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Badania nad neuroprzekaźnikami w patogenezie świądu mocznicowego

ROZPRAWA DOKTORSKA

Cykl publikacji powiązanych tematycznie

PROMOTOR:

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Mojemu promotorowi, panu ***prof. dr. hab. dr. h.c. Jackowi Szepietowskiemu*** *pragnę złożyć najszczersze podziękowania za wszystkie cenne wskazówki, cierpliwość i wyrozumiałość oraz nieocenioną pomoc na każdym etapie tworzenia rozprawy doktorskiej.*

Mojej wspaniałej rodzinie

Spis treści

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1. **Wala Kamila**, Szepietowski Jacek C.: Difelikefalin in the treatment of chronic kidney disease-associated pruritus: a systematic review, Pharmaceuticals, 2022, vol. 15, nr 8, art.934, DOI:10.3390/ph15080934

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3. **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 disease-associated pruritus in dialysis patients, Journal of Clinical Medicine, 2023, vol. 12, nr 7, art.2474, DOI:10.3390/jcm12072474

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2. WYKAZ SKRÓTÓW

BDNF	Neurotroficzny czynnik pochodzenia mózgowego (ang. *brain-derived neurotrophic factor*)
CI	Przewlekły świąd (ang. *chronic itch*)
DLQI	Dermatologiczny Kwestionariusz Oceny Jakości Życia (ang. *Dermatology Life Quality Index*)
DOPPS	Dialysis Outcomes and Practice Patterns Study
IFSI	Międzynarodowe Forum Badań Świądu (ang. *International Forum of Study of Itch*)
ItchyQoL	Kwestionariusz jakości życia specyficzny dla świądu
NRS	Numeryczna Skala Oceny (ang. *Numerical Rating Scale*)
NT-4	Neurotrofina 4 (ang. *neurothrophin-4*)
OUN	Ośrodkowy układ nerwowy
PChN	Przewlekła choroba nerek
SD	Odchylenie standardowe (ang. *standard deviation*)
UP	Świąd mocznicowy (ang. *uremic pruritus*)

3. OMÓWIENIE ROZPRAWY DOKTORSKIEJ

3.1. Wstęp

Przewlekły świąd (CI) jest definiowany jako nieprzyjemne odczucie trwające dłużej niż 6 tygodni, powodujące ciągłą potrzebę drapania. Zgodnie z klasyfikacją Międzynarodowego Forum Badań Świądu (IFSI) ze względu na etiologię wyróżniamy sześć kategorii świądu: (I) świąd skórny, (II) świąd układowy, (III) świąd neurologiczny, (IV) świąd psychogenny, (V) świąd mieszany i (VI) świąd o nieznanej etiologii. Do chorób układowych, którym może towarzyszyć CI należą m.in. cholestaza, choroby nerek, zaburzenia czynności tarczycy (nadczynność i niedoczynność) oraz choroby hematologiczne. Świąd mocznicowy (UP) występuje u pacjentów z przewleką chorobą nerek (PChN), a jego częstość zależy od stopnia zaawansowania choroby i wzrasta wraz z pogorszeniem funkcji nerek. Zgodnie z raportem Dialysis Outcomes and Practice Patterns Study (DOPPS) u pacjentów hemodializowanych częstość występowania świądu w stopniu od umiarkowanego do ciężkiego wynosi 37%. W piśmiennictwie pojawiają się liczne hipotezy dotyczące patogenezy CI u pacjentów z PChN, jednak jego etiologia wciąż pozostaje niejasna. Do czynników patogenetycznych mogących przyczynić się do wystąpienia świądu należą zaburzenia gospodarki wapniowo-fosforanowej, nagromadzenie toksyn mocznicowych, kseroza, a także dysfunkcje układu immunologicznego oraz neurologicznego. W przypadku świądu związanego z PChN często podkreślana jest rola zaburzonej interakcji między skórą a obwodowym układem nerwowym. Dlatego też kolejnym potencjalnym czynnikiem etiologicznym UP może być dysfunkcja prawidłowego przewodnictwa impulsów nerwowych wywołana działaniem neurotransmiterów, takich jak neurotrofiny oraz endogenne opioidy. Skuteczne terapia UP jest dużym wyzwaniem. Obecne metody terapeutyczne obejmują m.in. fototerapię UVB oraz leczenie miejscowe z zastosowaniem kapsaicyny, mocznika 10% czy takrolimusu. Doustne leki przeciwhistaminowe powszechnie stosowane w leczeniu CI często nie przynoszą istotnej poprawy u pacjentów z PChN. Pregabalina, gabapentyna i sertralina wykazują skuteczność w redukcji świądu, jednak ogólnoustrojowe działania niepożądane, takie jak zawroty głowy, senność, utrata równowagi czy zmęczenie, ograniczają ich zastosowanie. Z tego powodu obecne możliwości leczenia UP są nadal niewystarczające i część pacjentów nie uzyskuje optymalnej poprawy.

3.2. Cel badań i problemy badawcze

Celem badań wchodzących w skład rozprawy doktorskiej jest przegląd aktualnie dostępnych metod leczenia świądu mocznicowego, w tym ocena zastosowania agonisty kappa-opioidowego – difelikefaliny u pacjentów dializowanych oraz poszukiwanie nowych czynników patogenetycznych świądu mocznicowego koncentrując się na ocenie stężenia wybranych neuroprzekaźników w surowicy pacjentów dializowanych.

Cele szczegółowe:

3.2.1 Ocena stężenia neurotrofin (NT-4 oraz BDNF) w surowicy pacjentów dializowanych

3.2.2 Zbadanie stężenia poszczególnych składowych układu opioidowego (met-enkefaliny, leu-enkefaliny, dynorfiny A oraz beta-endorfiny) u pacjentów dializowanych

3.2.3 Analiza różnicy stężeń neuroprzekaźników między poszczególnymi grupami oraz zbadanie korelacji stężenia badanych substancji z nasileniem świądu i jakością życia pacjentów.

3.2.4 Dokonanie przeglądu piśmiennictwa dotyczącego efektywności oraz bezpieczeństwa zastosowania difelikefaliny u pacjentów dializowanych cierpiących z powodu przewlekłego świądu.

3.3. Materiał i metody

Pierwszą pracą spośród cyklu jest przegląd systematyczny piśmiennictwa dotyczący zastosowania nowego agonisty receptora kappa-opioidowego – difelikefaliny w leczeniu świądu mocznicowego u pacjentów dializowanych. Przeglądu dokonano zgodnie z wytycznymi protokołu PRISMA w maju 2022r. Bazy danych takie jak PubMed, ScienceDirect i Scholar Google zostały przeszukane pod kątem odpowiednich artykułów przy użyciu kombinacji słów kluczowych: „difelikefalina” lub „CR845” oraz „świąd” lub „przewlekła choroba nerek” lub „hemodializa”. Kryteria wykluczenia obejmowały wszystkie rodzaje publikacji z wyjątkiem prac badawczych (np. recenzje, listy) i artykuły w języku innym niż angielski. Do dalszej

analizy włączono oryginalne artykuły pełnotekstowe dotyczące zastosowania difelikefaliny w leczeniu świądu u pacjentów dializowanych.

