, which hinders their clearance. Only concentrations of free PBUT molecules may differ in terms of dialysis. Therefore, it is reasonable to assume that serum-free toxin levels may correlate with pruritus sensation or its severity. Unluckily, our results did not confirm this theory. Both free and total serum levels of IS and PCS were not statistically different between individuals reporting CKD-aP and those not reporting this symptom. The difference was observed only between healthy controls and patients undergoing HD ($p < 0.001$), which is clearly expected due to the accumulation of UTs in patients with ESRD. Otherwise, no correlation between concentrations of PBUT and itch severity was observed. In this study, a reliable and widely used tool—NRS, was employed to estimate the severity of itch, but also three other questionnaires which precisely characterized pruritus and described its influence on the quality of life (QoL) were in use. Despite prior reports, none of the total scores achieved by our participants correlate with serum levels of IS or PCS. These discrepancies between our research and previous studies may appear due to differences between studied populations, coexisting comorbidities, or even differentiated contributions of individual potential etiopathogenetic factors of CKD-aP among HD patients.

In case of confirmation of previous discoveries in this issue, it would be reasonable to use PBUT as a target for new antipruritic therapies. One past study showed a decrease in serum indoxyl sulfate concentration after administration of oral AST-120, which absorbs the indole—the precursor of indoxyl sulfate in the intestine, in a group of HD patients. Furthermore, the diminution of IS serum levels went hand in hand with the alleviating of CKD-aP [39]. Reduction in itch was observed in 9 of 10 patients, and as many as five patients reported complete remission of general pruritus. However, the initial IS serum level in a group of CKD-aP patients did not statistically differ from HD patients not reporting itch; 12 weeks after administration of AST-120, it declined significantly ($p < 0.05$) [39]. To the best of our knowledge, there is a lack of other recent studies reevaluating the mechanism of reducing CKD-aP. Moreover, AST-120 was recognized many times as effective in inhibiting the progression of kidney failure and has been accepted in most Asian countries as a therapeutic strategy for CKD [40]. Its influence on the elimination of IS decreases oxidative stress in tubular cells, mesangial cells, vascular smooth muscle cells, endothelial cells, and osteoblasts. Thus, it contributes to slowing down the cardiovascular disease and osteodystrophy of CKD patients [41]. Notwithstanding, another two randomized controlled trials did not support the beneficial aspect of long-term use of AST-120 in patients with advanced renal dysfunction [42,43]. On the other hand, as the proper method of removing PBUT remains uncertain, and their formation is stimulated by bacteria, recently gut microbiota has been considered a promising target to decrease toxins levels [44].

Despite suggestive results in the context of PBUT and findings presented in our study, the general role of UTs in the etiopathogenesis of CKD-aP should not be depreciated. Several middle molecules, which are included as uraemic toxins, were linked to CKD-aP. A higher concentration of β_2–Microglobulin (β_2-M) was associated with severe CKD-aP in a

study conducted on 1773 participants. Additionally, lower β_2-M levels played a protective role in patients' outcomes, contrary to severe itch, which increased mortality risk [45]. Authors of this research assumed that increased concentrations of β_2-M might stimulate the production of cytokines—IL-2 or TNF-α, which activate CD4 lymphocytes and raise the risk of CKD-aP. Kimmel et al. revealed the dependency between pruritus reporting by 171 HD patients and IL-6 serum level, thereby emphasizing the central role of microinflammation in the etiopathogenesis of this condition [46]. In addition, some free water-soluble low molecular weight molecules like uric acid were repeatedly evaluated in the context of CKD-aP, however, with different results [22,47]. Undoubtedly, UTs and other potential components of the pathogenesis of pruritus may serve as a target for new antipruritic therapies. Despite numerous studies on this topic, there are still no clear guidelines for the management of patients with CKD-aP and no objective comparison of available pharmacological methods [48]. This situation leads to different choices among doctors in clinical practice, and effects are often unsatisfactory and difficult to achieve. Nevertheless, it should be emphasized that difelikefalin is the first drug approved in August 2021 by the Food and Drug Administration (FDA) and in April 2022 by the European Medicines Agency (EMA) for the treatment of moderate-to-severe pruritus associated with CKD in adults undergoing haemodialysis [49]. Due to its efficacy and acceptable safety profile, it should be currently regarded as the primary treatment in a group of HD patients with refractory itch sensation [49,50].

The limitation of this cross-sectional study is restricted to dialysis stations only in two settings. The evaluation of the molecules level was performed in a one-point measurement. Moreover, the study assessed only PBUT without other inflammation markers and was narrowed to only HD patients, excluding CKD patients or individuals on peritoneal dialysis. Due to the unobvious role of toxins in CKD-aP, bigger multicenter studies, with an evaluation of additional, other proinflammatory markers, can bring even more valuable results.

5. Conclusions

In summary, so far, published research regarding the role of PBUT in CKD-aP etiopathogenesis is ambiguous and very limited. Our study does not support earlier findings about higher levels of IS and PCS in patients reporting CKD-aP. Further studies will be needed to investigate these discrepancies as well as to understand the cause of itch in CKD patients.

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Data Availability Statement: The datasets generated and analyzed in the current study are available from the corresponding author on reasonable request.

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8. STRESZCZENIE W JĘZYKU POLSKIM

Rozprawa doktorska składa się z cyklu czterech monotematycznych artykułów. Trzy z nich opublikowano w międzynarodowych czasopismach naukowych indeksowanych w bazie PubMed i uwzględnionych na liście Journal Citation Reports by Web of Science oraz znajdujących się w wykazie czasopism naukowych Ministerstwa Edukacji i Nauki (MEiN). Jeden artykuł został publikowany w międzynarodowym czasopiśmie indeksowanym w bazie PubMed oraz znajdującym się w wykazie MEiN. Łączny współczynnik wpływu (impact factor – IF) artykułów wchodzących w skład rozprawy doktorskiej wynosi 12,3, a punktacja MEiN 380 punktów. We wszystkich artykułach jestem pierwszym i wiodącym autorem.

Pierwszą pracą z cyklu jest przegląd piśmiennictwa dotyczący charakterystyki świądu mocznicowego. Stanowi on podsumowanie aktualnej wiedzy na temat epidemiologii, patogenezy oraz możliwych i poznanych do tej pory opcji terapeutycznych w danym schorzeniu. Przeglądu dokonano we wrześniu 2021 r.

Kolejną pracą z cyklu jest artykuł dotyczący tworzenia polskiej wersji językowej i walidacji kwestionariusza Uraemic Pruritus in Dialysis Patient (UP-Dial). Zgodnie z międzynarodowymi standardami stworzono polską wersję językową oraz dokonano walidacji kwestionariusza składającego się z 14 pytań, kompleksowo oceniającego i charakteryzującego świąd u pacjentów dializowanych. Kwestionariusz charakteryzował się wysoką spójnością wewnętrzną (Cronbach alfa), powtarzalnością oraz bardzo wysokimi współczynnikami korelacji wewnątrzklasowej (Intraclass Correlation Coefficient). Wykazano również silną korelację wyników nowego narzędzia z powszechnie używanymi instrumentami oceniającymi nasilenie świądu: skalą NRS, czteropunktowym kwestionariuszem oceny świądu, a także kwestionariuszem oceniającym jakość życia u pacjentów odczuwających przewlekły świąd - ItchyQoL.

Trzecia i czwarta publikacja to oryginalne prace badawcze, przedstawiające wyniki oceny stężenia interleukiny 31 oraz toksyn mocznicowych związanych z białkami (wolnego i całkowitego siarczanu indoksylu i siarczanu p-krezolu) u pacjentów dializowanych oraz w grupie kontrolnej. Badania prowadzono w latach 2020-2023 w dwóch ośrodkach – w Stacji Dializ Uniwersyteckiego Szpitala Klinicznego im. Jana Mikulicza-Radeckiego we Wrocławiu oraz w Stacji Dializ Uniwersyteckiego Szpitala Klinicznego w Opolu. Do badań włączono grupę liczącą odpowiednio 175 i 174 pacjentów przewlekle hemodializowanych oraz 49 i 50 osób do grup kontrolnych.