Następnie, w badaniach będących podstawą drugiej i trzeciej publikacji cyklu oceniono stężenie neurotrofin oraz endogennych opioidów w surowicy pacjentów dializowanych. Badania prowadzono w latach 2020-2023. Do badania zakwalifikowano pacjentów powyżej 18 roku życia poddawanych hemodializie 2 lub 3 razy w tygodniu przez co najmniej 3 miesiące, którzy podpisali świadomą zgodę na udział w badaniu. Kryteria wyłączenia obejmowały: leczenie przeciwświądowe, zaburzenia psychiczne oraz inne choroby towarzyszące, które mogą powodować świąd. Ostatecznie do badań włączono grupę liczącą 126 pacjentów przewlekle hemodializowanych, z których prawie połowa (62 pacjentów) cierpiała na świąd skóry. Grupę kontrolną w badaniach oceniających stężenie endogennych opioidów stanowiło 50 zdrowych osób. Od wszystkich pacjentów zostały zebrane dane demograficzne oraz kliniczne (płeć, wiek, przyczyna niewydolności nerek, czas trwania hemodializy oraz rodzaj dostępu naczyniowego). Następnie, tuż przed dializoterapią, od każdego pacjenta została pobrana próbka krwi (9ml), którą następnie odwirowano, a surowicę przechowywano w -80°C do czasu wykonania dalszych badań. Stężenie neuroprzekaźników oceniono metodą ELISA zgodnie z protokołem producenta. W badaniach wykorzystano komercyjnie dostępne zestawy do oznaczania NT-4 (Nori® Human Neurotrophin 4 ELISA Kit, GR111502, Genorise Scientific, Inc., Pensylwania, PA, USA), BDNF (Nori® Human BDNF ELISA, GR111085, Genorise Scientific, Inc., Pensylwania, Pensylwania, USA), met-enkefaliny (Met-Enkephalin ELISA Kit, BMA BIOMEDICALS, Augst, Switzerland), leu-enkefaliny (Leu-Enkephalin EIA Kit, Phoenix Pharmaceuticals, Inc., Burlingame, CA, USA), dynorfiny A (RayBio® Human Dynorphin A ELISA Kit, Ray Biotech, Inc., Peachtree Corners, GA, USA) oraz beta-endorfiny (Nori® Human beta-endorphin ELISA Kit, GR111460-1, Genorise Scientific, Inc., Pennsylvania, PA, USA). Absorbancję mierzono przy użyciu wielopłytkowego czytnika EPOCH (BioTEK® Instruments, Inc., Winooski, VT, USA) przy długości fali 450 nm.

Nasilenie świądu (największe nasilenie świądu w ciągu ostatnich trzech dni w skali od 0 do 10 punktów) oceniano za pomocą skali numerycznej (NRS). W zależności od wyników nasilenie świądu podzielono na łagodne (< 3 punkty), umiarkowane (≥3–7 punktów), ciężkie (≥ 7–9 punktów) i bardzo ciężkie (≥9 punktów). Ponadto, pacjenci byli proszeni o wypełnienie kwestionariusza jakości życia specyficznego dla świądu (ItchyQoL), który ocenia jakość życia u pacjentów ze świądem biorącego pod uwagę 3 domeny: objawy, funkcje i emocje. Kwestionariusz ten składa się z 22 pozycji, każda punktowana od 1 do 5 punktów. Pacjenci z UP wypełnili też kwestionariusz UP-Dial, który został stworzony do oceny nasilenia świądu i

jego wpływu na jakość życia pacjentów dializowanych. Następnie, przeanalizowano różnicę stężeń neuroprzekaźników między poszczególnymi grupami oraz zbadano korelację stężenia badanych substancji z nasileniem świądu i jakością życia pacjentów.

Do analizy statystycznej wykorzystano oprogramowanie IBM SPSS Statistics v. 26 (SPSS Inc., Chicago, IL, USA). Wszystkie dane przedstawiono jako średnia ± odchylenie standardowe (SD). $P < 0,05$ uznano za istotne statystycznie.

3.4. Podsumowanie wyników

W badaniach przeprowadzonych wśród pacjentów dializowanych wykazano, że pacjenci ze świądem mają istotnie wyższe stężenie NT-4 w porównaniu do grupy bez świądu (224.4 ± 128.8 pg/mL vs. 159.1 ± 90.0 pg/mL, p=0.003). Stężenie BDNF w surowicy w grupie ze świądem wynosiło 55.3 ± 66.0 pg/ml, natomiast w grupie bez świądu 64.2 ± 62.7 pg/ml. Różnica ta nie była istotna statystycznie.

W kolejnym etapie pracy badawczej wykazano istotnie niższe stężenie beta-endorfiny w grupie pacjentów dializowanych ze świądem (216.25 ± 171.21 pg/mL) w porównaniu z pacjentami bez świądu (344.84 ± 268.3 pg/mL, p=0.005) oraz grupą kontrolną (658.51 ± 377.66 pg/mL, p<0.001). Stężenie dynorfiny A u pacjentów dializowanych wyniosło odpowiednio 4.32 ± 3.95 ng/ml w grupie ze świądem oraz 4.62 ± 3.87 ng/ml w grupie bez świądu i było istotnie niższe w porównaniu do grupy kontrolnej – 8.1 ± 6.2 ng/ml (p<0.001). Ponadto, zaobserwowano istotnie niższy stosunek stężenia beta-endorfiny do stężenia dynorfiny A w grupie pacjentów ze świądem w porównaniu z pacjentami bez świądu i grupą kontrolną (p=0.005). Wykazano też wyższe stężenie met-enkefaliny w grupie chorych ze świądem w porównaniu z grupą kontrolną (p=0.009).

Średnie maksymalne nasilenie świądu zgłaszane przed pacjentów wynosiło 4.9 ± 2.2 punktów w NRS. Świąd w stopniu co najmniej umiarkowanym występował u 46 (74.2%) pacjentów. Jakość życia pacjentów ze świądem została oceniona na 14.2 ± 9.8 punktów według kwestionariusza UP-Dial oraz 36.7 ± 13.7 według kwestionariusza ItchyQoL. Stężenia badanych opioidów oraz neurotrofin nie korelowały z nasileniem świądu ani jakością życia pacjentów.

Analizowane w przeglądzie systematycznym badania kliniczne wykazały, że difelikefalina stosowana w dawce 0.5 μg/kg przez 8-12 tygodni skutecznie zmniejsza świąd u pacjentów dializowanych z redukcją średnio o 3.65 – 3.8 punktów w skali NRS. Zmniejszenie nasilenia świądu o minimum 3 punkty w skali NRS uzyskano u 49.1 – 64% pacjentów biorących udział

w badaniach klinicznych, a o 4 punkty u 40.5 – 51% badanych. Odnotowano również poprawę jakości życia ocenianej na podstawie m.in. skali Skindex oraz 5-D itch scale. Po zastosowaniu placebo lub difelikefaliny w innych dawkach (0.25, 1 lub 1.5 μg/kg) obserwowano mniejszą redukcję świądu. Najczęściej zgłaszane działania niepożądane były łagodne i obejmowały nudności, wymioty, zawroty głowy i biegunkę.

3.5 Etyka

Projekt pracy doktorskiej opartej na poniższych publikacjach został zatwierdzony przez Komisję Bioetyczną 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. Badania zostały przeprowadzone z zachowaniem anonimowości uzyskanych danych.

3.6 Wnioski

3.6.1. Neurotrofina 4 może odgrywać istotną rolę w patogenezie świądu u pacjentów dializowanych.

3.6.2. Zaburzenia równowagi między stężeniami poszczególnych składowych układu opioidowego mogą przyczyniać się do występowania świądu oraz modulować odczucie świądu u pacjentów dializowanych.

3.6.3. Difelikefalina, ze względu na udowodnioną skuteczność i dobry profil bezpieczeństwa, stanowi jedną z podstawowych metod leczenia przewlekłego świądu u pacjentów dializowanych.

3.6.4. Konieczne są dalsze badania w celu oceny długoterminowej skuteczności oraz bezpieczeństwa stosowania difelikefaliny, a także w celu poszukiwania nowych substancji terapeutycznych, które poprzez hamowanie szlaków działania niektórych neurotransmiterów, mogłyby skutecznie redukować przewlekły świąd u pacjentów dializowanych.

4. ARTYKUŁ PIERWSZY

Difelikefalin in the treatment of chronic kidney disease-associated pruritus: a systematic review

pharmaceuticals

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Systematic Review

Difelikefalin in the Treatment of Chronic Kidney Disease-Associated Pruritus: A Systematic Review

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Abstract: Chronic kidney disease-associated pruritus (CKD-aP) is a chronic condition that significantly reduces the quality of life of patients with end-stage renal disease. The etiology is not fully understood, but imbalance in the activity of the opioid pathways, including downregulation of the kappa-opioid receptor, may contribute to itching sensation. Difelikefalin is a selective, peripherally acting kappa-opioid receptor (KOR) agonist. Recently, difelikefalin has been approved as a first drug for the treatment of pruritus associated with chronic kidney disease (CKD) in adult hemodialysis patients. A systematic review of currently available clinical trials was performed to assess the efficacy and safety of difelikefalin in patients with uremic pruritus. A literature review was conducted in May 2022 based on the PRISMA 2020 guidelines. The analyzed clinical trials showed that difelikefalin was effective in reducing pruritus in patients as assessed by the Worst Itching Intensity Numerical Rating Scale. Improvement in quality of life assessed on the basis of the Skindex score and the 5-D itch scale was also noticed. The most commonly reported side effects were mild and included nausea, vomiting, dizziness, and diarrhea. Due to its proven efficacy and good safety profile, difelikefalin is a promising drug for the treatment of pruritus in patients with chronic kidney disease.

Keywords: difelikefalin; kappa-opioid receptor; chronic kidney disease; pruritus; hemodialysis; itch

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1. Introduction

Chronic kidney disease-associated pruritus (CKD-aP), also known as uremic pruritus, is a condition that significantly reduces the quality of life of patients with end-stage renal disease [1]. Persistent pruritus negatively affects both physical and mental health. Patients with CKD-aP suffer from sleep disorders, depression, and also have an increased risk of cardiovascular diseases [2]. In addition, constant scratching of the skin contributes to the formation of secondary changes, including bacterial infections [3].

The prevalence of CKD-aP reported in the literature ranges from 20 to 80% and varies depending on the stage of the kidney disease and the type of dialysis used (hemodialysis or peritoneal dialysis) [4]. Based on current studies, it is estimated that moderate to severe pruritus occurs in approximately 40% of patients with chronic kidney disease (CKD) [5]. The etiology is not fully understood, but there are many hypotheses that may contribute to the onset and severity of CKD-aP. Among others, mediators such as histamine or serotonin, dysregulation of the activity of opioid pathways (including kappa-opioid receptor (KOR) downregulation), xerosis, hyperparathyroidism, accumulation of uremic toxins, and dysregulation of the immune system are suspected to be significant factors of chronic itch [4,6,7].

Despite the many different therapeutic options for treating pruritus, CKD-aP remains a significant therapeutic challenge. The treatment of CKD-aP with commonly used antihistamines has been shown to be ineffective in this group of patients [8,9]. Drugs that act on the central nervous system (CNS), such as gabapentin or pregabalin, appear to be of greatest importance among oral medications in the treatment of this type of pruritus. However,

systemic side effects, such as dizziness, somnolence, loss of balance, and fatigue, have been noted [10]. In clinical trials by Seckin et al. [11] and Gilchrest et al. [12] with ultraviolet (UV) B therapy in patients with CKD-aP, significant improvement in pruritus severity was observed, with the most common adverse reaction being mild local sunburn. On the other hand, in alternative studies by Hsu et al. [13] and Ko et al. [14], after narrowband UVB application, no side effects were noticed, but also no statistically significant improvement was shown compared to the control group. It is worth mentioning that studies on the effects of UVB phototherapy in patients with CKD-aP were conducted on small groups of patients, and the control group and possible placebo effect were not taken into account [13,14]. Topical treatment, due to the patient's good tolerance, can be used in CKD-aP patients; however, it is often insufficient in monotherapy. In turn, emollients should be included in any treatment regimen, regardless of the use of additional therapy [15]. Despite the increasing awareness of the importance of the CKD-aP problem, this condition is underdiagnosed, and some patients still do not receive sufficient treatment for chronic pruritus.

In recent years, many studies have focused on understanding the correlation between an imbalance in opioid signaling and the incidence of pruritus. Activation of mu-opioid receptors (MOR) in analgesia (e.g., by morphine) has been shown to cause an itching sensation [16]. Furthermore, it has been noticed that lowering the KOR level and increased activation of MOR occurs in patients with chronic pruritus, including CKD-aP [15,17]. In clinical trials and in case reports, the antipruritic effect of substances belonging to MOR antagonists (MORA) has been demonstrated. A beneficial effect of MORA, especially in the treatment of cholestatic pruritus, has been noted; however, the data on the effectiveness of this substances in the treatment of CKD-aP are divergent [18–22]. On the other hand, the activation of opioid pathways by acting on KOR has strong antipruritic properties [23]. KOR agonists, such as nalbuphine, nalfurafine, and ZYKR1, have been shown to be effective in preclinical animal studies, in which these compounds reduce scratching caused by variable pruritogens [24–27]. Moreover, no similar antipruritic effect was observed after administration of nalbuphine in mice lacking the KORs, which confirms the mechanism of action of this substance through activation of this receptors [26]. For nalfurafine, in addition to favorably inhibiting scratching in male rats, the addictive potential of this agonist was reported [24]. However, no psychological or physical dependence was demonstrated in preclinical studies in Rhesus monkeys or during 52 weeks of follow-up in clinical trials [28–30]. In randomized, placebo-controlled clinical trials of the KOR agonists nalfurafine and nalbuphine, statistically significant reductions in pruritus were reported in patients with CKD-aP and prurigo nodularis, respectively [31,32].

Difelikefalin is a novel opioid agonist with high selectivity for KOR that has been shown to be effective in the treatment of chronic pruritus and post operative pain [33]. By activating KOR on peripheral sensory neurons, it inhibits the afferent transmission of sensory signals to the CNS. Furthermore, this drug has an immunomodulatory effect. It has been shown to activate KORs on cells of the immune system, leading to a reduction in the production of pro-inflammatory cytokines and a reduction in inflammation [23,34]. Importantly, with hydrophilic properties, its transport across the blood–brain barrier is limited. Compared to many other opioids, such as fentanyl or morphine, difelikefalin exhibits a minimal effect on the central nervous system and does not cause, among others, respiratory depression or sedation [33]. In a randomized clinical trial, Viscusi et al. [35] showed that difelikefalin administered intravenously at a dose of 1.0 and 5.0 μg/kg did not cause respiratory depression, and all the noted side effects, such as somnolence or paresthesia, were mild and did not require any intervention. Due to the lack of influence on MOR, no euphoric effect was observed when using difelikefalin; therefore, the addictive potential of this substance is low [36]. In August 2021, difelikefalin was approved by the Food and Drug Administration (FDA) and in April 2022 by European Medicines Agency (EMA) as a first drug for the treatment of CKD-aP in adult, hemodialysis patients. The recommended dose is 0.5 μg/kg body weight. The drug is administered as an intravenous

injection at the end of hemodialysis session [37]. The structure of difelikefalin is shown in Figure 1.