Od wszystkich pacjentów zostały zebrane dane demograficzne oraz kliniczne, a następnie zostało pobrane 9ml krwi. Stężenie IL-31 oceniono metodą ELISA z wykorzystaniem komercyjnie dostępnych kitów. Stężenia toksyn mocznicowych związanych z białkami (wolnego i całkowitego siarczanu indoksylu i siarczanu p-krezolu) zmierzono za pomocą metody chromatografii cieczowej. Ocenę największego nasilenia świądu w ciągu ostatnich trzech dni dokonano za pomocą skali NRS. Uczestnicy badań wypełnili także kwestionariusz UP-Dial, który ocenia nasilenie świądu i jego wpływ na jakość życia pacjentów dializowanych. Pacjenci biorący udział w czwartym badaniu, dotyczącym toksyn mocznicowych, wypełnili również kwestionariusz ItchyQoL, stworzony do oceny jakości życia u pacjentów odczuwających przewlekły świąd oraz czteropunktowy kwestionariusz oceny świądu. Dokonano analizy statystycznej różnicy stężeń badanych molekuł między poszczególnymi grupami (pacjenci dializowani odczuwający świąd, pacjenci dializowani bez świądu oraz grupa kontrolna osób zdrowych), a także zbadano korelację pomiędzy badanymi substancjami, a nasileniem świądu i jakością życia pacjentów.

Wśród badanych poziom IL-31 w surowicy był znacząco wyższy w grupie pacjentów dializowanych zgłaszających świąd ($p < 0,001$) w porównaniu do pacjentów dializowanych nieodczuwających świądu. Ponadto istniała statystycznie istotna różnica ($p < 0,001$) w poziomach IL-31 między pacjentami poddawanymi HD z i bez świądu oraz grupą kontrolną (odpowiednio $p < 0,001$ i $p = 0,019$). Zaobserwowano również marginalną tendencję w kierunku istotności ($r = 0,242$, $p = 0,058$) pomiędzy poziomem IL-31, a nasileniem świądu w ciągu ostatnich 3 dniach ocenianym za pomocą NRS. Średni wynik NRS wyniósł 4,9 ± 2,2 punktu. Według wartości granicznych NRS łagodny świąd zgłoszono w 14,5% przypadków, umiarkowany w 59,7%, ciężki w 22,6% i bardzo ciężki w 3,2%. Średni wynik UP-Dial w badaniu oceniającym poziom IL-31 wyniósł 14,2 ± 9,8 punktu. U 58% pacjentów z UP świąd zakłócał sen, a tylko 29% nie zgłaszało wpływu świądu na następujące czynności: pracę lub naukę, interakcje społeczne, nastrój bądź jakąkolwiek aktywność seksualną.

Wyniki etapu dotyczącego toksyn mocznicowych związanych z białkami wykazały, iż stężenia wolnego i całkowitego IS i PCS w surowicy były istotnie wyższe zarówno u pacjentów dializowanych ze świądem, jak i u pacjentów dializowanych bez świądu w porównaniu ze zdrową grupą kontrolną ($p < 0,001$). Nie zaobserwowano jednak istotnej różnicy w stężeniu wolnego i całkowitego IS oraz PCS, w surowicy pomiędzy pacjentami zgłaszającymi UP, a pacjentami bez świądu. Nie stwierdzono również korelacji pomiędzy stężeniem PBUTs w surowicy, a nasileniem świądu ocenianym skalą NRS. Podobnie wyniki innych kwestionariuszy zastosowanych w tym badaniu (Up-Dial, 4IIQ i ItchyQoL) nie wykazały

istotnego związku ze stężeniami PBUTs w surowicy. W badaniu oceniającym toksyny mocznicowe średnie natężenie świądu oceniane w skali NRS wyniosło 4,87 ± 2,21 punktu. Według wartości odcięcia NRS tutaj również najczęściej zgłaszano umiarkowany świąd – w 60,65% przypadków. Średni całkowity wynik UP-Dial w grupie pacjentów ze świądem wyniósł 14,31 ± 9,85 punktu. Dodatkowo średni wynik kwestionariusz 4IIQ i ItchyQoL w tej grupie wyniosły odpowiednio 8,44 ± 3,64 i 36,84 ± 13,65 punktu.

Podsumowując, przeprowadzone badania umożliwiły stworzenie polskojęzycznej wersji kwestionariusza UP-Dial umożliwiającego rzetelną ocenę i charakterystykę świądu mocznicowego w codziennej praktyce klinicznej i badaniach naukowych. Uzyskane wyniki podkreślają, iż konieczne jest kontynuowanie badań poszukujących nowych czynników odpowiedzialnych za patogenezę UP w celu opracowania nowych, skutecznych opcji terapeutycznych w tej jednostce chorobowej. Wyniki prac zawartych w rozprawie potwierdzają możliwą rolę IL-31 w patogenezie przewlekłego świądu u pacjentów dializowanych. Wykazano także, iż zaburzenia stężeń PBUTs w surowicy pacjentów dializowanych nie odgrywają roli w genezie świądu mocznicowego. Sformułowane wnioski wskazują na możliwy kierunek dalszych badań dotyczących sprawdzenia czy hamowanie interleukiny 31 może prowadzić do ustąpienia świądu u pacjentów ze schyłkową niewydolnością nerek.