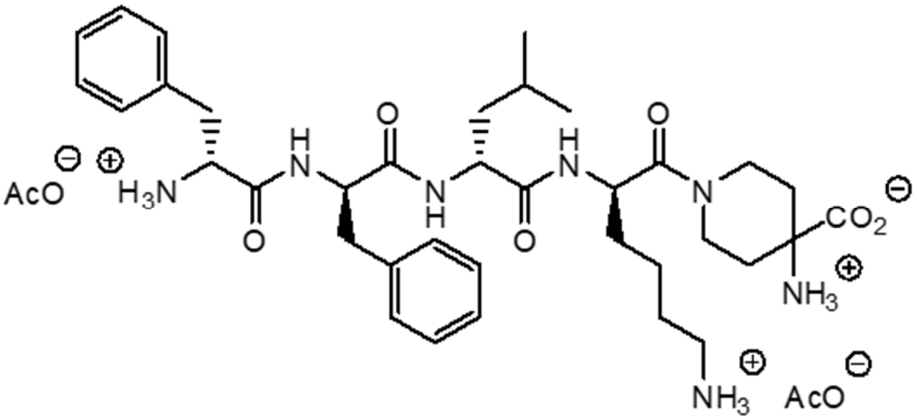

Figure 1. Chemical structure of difelikefalin.

The aim of this study is to evaluate the clinical efficacy and safety as well as to summarize the current knowledge of difelikefalin in treatment of patients with CKD-aP based on the available clinical trials.

2. Methods

The literature review was conducted independently by two authors in May 2022 based on the PRISMA 2020 guideline [38]. The systematic review has been registered in International Platform of Registered Systematic Review and Marta-Analysis Protocols–INPLASY (registration number: INPLASY202250154). The PubMed, ScienceDirect, and Scholar Google databases were searched for relevant articles using the combination of the keywords "difelikefalin" or "CR845" AND "pruritus" or "itch" or "chronic kidney disease" or "hemodialysis". Initially, 457 articles were found. Firstly, after excluding duplicate records, 375 works were included in the further screening.

Then, a gradual selection was made, as shown in Figure 2. The flow diagram was created based on the PRISMA template [38]. The exclusion criteria included all types of articles except for research works (e.g., reviews, letters) and a language other than English. Inclusion criteria were full-text original articles on the effects of difelikefalin in dialysis on adult patients with chronic pruritus. Based on abstracts, unrelated topics, review articles, and letters were rejected. In addition, articles written in a language other than English were not eligible for further scanning. The remaining studies were then analyzed. At the final stage, incomplete and ineligible articles were excluded. Eventually, three articles were included in the work.

In addition, the website of the National Institute of Health was searched for information related to new clinical trials related to the topic.

Selected publications were carefully analyzed independently by two authors for possible deviations in the results, which could result from inappropriate selection of participants, randomization, or evaluation of the results. The included clinical trials passed the randomization process and had a low overall risk of misleading results. The criteria for qualifying patients to participate in the study were defined in detail. The research was carried out according to the protocol. The results of both studies by Fishbane et al. [39,40] have been well presented, both the baseline data and the data, at the end of the entire study. Narita et al. [41] described the results, but not every value was presented—some results from the placebo groups were missing from the main text. However, all data from the difelikefalin and placebo groups are presented in the tables attached to the article.

The overall risk of misleading results was assessed as low. The risk of bias for individual domains in analyzed clinical trials is presented in Figure 3.

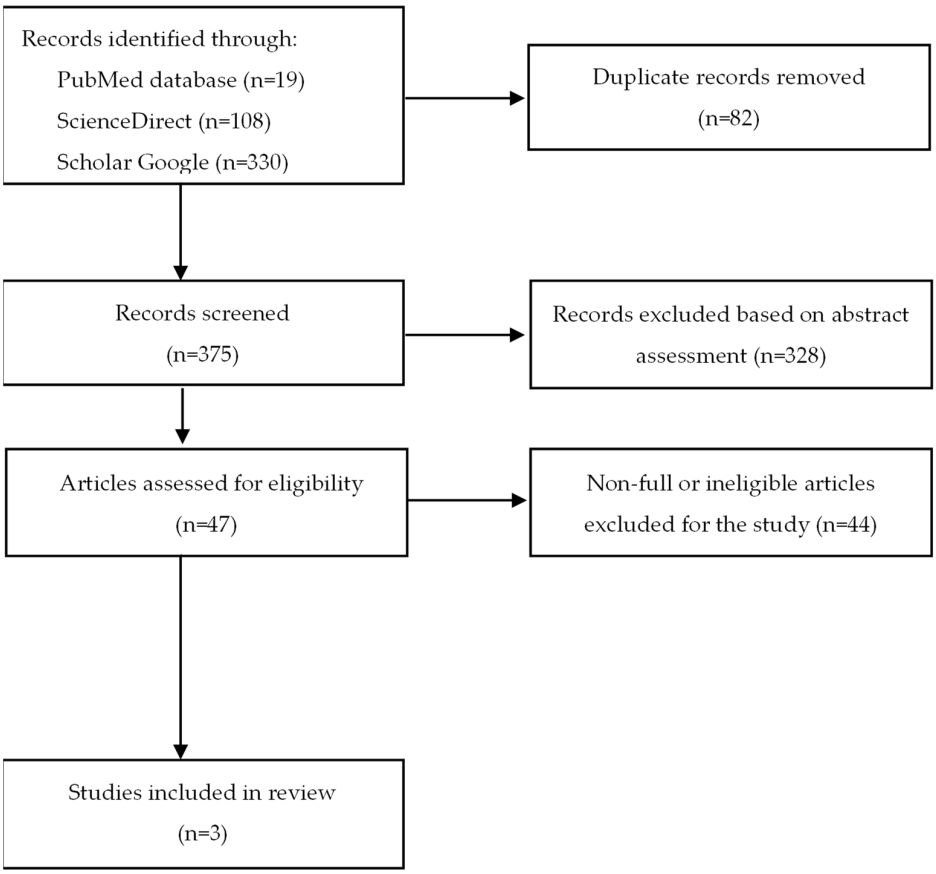

Figure 2. Flow diagram of the literature search procedure.

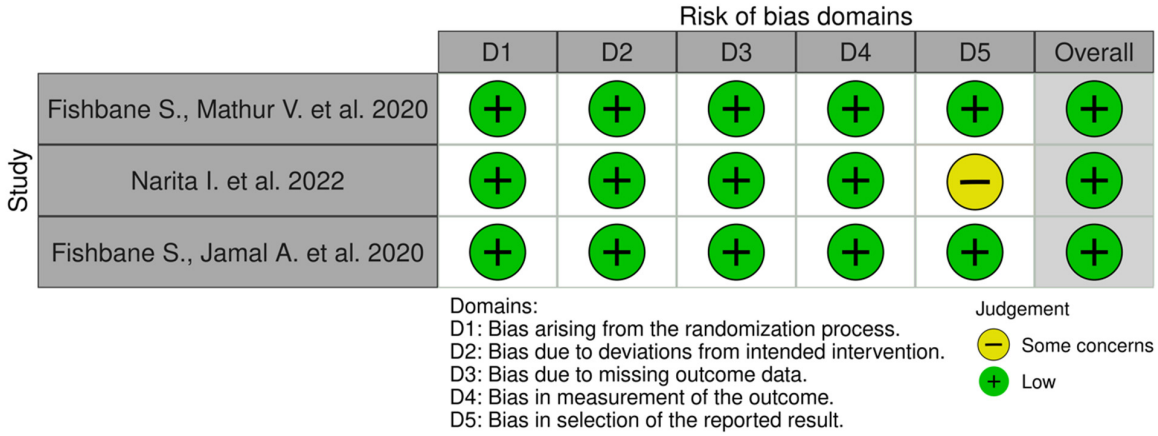

Figure 3. Risk of bias. The Robvis tool was used to create the risk-of-bias plots [39–42].

3. Results

Until May 2022, three clinical trials evaluating the effectiveness of difelikefalin in the treatment of CKD-aP have been published, in which a total of 800 patients with moderate to severe CKD-aP participated [39–41]. Patients assessed the intensity of symptoms before, during, and after the trial.

In a randomized, double-blind, placebo-controlled phase 2 study conducted in the United States (NCT02858726), participants (n = 174) were divided into a total of four groups and received placebo or difelikefalin at different doses: 0.5 µg/kg (n = 44), 1.0 µg/kg (n = 41), or 1.5 µg/kg (n = 44). The substances were administered intravenously after each hemodialysis session 3 times a week for 8 weeks. Participants were asked to complete the questionnaires: WI-NRS (Worst Itching Intensity Numerical Rating Scale); Skindex-10; 5-D itch scale; Medical Outcomes Study sleep disturbance subscale; Patient Global Impression of Worst Itch Severity; and Patient Global Impression of Change [39]. Another randomized, multicenter, double-blind, placebo-controlled phase 2 trial included 247 participants from Japan with moderate to severe pruritus (NCT03802617). Patients were administered placebo or difelikefalin at a dose of 0.25 µg/kg, 0.5 µg/kg or 1.0 µg/kg in the form of intravenous boluses. As in the previous study, the effect of difelikefalin was based on the changes in the weekly mean NRS score. Secondary outcomes included Skindex-16 and the 5-D itch scale [41]. In turn, in a randomized, double-blind, placebo-controlled phase 3 trial (NCT03422653, KALM-1), all participants (n = 378) were divided into two groups: the placebo group (n = 165) and the group receiving difelikefalin at a dose of 0.5 µg/kg (n = 158). Patients were administered either the drug or placebo injection at the end of the hemodialysis session, 3 times per week for 12 weeks. Then, after finishing the treatment protocol, patients were observed for a further 2 weeks to exclude any addictive effect of opioid drug. The results were assessed using the following scales: WI-NRS, Skindex-10, and 5-D itch scale. The safety of difelikefalin in all clinical trials was evaluated on the basis of laboratory tests, vital signs, a 12-lead electrocardiogram, and patient-reported side effects occurring throughout the clinical trial [40].

3.1. Evaluation of Effectiveness of Difelikefalin

The effectiveness of the new drug was evaluated on the basis of the changes in pruritus severity reported by the patients and the assessment of the impact of pruritus on quality of life in its various aspects, including sleep quality.

3.1.1. Effect of Difelikefalin on Pruritus Severity

In all the analyzed studies, difelikefalin significantly reduced the severity of pruritus compared to the control group receiving placebo. In a phase 2 clinical trial among patients receiving difelikefalin, there was a reduction in itching severity of −3.8, −2.8, and −3.2 for a dose of 0.5 µg/kg, 1.0 µg/kg, and 1.5 µg/kg, respectively. The difference was statistically significant in the 0.5 µg/kg ($p < 0.001$) and 1.5 µg/kg ($p = 0.019$) difelikefalin groups. Furthermore, after 8 weeks of treatment, a depletion in pruritus of at least 3 points from baseline on the WI-NRS was reported in 59–64% of patients in groups receiving difelikefalin compared to 29% in the placebo group [39]. In clinical trial conducted in Japan Narita et al. [41] reported a significant reduction in itching on the NRS score at week 8 in the difelikefalin 0.5 and 1.0 µg/kg group (−3.65 and −3.64, respectively) compared to the placebo group (−2.86). An improvement of 3 points from the mean weekly NRS score was seen in 53%, 60%, and 57% for difelikefalin concentrations of 0.25, 0.5, and 1.0 µg/kg, respectively, compared to 50% in the placebo group. A 4-point reduction in the pruritus score occurred in 36% of patients in the placebo group, 34% in the difelikefalin 0.25 µg/kg group, 51% in the difelikefalin 0.5 µg/kg group, and 43% in the difelikefalin 1.0 µg/kg. Only for the 0.5 and 1.0 µg/kg groups was the difference statistically significant [41]. In contrast, in a phase 3 clinical trial from Fishbane et al. [40], the reduction in WI-NRS of 3 or more points after 12 weeks was observed in 49.1% and 27.9% of patients in the difelikefalin and placebo groups, respectively. In turn, an improvement from baseline of at least 4 points

on the WI-NRS scale was reported in 37.1% of patients treated with difelikefalin and 17.9% of participants in the control group.

3.1.2. Effect of Difelikefalin on Itch-Related Quality of Life

Difelikefalin has also been shown to be effective in improving itch-related quality of life. At week 8, the mean total Skindex-10 score reported by Fishbane et al. [39] changed by −16.4 points in the difelikefalin groups and the decrease was twice as high as in placebo group, where the score diminished by −8.2 points ($p < 0.001$). A similar improvement was seen on the 5-D itch scale with a reduction ranging from 4.7 to 5.7 points at week 8 in the difelikefalin groups compared to 2.8 points in the placebo group ($p < 0.001$). After 8 weeks of the Japanese clinical trial, an improvement in the 5-D itch scale total score and Skindex-16 overall score was also shown in all the studied groups [41]. However, the weekly mean reduction of the Skindex-16 overall score differs only for difelikefalin at the dose of 0.5 µg/kg from the placebo group (−27.79 points versus the placebo at −24.04 points). Interestingly, in the final Patient Global Impression of Change at the end of the treatment period, answers "very much improved" or "much improved" were reported by 26 (41.9%) patients in the placebo group. The same degrees of improvement were significantly more frequently marked by participants from the difelikefalin groups (33 (54.1%), 39 (66.1%), and 42 (70%) at doses of 0.25 µg/kg, 0.5 µg/kg, and 1.0 µg/kg, respectively) [41]. In phase 3, after administration of difelikefalin (0.5 µg/kg) at week 12, patients improved from baseline on the Skindex-10 scale by -17.2 ± 1.3 points and on the 5-D itch scale by -5.0 ± 0.3 points. In the placebo group, the mean changes were -12.0 ± 1.2 and -3.7 ± 0.3 points, respectively. The differences were statistically significant with *p*-values less than 0.001. An equally important disturbance aspect in patients with chronic pruritus is sleep quality. Patients in all difelikefalin groups reported an improvement in Itch MOS sleep disturbance by an average of -11.8 ± 2.0 points ($p = 0.005$). In the placebo group, the difference was much less pronounced, at -1.3 ± 3.1 points from the baseline value [39].

3.2. Adverse Effects

The most common adverse effect in all clinical trials was diarrhea, nausea, vomiting, dizziness, fall, and headache. They were usually mild to moderate in intensity. The more severe side effects included somnolence, other mental status changes, hypotension, pneumonia, and sepsis [39–41]. There were also four deaths due to septic shock during the phase 3 studies, but with equal frequency in the placebo group and with difelikefalin 0.5 µg/kg [40]. In a second phase clinical trial by Narita et al. [41] an enhancement in the incidence of side effects has been noticed when increasing the difelikefalin dose. However, a similar dependence did not occur in the study from Fishbane et al. [39], which also investigated different doses of the drug. Nevertheless, in each analyzed study, side effects were more frequently observed after injection of difelikefalin compared to the placebo. Interestingly, in a phase 3 trial, more severe adverse events were similarly common in the placebo and 0.5 µg/kg difelikefalin group [40]. Additionally, after the end of the treatment, no symptoms of physical or psychological dependence on the administered drug were noticed during the two-week observation.