9. STRESZCZENIE W JĘZYKU ANGIELSKIM

The doctoral dissertation consists of a series of four monothematic articles. Three of them were published in international scientific journals indexed in the PubMed database and included in the Journal Citation Reports list by Web of Science, as well as listed in the Ministry of Education and Science (MEiN) list of scientific journals. One article was published in international scientific journal indexed in the PubMed database and listed in MEiN list of scientific journals. The total impact factor (IF) of the articles included in the doctoral dissertation is 12.3, and the MEiN score is 380 points. I am the first and lead author in all articles.

The first article in the series is a review of the literature regarding characteristics of uraemic pruritus. It summarizes the current knowledge about epidemiology, pathogenesis and possible therapeutic options in uraemic pruritus. The review was carried out in September 2021.

The next article concerning the creation and validation of a Polish language version of the Uraemic Pruritus in Dialysis Patient (UP-Dial) questionnaire. In accordance with international standards, a Polish language version was developed, and the questionnaire was validated. UP-dial questionnaire consists of 14 questions and comprehensively assesses and characterizes pruritus in dialysis patients. The questionnaire demonstrated high internal consistency (Cronbach's alpha), reproducibility, and very high intraclass correlation coefficients. Additionally, a strong correlation was shown between the results of the new tool and commonly used instruments assessing pruritus severity such as the Numerical Rating Scale (NRS), 4-Item Itch Questionnaire (4IIQ), as well as a questionnaire assessing quality of life in patients experiencing chronic pruritus - ItchyQoL.

The third and fourth publications are original research papers presenting the results of evaluating the interleukin 31 concentration and protein-bound uraemic toxins (free and total levels of indoxyl sulfate and p-cresyl sulfate) in dialysis patients and in a healthy control group. The studies were conducted between 2020 and 2023 in two clinical centers – Dialysis Centre of University Hospital in Wrocław and Dialysis Centre of University Hospital in Opole. The studies included a group of 175 and 174 chronic hemodialysis patients and 49 and 50 people in control groups, respectively. Demographic and clinical data were obtained from all patients, and blood samples were collected. IL-31 concentration was assessed by ELISA using commercially available kits. Concentrations of protein-bound uraemic toxins (free and total indoxyl sulfate and p-cresol sulfate) were measured by liquid chromatography system.

The worst itch intensity experienced over the last 3 days was assessed using NRS. Study participants also completed the UP-Dial questionnaire, which assesses the severity of pruritus and its impact on the quality of life of dialysis patients. Patients studied in the fourth article also completed the ItchyQoL questionnaire, designed to assess the quality of life in patients suffering from chronic itch, and 4IIQ. Statistical analysis was performed to assess the differences in concentrations of the studied molecules among the different groups (dialysis patients reporting pruritus, dialysis patients without pruritus, and a control group of healthy individuals), as well as to examine the correlation between the studied substances, the severity of pruritus and the quality of patients life.

The IL-31 serum level was significantly higher in the itchy group ($p < 0.001$) in comparison to the patients free from pruritus. Moreover, there was a significant difference ($p < 0.001$) in IL-31 serum levels between HD patients with and without pruritus and healthy controls ($p < 0.001$ and $p = 0.019$, respectively). Additionally, a marginal trend towards significance ($r = 0.242$, $p = 0.058$) was observed between the IL-31 serum level and the worst itch intensity during the last 3 days assessed by the NRS. The mean NRS score was 4.9 ± 2.2 points. According to the NRS cut-offs, mild pruritus was reported in 14.5% of the cases, moderate in 59.7%, severe in 22.6% and very severe in 3.2%. The mean UP-Dial score in the study assessing IL-31 levels was 14.2 ± 9.8 points. In 58% of the UP patients itch interfered with their sleep and only 29% did not report the influence of itch on the following activities: work or study, social interaction, mood, or any sexual activities.