The summary of the data from the analyzed clinical trials is presented in Table 1.

Table 1. Summary of the analyzed clinical trials data.

Title	Fishbane et al. [39]	Narita et al. [41]	Fishbane et al. [40]
Phase	2	2	3
Country	US	Japan	US
Number of patients	175	247	378
Time to end-point	8 weeks	8 weeks	12 weeks
Reserach groups	Placebo (n = 45) Difelikefalin 0.5 µg/kg (n = 44) Difelikefalin 1.0 µg/kg (n = 42) Difelikefalin 1.5 µg/kg (n = 44)	Placebo (n = 63) Difelikefalin 0.25 µg/kg (n = 61) Difelikefalin 0.5 µg/kg (n = 61) Difelikefalin 1.0 µg/kg (n = 62)	Placebo (n = 165) Difelikefalin 0.5 µg/kg (n = 158)
Evaluated parameters	WI-NRS Skindex-10 5-D itch scale Medical Outcomes Study sleep disturbance subscale Patient Global Impression of Worst Itch Severity Patient Global Impression of Change	WI-NRS Skindex-16 5-D itch scale Patient Global Impression of Change	WI-NRS Skindex-10 5-D itch scale
Changes from baseline in WI-NRS			
-reduction of weekly mean WI-NRS	Placebo group: −1.9 Difelikefalin 0.5 µg/kg: −3.8 Difelikefalin 1.0 µg/kg: −2.8 Difelikefalin 1.5 µg/kg: −3.2	Placebo group: −2.86, Difelikefalin 0.25 µg/kg: −2.97 Difelikefalin 0.5 µg/kg: −3.65 Difelikefalin 1.0 µg/kg: −3.64	N/A
-reduction of at least 3 points	Placebo group: 29% Difelikefalin 0.5 µg/kg: 64% Difelikefalin 1.0 µg/kg: N/A Difelikefalin 1.5 µg/kg: 67%	Placebo group: 50% Difelikefalin 0.25 µg/kg: 53% Difelikefalin 0.5 µg/kg: 60% Difelikefalin 1.0 µg/kg: 57%	Placebo group: 27.9% Difelikefalin 0.5 µg/kg: 49.1%
-reduction of at least 4 points	Placebo group: 24% Difelikefalin 0.5 µg/kg: 51% Difelikefalin 1.0 µg/kg: N/A Difelikefalin 1.5 µg/kg: N/A	Placebo group: 36%, Difelikefalin 0.25 µg/kg: 34% Difelikefalin 0.5 µg/kg: 51% Difelikefalin 1.0 µg/kg: 43%	Placebo group: 21.2% Difelikefalin 0.5 µg/kg: 40.5%

Table 1. *Cont.*

Title	Fishbane et al. [39]	Narita et al. [41]	Fishbane et al. [40]
Changes from baseline after treatment in Skindex-10 or Skindex-16 (points)	Placebo group: −8.2 Difelikefalin 0.5 μg/kg: −18.7 Difelikefalin 1.0 μg/kg: −15.5 Difelikefalin 1.5 μg/kg: −15.1	* Placebo group: −24.04 * Difelikefalin 0.25 μg/kg: −24.25 * Difelikefalin 0.5 μg/kg: −27.79 * Difelikefalin 1.0 μg/kg: −22.69	Placebo group: –12.0 Difelikefalin 0.5 μg/kg: −17.2
Changes from baseline after treatment in 5-D itch scale (points)	Placebo group: −2.8 Difelikefalin 0.5 μg/kg: −5.7 Difelikefalin 1.0 μg/kg: −5.4 Difelikefalin 1.5 μg/kg: −4.7	Placebo group: −5.8 Difelikefalin 0.25 μg/kg: −6.6 Difelikefalin 0.5 μg/kg: −6.5 Difelikefalin 1.0 μg/kg: −6.8	Placebo group: –3.7 Difelikefalin 0.5 μg/kg: –5.0
Adverse effects			
-overall incidence	Placebo group: 4 patients (8.9%) Difelikefalin 0.5 μg/kg: 10 patients (22.7%) Difelikefalin 1.0 μg/kg: 6 patients (14.6%) Difelikefalin 1.5 μg/kg: 11 patients (25.0%)	Placebo group: 42 patients (67%) Difelikefalin 0.25 μg/kg: 44 patients (72%), Difelikefalin 0.5 μg/kg: 47 of 61 patients (77%), Difelikefalin 1.0 μg/kg: 53 of 62 patients (85%)	Placebo group: 117 patients (62.2%) Difelikefalin 0.5 μg/kg: 130 patients (68.8%)
-symptoms	Mild: diarrhea, dizziness, nausea, fall, headache More severe: somnolence, abdominal pain, mental status changes	Mild: dizziness, vomiting, nasopharyngitis More severe: somnolence, hypotension	Mild: diarrhea, dizziness, vomiting More severe: hyperkalemia, pneumonia, sepsis, hypotension and chronic obstructive pulmonary disease

(N/A–not available; *—Skindex-16 score).

4. Discussion

Pruritus is defined as an unpleasant sensation that makes you scratch. It is a common symptom of many dermatological diseases, but it can also be associated with systemic disorders, such as liver and chronic kidney diseases, or some neoplastic diseases [43]. In the case of advanced chronic renal failure (stages 3–5), the average incidence is about 45% [44]. Importantly, 18% of dialysis patients say that the severity of itch is "very much" or "extreme", confirming the importance of the problem of pruritus in patients with end-stage CKD and the need to improve pruritus treatment [45].

In the studies analyzed in this review, several scales were used to assess the severity of itching, which allowed to assess the effectiveness of difelikefalin and to compare the results of various studies with each other. Itching is a subjective sensation reported by patients. Many scales have been developed to standardize this symptom and compare the severity of pruritus and its impact on different domains of life in different patient groups, as well as changes in severity over time in the same patient. The primary methods include the itch severity assessment with Numerical Rating Scale (NRS) in which the patient rates itch from 1 point (no itch) to 10 points (worst imaginable pruritus). Based on the score, pruritus is divided into mild (1–3 points), moderate (4–6 points), severe (7–8 points), and very severe (9 points or more) [46]. WI-NRS determines the worst possible itching intensity that patients have experienced. It has been shown to be very easy to use and exhibits a high accuracy and reliability in patients with CKD-aP, as well as with psoriasis or nodular pruritus [47–49]. Therefore, this scale is very willingly used in clinical trials. In the publications analyzed in this review, the authors used WI-NRS to assess the severity of baseline pruritus before treatment and the change in pruritus severity after administration of the study drug. The results are presented as the weekly average of the reported WI-NRS score. Additionally, the percentage of people who improved on this scale by at least 3 or 4 points was compared. However, a single assessment of the severity of itch only does not reflect the significance of the problem of chronic pruritus. Therefore, an additional multi-directional pruritus assessment tool has been developed [7]. The 5-D itch scale (five dimensions: degree, duration, direction, disability, and distribution) assesses not only the severity of the itching but also the duration, changes over time, and its impact on sleep and daily functioning. This scale has been shown to be reliable and appropriate for assessing pruritus in patients with dermatological diseases as well as in patients with chronic kidney disease [50]. Other tools to assess health-related QoL include the multidimensional Skindex-10 and the MOS Sleep Disorder subscale, which again demonstrate high reliability and validity in hemodialysis patients with CKD-aP [51]. Moreover, in a study of 2323 participants with chronic pruritus, individual scales (itch NRS, WI-NRS, and 5-D itch scale) show a significant positive correlation and can be effectively used simultaneously to assess chronic pruritus intensity in clinical trials [52]. Fishbane et al. [39] also emphasized that the reduction in the weekly average of the WI-NRS score after difelikefalin or placebo administration is highly correlated with an improvement in the itch 5-D total score and Skindex-10 score, where the Pearson's correlation coefficient (r) was set at 0.71 and 0.67, respectively [39].