The results regarding protein-bound uraemic toxins showed that serum concentrations of free and total IS and PCS were significantly higher in both HD patients with pruritus and HD patients without pruritus compared to healthy controls ($p < 0.001$). However, no significant difference was observed in the concentration of free and total IS or PCS in serum between patients reporting UP and patients without pruritus. There was also no correlation between the serum PBUTs concentration and the severity of itch assessed with the NRS scale. Likewise, the total score of other instruments used in this study (Up-Dial, 4IIQ, and ItchyQoL) also did not reveal significant relationships with serum concentrations of studied PBUTs. The mean intensity of pruritus assessed by NRS was 4.87 ± 2.21 points. According to the NRS cut-offs, moderate pruritus was reported most frequently—in 60.65% of the cases. The mean total UP-Dial score in the pruritus group was 14.31 ± 9.85 points. Additionally, the mean score of the 4-item Itch Questionnaire and ItchyQoL in this group were 8.44 ± 3.64 and 36.84 ± 13.65 points, respectively.

In conclusion, the conducted research provided the creation of Polish-language versions of the UP-Dial questionnaire, which enables reliable assessment and characterization of uraemic pruritus in clinical practice and scientific research. The studies emphasize that it is necessary to continue research for new factors taking part in pathogenesis of uraemic pruritus to develop the new effective therapeutic options in this disease. The results of publications included in the dissertation confirmed the possible role of IL-31 in the pathogenesis of chronic pruritus in dialysis patients. It has also been shown that disturbances in PBUTs concentrations in the serum of dialysis patients do not play a role in the genesis of uraemic pruritus. The results indicate a possible direction for further research on whether interleukin-31 inhibition can lead to the resolution of pruritus in patients with end-stage renal disease.

10. OPINIA KOMISJI BIOETYCZNEJ

KOMISJA BIOETYCZNA
przy
Uniwersytecie Medycznym
we Wrocławiu
ul. Pasteura 1; 50-367 WROCŁAW

OPINIA KOMISJI BIOETYCZNEJ Nr KB – 26/2021

Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu, powołana zarządzeniem Rektora Uniwersytetu Medycznego we Wrocławiu nr 278/XVI R/2020 z dnia 21 grudnia 2020 r. oraz działająca w trybie przewidzianym rozporządzeniem Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. (Dz.U. nr 47, poz. 480) na podstawie ustawy o zawodzie lekarza z dnia 5 grudnia 1996 r. (Dz.U. nr 514 z 2020 r.) w składzie:

dr Joanna Birecka (psychiatria)
dr Beata Freier (onkologia)
dr hab. Tomasz Fuchs (ginekologia, położnictwo)
prof. dr hab. Dariusz Janczak (chirurgia naczyniowa, transplantologia)
dr hab. Krzysztof Kaliszewski (chirurgia endokrynologiczna)
dr prawa Andrzej Malicki (prawo)
dr hab. Marcin Mączyński (farmacja)
Urszula Olechowska (pielęgniarstwo)
prof. dr hab. Leszek Szenborn (pediatria, choroby zakaźne)
prof. dr hab. Andrzej Szuba (choroby wewnętrzne, angiologia
ks. prof. Andrzej Tomko (duchowny)
prof. dr hab. Mieszko Więckiewicz (stomatologia)
dr hab. Andrzej Wojnar, prof. nadzw. (histopatologia, dermatologia) przedstawiciel Dolnośląskiej Izby Lekarskiej)
dr hab. Jacek Zieliński (filozofia)

pod przewodnictwem
prof. dr hab. Jerzego Rudnickiego (chirurgia, proktologia)

Przestrzegając w działalności zasad Good Clinical Practice oraz zasad Deklaracji Helsińskiej, po zapoznaniu się z projektem badawczym pt.:

„Kliniczne i patogenetyczne aspekty świądu mocznicowego "

zgłoszonym przez **lek. Karolinę Świerczyńską** uczestniczkę Szkoły Doktorskiej Wydziału Lekarskiego Uniwersytetu Medycznego we Wrocławiu oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła **wyrazić zgodę** na przeprowadzenie badania w Klinice Dermatologii, Wenerologii i Alergologii Uniwersyteckiego Szpitala Klinicznego we Wrocławiu; Klinice Nefrologii i Medycyny Transplantacyjnej Uniwersyteckiego Szpitala Klinicznego we Wrocławiu i Oddziale Nefrologii ze Stacją Dializ Uniwersyteckiego Szpitala Klinicznego w Opolu pod nadzorem dr hab. Rafała Białynickiego-Birula **pod warunkiem zachowania anonimowości uzyskanych danych**.