In recent years, numerous clinical trials have been conducted to evaluate the efficacy and safety of difelikefalin in patients with persistent pruritus. Most of them are related to CKD-aP. A total of 13 clinical trials have been performed or are currently ongoing in patients with CKD undergoing hemodialysis [53–64]. The effect of this drug in reducing itching in patients with cholestatic or atopic dermatitis-related pruritus is also being investigated [65,66]. Table 2 presents a summary of clinical trials along with their brief characteristics.

Table 2. Clinical trials of difelikefalin conducted in patients with pruritus (N/A—not available; table created on the basis of data available on the website https://www.clinicaltrials.gov/ [67]).

Title	ClinicalTrials.Gov Identifier	Condition	Phase	Status	Number of Participants	Dose of Difelikefalin	Year
Safety and Pharmacokinetics of IV CR845 in Hemodialysis Patients, and Its Efficacy in Patients With Uremic Pruritus	NCT02229929	CKD-aP	2	Completed	89	0.5 µg, 1.0 µg, or 2.5 µg/kg administered after each dialysis session over a 1 week treatment period (3 times/week)	2014–2016
Study to Evaluate IV CR845 in Hemodialysis Patients With Moderate-to-Severe Pruritus	NCT02858726	CKD-aP	2/3	Completed	226	0.5 µg, 1.0 µg, or 1.5 µg/kg administered after each dialysis session (3 times/week)	2016–2018
Extension Study to Evaluate IV CR845 in Hemodialysis Patients With Moderate-to-Severe Pruritus	NCT03281538	CKD-aP	3	Completed	288	0.5 µg/kg administered after each dialysis session (3 times/week)	2017–2021
A Study to Evaluate the Safety and Efficacy of CR845 in Chronic Kidney Disease Patients With Moderate-to-Severe Pruritus	NCT03617536	CKD-aP	2	Completed	271	0.25, 0.5 or 1 mg; oral; once a day	2018–2020
A Study to Evaluate the Safety and Efficacy of CR845 in Hemodialysis Patients With Moderate-to-Severe Pruritus (KALM-1)	NCT03422653	CKD-aP	3	Completed	378	0.5 µg/kg administered after each dialysis session (3 times/week)	2018–2020
CR845-CLIN3103: A Global Study to Evaluate the Safety and Efficacy of CR845 in Hemodialysis Patients With Moderate-to-Severe Pruritus	NCT03636269	CKD-aP	3	Completed	474	0.5 µg/kg administered after each dialysis session (3 times/week)	2018–2021
CR845-CLIN3105: A Study to Evaluate the Safety and Effectiveness of CR845 in Hemodialysis Patients With Moderate-to-Severe Pruritus	NCT03998163	CKD-aP	3	Completed	222	0.5 µg/kg administered after each dialysis session (3 times/week)	2019–2021
A Clinical Study of MR13A9 in Hemodialysis Patients With Pruritus	NCT03802617	CKD-aP	2	Completed	247	0.25 mg, 0.5 mg, or 1.0 mg/kg administered after each dialysis session (3 times/week)	2019–2019
Study to Evaluate the Pharmacokinetics and Metabolism of [14C] CR845 (Difelikefalin) in Patients With End Stage Renal Disease on Hemodialysis and in Healthy Subjects	NCT03947970	Healthy and hemodialysis patients	1	Completed	12	intravenous bolus-the total dose of CR845 will range from 1.7 to 3.1 µg/kg	2019–2019

Table 2. *Cont.*

Title	ClinicalTrials.Gov Identifier	Condition	Phase	Status	Number of Participants	Dose of Difelikefalin	Year
Intermediate-Size Patient Population Expanded Access Program for Intravenous Difelikefalin	NCT05031546	CKD-aP	N/A	Available	N/A Expanded Access to Treatmend	0.5 µg kg administered after each dialysis session (3 times/week)	2021-
A Phase III Clinical Study of MR13A9 in Hemodialysis Patients With Pruritus	NCT04711603	CKD-aP	3	Active, not recruiting	172	dose undefined, administered after each dialysis session (3 times/week)	2021-
Study to Evaluate the Efficacy and Safety of Oral Difelikefalin (CR845) for Moderate to Severe Pruritus in Subjects With Notalgia Paresthetica (KOMFORT)	NCT04706975	CKD-aP and notalgia paresthetica	2	Recruiting	120	2.0 mg; oral; twice a day	2021-
A Study to Evaluate the Safety and Efficacy of Difelikefalin in Advanced Chronic Kidney Disease Patients With Moderate-to-Severe Pruritus and Not on Dialysis	NCT05342623	CKD-aP	3	Before recruiting	400	1.0 mg; oral; once a day	2022-
Study to Evaluate the Efficacy and Safety of Oral Difelikefalin (CR845) for Moderate to Severe Pruritus in Subjects With Atopic Dermatitis	NCT04018027	Atopic Dermatitis associated pruritus	2	Completed	401	0.25 mg, 0.5 mg, or 1.0 mg, oral; twice a day	2019–2022
Study to Evaluate the Safety and Efficacy of Oral CR845 (Difelikefalin) in Patients With Primary Biliary Cholangitis (PBC) and Moderate-to-Severe Pruritus	NCT03995212	Cholestatic Pruritus	2	Recruiting	60	1.0 mg; oral; twice a day	2019–2021

In the clinical trials analyzed in this review, difelikefalin was administered by intravenous injection at doses of 0.25–1.5 μg/kg three times per week on dialysis days. The available research results from a phase 2 clinical trial show no statistically significant improvement with difelikefalin at a dose of 0.25 μg/kg compared to the placebo group. In turn, the effectiveness of difelikefalin at a dose of 0.5, 1.0, and 1.5 μg/kg was comparable in both studies of the second phase. No explicit results indicating an enhancement in the frequency of side effects with increasing doses of the drug have been seen. Incidence of side effects in dose-dependent manner was found in only one analyzed study [41]. However, Fishbane et al. [39] reported a similar frequency of adverse events in all difelikefalin groups. In turn, in a randomized, double-blinded, placebo-controlled trial in healthy volunteers, difelikefalin in doses up to 4 μg/kg was well tolerated. The incidence of side effects such as paresthaesia, dizziness, fatigue, or nausea was dose dependent, but even at the highest dose these events were mild in intensity [68]. Studies in CKD-aP patients have not shown any superiority in the use of difelikefalin at doses greater than 0.5 μg/kg, with a comparable or even greater risk of side effects. Therefore, in phase 3 clinical trials, the 0.5 μg/kg dose of difelikefalin is most commonly used to further evaluate the efficacy and safety of this drug in a larger population and over a longer period of time [40,55,56,59].