Uwaga: Badanie to zostało objęte ubezpieczeniem odpowiedzialności cywilnej Uniwersytetu Medycznego we Wrocławiu z tytułu prowadzonej działalności.

Pouczenie: W ciągu 14 dni od otrzymania decyzji wnioskodawcy przysługuje prawo odwołania do Komisji Odwoławczej za pośrednictwem Komisji Bioetycznej UM we Wrocławiu.

Opinia powyższa dotyczy projektu badawczego będącego podstawą rozprawy doktorskiej.

Przewodniczący Komisji Bioetycznej
przy Uniwersytecie Medycznym

prof. dr hab. Jerzy Rudnicki

Wrocław, dnia 29 stycznia 2021 r.

11. CURRICULUM VITAE

CURRICULUM VITAE

KAROLINA ŚWIERCZYŃSKA-MRÓZ

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Drezno, Niemcy - ERASMUS + Exchange Scholarship

Szkoła Doktorska Uniwersytetu Medycznego 10/2020 -09/2024

im. Piastów Śląskich we Wrocławiu,

Katedra *Dermatologii, Wenerologii i Alergologii*

Doświadczenie:

Zawodowe:

Lekarz rezydent (w trakcie specjalizacji) 01/11/2020 – obecnie

Klinika Dermatologii, Wenerologii i Alergologii,
Uniwersytecki Szpital Kliniczny
im. Mikulicza Radeckiego we Wrocławiu

Lekarz (stażysta)

Dolnośląskie Centrum Onkologii we Wrocławiu 01/10/2019 – 31/10/2020

Naukowe:

Publikacje:

- 8 pełnotekstowych artykułów opublikowanych w międzynarodowych czasopismach indeksowanych w bazie PubMed, z czego 4 jako pierwszy autor
- Całkowity współczynnik wpływu (Impact Factor) opublikowanych prac = 23,755
- Punktacja ministerialna: 775

Granty i Nagrody:

- „Dolnośląscy liderzy medycyny" – Europejskie stypendium wspierające doktorantów
- medycyny. Czas trwania 10.2020 - 12.2021. Kwota 25000 PLN. Kwota na poszerzenie i rozwój umiejętności bezpośrednio związanych z prowadzonymi badaniami.
- Eli Lilly Scholarship 2021 European Academy of Dermatology and Venereology
- III miejsce za wystąpienie pt.: "14-punktowa skala świądu mocznicowego u chorych dializowanych, utworzenie i walidacja polskiej wersji językowej" podczas VII Ogólnopolskiej i Międzynarodowej Konferencji Naukowej "Interdyscyplinarne aspekty chorób skóry i błon śluzowych", Warszawa, Polska, Marzec 2021
- II miejsce za wystąpienie pt: „Poziom interleukiny 31 w surowicy pacjentów ze świądem związanym z przewlekłą niewydolnością nerek. Czego możemy się spodziewać?" podczas VIII Ogólnopolskiej i Międzynarodowej Konferencji Naukowej "Interdyscyplinarne aspekty chorób skóry i błon śluzowych", Warszawa, Polska, Marzec 2022
- Subwencja konkursowa UMW: "Ocena surowiczego stężenia interleukiny 31 neurotrofiny 4 i neurotroficznego czynnika pochodzenia mózgowego (BDNF) u chorych ze świądem mocznicowym". 01.2022 – 12.2022. Kwota 50 000 PLN, SUBK.C260.22.076
- Subwencja konkursowa UMW: "Periostyna i interleukina 13 jako nowe czynniki immunopatogenezy świądu u chorych hemodializowanych." 01.2022 – 12.2022. Kwota 50 000 PLN, SUBK.C260.23.044

- Travel Grant International Forum for the Study of Itch (IFSI) za pracę "Determination of Serum Level of IL-31 in Patients Suffering from Chronic Kidney Disease-Associated Pruritus". Kwota 2000$. Miami, USA, Listopad 2023

Członkostwo w towarzystwach naukowych:

• Polskie Towarzystwo Dermatologiczne

• International Society of Dermatology

• European Academy of Dermatology and Venerology

• International Forum for the Study of Itch

12. DOROBEK NAUKOWY

I. Publikacje w czasopiśmie naukowym z IF

1. **Świerczyńska Karolina**, Białynicki-Birula Rafał, Szepietowski Jacek C.: Chronic intractable pruritus in chronic kidney disease patients: prevalence, impact, and management challenges - a narrative review, Therapeutics and Clinical Risk Management, 2021, vol. 17, s. 1267-1282, DOI:10.2147/TCRM.S310550

2. Rymsza Aleksandra, **Świerczyńska Karolina**, Piotrowska Aleksandra, Dzięgiel Piotr, Szepietowski Jacek C.: Expression of MCM2 as a proliferative marker in actinic keratosis and cutaneous squamous cell carcinoma, In Vivo, 2022, vol. 36, nr 3, s. 1245- 1251, DOI:10.21873/invivo.12823

3. Wala-Zielińska Kamila, **Świerczyńska-Mróz Karolina**, Krajewski Piotr K., Nowicka-Suszko Danuta, Krajewska Magdalena, Szepietowski Jacek C.: Elevated level of serum neurotrophin-4, but not of brain-derived neurotrophic factor, in patients with chronic kidney disease-associated pruritus, Journal of Clinical Medicine, 2022, vol. 11, nr 21, art.6292 [11 s.], DOI:10.3390/jcm11216292

4. **Świerczyńska Karolina**, Krajewski Piotr, Reszke Radomir, Krajewska Magdalena, Nochaiwong Surapon, Białynicki-Birula Rafał, Szepietowski Jacek C.: Uraemic Pruritus in Dialysis Patient (UP-Dial) questionnaire: creation and validation of the Polish language version, Postępy Dermatologii i Alergologii, 2022, vol. 39, nr 3, s. 538-544, DOI:10.5114/ada.2021.107271

5. **Świerczyńska Karolina**, Krajewski Piotr, Nowicka-Suszko Danuta, Białynicki-Birula Rafał, Krajewska Magdalena, Szepietowski Jacek C.: The serum level of IL-31 in patients with chronic kidney disease-associated pruritus: what can we expect?, Toxins, 2022, vol. 14, nr 3, art.197 [9 s.], DOI:10.3390/toxins14030197

6. **Świerczyńska-Mróz Karolina**, Nowicka-Suszko Danuta Barbara, Fleszar Mariusz G., Fortuna Paulina, Krajewski Piotr K., Krajewska Magdalena, Białynicki-Birula Rafał, Szepietowski Jacek C.: Serum level of protein-bound uraemic toxins in haemodialysis patients with chronic kidney disease-associated pruritus: myths and facts, Journal of Clinical Medicine, 2023, vol. 12, nr 6, art.2310 [11s.], DOI:10.3390/jcm12062310

7. Wala-Zielińska Kamila, **Świerczyńska-Mróz Karolina**, Krajewski Piotr K., Nowicka-Suszko Danuta, Krajewska Magdalena, Szepietowski Jacek C.: Endogenous opioid imbalance as a potential factor involved in the pathogenesis of chronic kidney diseaseassociated pruritus in dialysis patients, Journal of Clinical Medicine, 2023, vol. 12, nr 7, art.2474 [12 s.], DOI:10.3390 /jcm12072474

8. Mateuszczyk Mateusz K., **Świerczyńska-Mróz Karolina**, Chlebicka Iwona, Szepietowski Jacek Cezary: Non-multiple medium-sized congenital melanocytic nevi: to excise or to follow up?, Postępy Dermatologii i Alergologii, 2023, vol. 40, nr 4, s. 561-566, DOI: 10.5114/ada.2023.128718\

II. Publikacje w czasopiśmie naukowym bez IF

1. **Świerczyńska Karolina**, Białynicki-Birula Rafał: Mupirocyna - sprawdzony klasyczny antybiotyk o działaniu miejscowym, Wiadomości Dermatologiczne, 2021, nr 9, s. 28-34,

Sumaryczny Impact Factor: 23,755

Punktacja ministerialna: 775

III. Doniesienia zjazdowe

1. **Karolina Świerczyńska,** Piotr Krajewski, Radomir Reszke, Magdalena Krajewska, Surapon Nochaiwong, Rafał Białynicki-Birula, Jacek C Szepietowski. Uraemic Pruritus in Dialysis Patient (UP-Dial): creation and validation of the Polish language version Virtual 19th Congress of the European Society for Dermatology and Psychiatry (ESDaP) and 2nd Brain Skin Colloquium Conference (BSC), Virtual 11.06-13.06.2021
2. **Karolina Świerczyńska,** Piotr Krajewski, Radomir Reszke, Magdalena Krajewska, Surapon Nochaiwong, Rafał Białynicki-Birula, Jacek C Szepietowski**.** 14-punktowa skala świądu mocznicowego u chorych dializowanych, utworzenie i walidacja polskiej wersji językowej, VII Ogólnopolska i Międzynarodowa Konferencja Naukowa „Interdyscyplinarne aspekty chorób skóry i błon śluzowych", Warszawa, Polska, 05.03-06.03.2021
3. **Karolina Świerczyńska**, Piotr K. Krajewski, Danuta Nowicka-Suszko, Rafał Białynicki-Birula, Magdalena Krajewska, Jacek C. Szepietowski. Poziom interleukiny 31 w surowicy pacjentów ze świądem związanym z przewlekłą niewydolnością nerek. Czego możemy się spodziewać? VII Ogólnopolska i Międzynarodowa Konferencja Naukowa „Interdyscyplinarne aspekty chorób skóry i błon śluzowych", Warszawa, Polska, 11.03-12.03.2022
4. **Karolina Świerczyńska-Mróz,** Piotr K. Krajewski, Danuta Nowicka-Suszko, Rafał Białynicki-Birula, Magdalena Krajewska, Jacek C. Szepietowski. Determination of serum level of IL-31 in patients suffering from chronic kidney disease-associated

pruritus. American Academy of Dermatology (AAD) Annual Meeting, New Orlean, USA, 17.03-21.03.2023

5. **Karolina Świerczyńska-Mróz**, Danuta Nowicka-Suszko, Mariusz G Fleszar , Paulina Fortuna , Piotr K Krajewski, Magdalena Krajewska, Rafał Białynicki-Birula, Jacek C Szepietowski. Poziom toksyn mocznicowych związanych z białkami w surowicy pacjentów ze świądem związanym z przewlekłą niewydolnością nerek. Fakty i mity. 32. Zjazd Polskiego Towarzystwa Dermatologicznego, Lublin, Polska, 31.05 - 03.06.2023
6. **Karolina Świerczyńska-Mróz** Danuta Nowicka-Suszko, Mariusz G Fleszar , Paulina Fortuna , Piotr K Krajewski, Magdalena Krajewska, Rafał Białynicki-Birula, Jacek C Szepietowski. Serum Level of Protein-Bound Uraemic Toxins in Patients with Chronic Kidney Disease-Associated Pruritus: Myths and Facts. 25th World Congress of Dermatology, Singapur, 03.07-08.07.2023
7. **Karolina Świerczyńska-Mróz,** Kamila Wala-Zielińska, Joanna Maj. Mpox - nasze doświadczenia. V Bieszczadzkie Spotkania z Dermatologią, Arłamów, Polska, 06.09-08.09.2023

13. OŚWIADCZENIA WSPÓŁAUTORÓW

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Chiang Mai, 22nd of April 2024

COAUTHOR STATEMENT

Herby, I declare, that in article:

Świerczyńska K, Krajewski P, Reszke R, Krajewska M, Nochaiwong S, Białynicki-Birula R, Szepietowski JC. Uraemic Pruritus in Dialysis Patient (UP-Dial) questionnaire: creation and validation of the Polish language version. Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii. 2022;39(3):538-544.

my contribution consisted of co-creating the research concept and scientific supervision.

.....Surapon.....

Signature

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Wrocław, 2024-25-04

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Oświadczam, że w pracy:

Świerczyńska K, Krajewski P, Nowicka-Suszko D, Białynicki-Birula R, Krajewska M, Szepietowski JC. The Serum Level of IL-31 in Patients with Chronic Kidney Disease-Associated Pruritus: What Can We Expect?. Toxins (Basel). 2022;14(3):197. Published 2022 Mar 7. doi:10.3390/toxins14030197

mój udział polegał na wykonaniu badań metodą ELISA.

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mój udział polegał na tłumaczeniu kwestionariusza według międzynarodowych standardów oraz współtworzeniu koncepcji badań.

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