Despite the fact that some studies are completed, their results have not been published so far. Nevertheless, a few studies are available in the form of conference abstracts. This applies, among others, to the KALM-2 study, the results of which were important for the approval of difelikefalin by the FDA for clinical use [69]. The published results of phase 2 and 3 studies have already confirmed both the efficacy and safety of difelikefalin in patients with end-stage renal disease undergoing hemodialysis. However, the duration of the studies analyzed was a maximum of 12 weeks [39–41]. In turn, a randomized, multicenter, placebo-controlled phase 3 study (KALM-2) enrolled 473 participants and showed good tolerance with an acceptable long-term safety profile during the 52-week study [69]. In August 2021, the FDA approved the use of difelikefalin (under the trade name Korsuva) for the treatment of CKD-aP in adult hemodialysis patients. Thus, this drug became the first substance specifically indicated for the treatment of uremic pruritus [37]. Subsequently, in April 2022, EMA also approved the use of difelikefalin (trade name: Kapruvia) for the treatment of moderate to severe pruritus in dialysis patients in EU countries [70]. Both the FDA and EMA have approved the use of difelikefalin at a dose of 0.5 μg/kg dry weight administered as an intravenous injection at the end of a hemodialysis session. However, the results of ongoing studies evaluating the efficacy of oral administration of difelikefalin at doses of 0.25, 0.5, 1.0, or 2.0 mg per day in the treatment of CKD-aP are also awaited [60,63,64]. Importantly, with the documented efficacy and safety of the oral form of the drug, this method of administering difelikefalin would be much more favorable in patients with CKD-aP, but not requiring dialysis.

The most common side effects of difelikefalin reported in clinical trials were mild and included nausea, vomiting, diarrhea, dizziness, and headache. In the phase 3 of the clinical trial, no symptoms of drug addiction were observed for 2 weeks of follow-up after the end of treatment [40]. Interestingly, another study also showed that even many times higher doses (5 and 15 μg/kg) of difelikefalin have a low addictive potential [36]. Moreover, unlike other opioid drugs, such as nalbuphine or nalfurafine, difelikefalin has limited penetration into the CNS. In a phase 3 clinical trial with nalfurafine, a centrally acting selective KOR activator, insomnia was observed much more often compared to the difelikefalin trials, and was the most frequently reported symptom [32]. None of the analyzed studies in this article reported a depressive effect of difelikefalin on the respiratory system, which is major limitation in the use of centrally acting opioids [39–41]. Therefore, difelikefalin, as new drug that selectively acts on peripheral KOR, has a more favorable safety profile compared to the other opioid agents. In clinical trials investigating the analgesic efficacy and safety profile of difelikefalin at a dose of 5 μg/kg, the most common side effects were headache and dizziness; no serious side effects were observed [71]. Importantly, in studies on the effectiveness of difelikefalin in patients with CKD-aP, even after the administration of a

low dose of 0.5 μg/kg, statistically significant better results were obtained compared to the placebo group. As mentioned above, higher doses of difelikefalin (up to 1.5 μg/kg) did not show any advantage over the dose of 0.5 μg/kg. This may be the reason why there are no clinical trials testing this drug at much higher doses; for example, those used to relieve pain.

Limitation of the Study

A significant limitation of this systematic review was the lack of access to the results of completed trials; however, these are not yet published. In addition, the interpretation and comparison of the results of studies conducted in different countries, i.e., among other populations with different access to treatment (for example, the use of nalfurafine in the treatment of CKD-aP only in Japan, or different preferences for dialysis methods used), may lead to misleading conclusions. Furthermore, data on the efficacy of difelikefalin in the treatment of CKD-aP are limited to a small dose range (0.25–1.5 μg/kg). The efficacy of difelikefalin at higher doses in patients with CKD-aP has not been analyzed.

5. Conclusions

Our systematic review shows that difelikefalin, due to its efficacy and good safety profile, can be regarded as the primary treatment for pruritus in patients with chronic kidney disease. Research on this subject should be continued to evaluate the long-term effects of difelikefalin administration.

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References

1. Metzger, M.; Abdel-Rahman, E.M.; Boykin, H.; Song, M.-K. A Narrative Review of Management Strategies for Common Symptoms in Advanced CKD. *Kidney Int. Rep.* **2021**, *6*, 894–904. [CrossRef] [PubMed]
2. Nair, D.; Finkelstein, F.O. Pruritus as a Patient-Reported Primary Trial End Point in Hemodialysis: Evaluation and Implications. *Am. J. Kidney Dis.* **2020**, *76*, 148–151. [CrossRef] [PubMed]
3. Makar, M.; Smyth, B.; Brennan, F. Chronic Kidney Disease-Associated Pruritus: A Review. *Kidney Blood Press. Res.* **2021**, *46*, 659–669. [CrossRef] [PubMed]
4. Agarwal, P.; Garg, V.; Karagaiah, P.; Szepietowski, J.C.; Grabbe, S.; Goldust, M. Chronic Kidney Disease-Associated Pruritus. *Toxins* **2021**, *13*, 527. [CrossRef] [PubMed]
5. Kim, D.; Pollock, C. Epidemiology and Burden of Chronic Kidney Disease-Associated Pruritus. *Clin. Kidney J.* **2021**, *14*, i1–i7. [CrossRef] [PubMed]
6. Reszke, R.; Szepietowski, J.C. End-Stage Renal Disease Chronic Itch and Its Management. *Dermatol. Clin.* **2018**, *36*, 277–292. [CrossRef]
7. Verduzco, H.A.; Shirazian, S. CKD-Associated Pruritus: New Insights Into Diagnosis, Pathogenesis, and Management. *Kidney Int. Rep.* **2020**, *5*, 1387. [CrossRef]
8. Martin, C.E.; Clotet-Freixas, S.; Farragher, J.F.; Hundemer, G.L. Have We Just Scratched the Surface? A Narrative Review of Uremic Pruritus in 2020. *Can. J. Kidney Health Dis.* **2020**, *7*, 2054358120954024. [CrossRef]

9. Urbonas, A.; Schwartz, R.A.; Szepietowski, J.C. Uremic Pruritus—An Update. *Am. J. Nephrol.* **2001**, *21*, 343–350. [CrossRef]
10. Simonsen, E.; Komenda, P.; Lerner, B.; Askin, N.; Bohm, C.; Shaw, J.; Tangri, N.; Rigatto, C. Treatment of Uremic Pruritus: A Systematic Review. *Am. J. Kidney Dis.* **2017**, *70*, 638–655. [CrossRef]
11. Seckin, D.; Demircay, Z.; Akin, O. Generalized Pruritus Treated with Narrowband UVB. *Int. J. Dermatol.* **2007**, *46*, 367–370. [CrossRef] [PubMed]
12. Gilchrest, B.A. Ultraviolet Phototherapy of Uremic Pruritus. *Int. J. Dermatol.* **1979**, *18*, 741–748. [CrossRef] [PubMed]
13. Hsu, M.M.L.; Yang, C.C. Uraemic Pruritus Responsive to Broadband Ultraviolet (UV) B Therapy Does Not Readily Respond to Narrowband UVB Therapy. *Br. J. Dermatol.* **2003**, *149*, 888–889. [CrossRef] [PubMed]
14. Ko, M.J.; Yang, J.Y.; Wu, H.Y.; Hu, F.C.; Chen, S.I.; Tsai, P.J.; Jee, S.H.; Chiu, H.C. Narrowband Ultraviolet B Phototherapy for Patients with Refractory Uraemic Pruritus: A Randomized Controlled Trial. *Br. J. Dermatol.* **2011**, *165*, 633–639. [CrossRef]
15. Mettang, T.; Kremer, A.E. Uremic Pruritus. *Kidney Int.* **2015**, *87*, 685–691. [CrossRef]
16. Reich, A.; Szepietowski, J.C. Opioid-Induced Pruritus: An Update. *Clin. Exp. Dermatol.* **2010**, *35*, 2–6. [CrossRef]
17. Wieczorek, A.; Krajewski, P.; Kozioł-Gałczyńska, M.; Szepietowski, J.C. Opioid Receptors Expression in the Skin of Haemodialysis Patients Suffering from Uraemic Pruritus. *J. Eur. Acad. Dermatol. Venereol.* **2020**, *34*, 2368–2372. [CrossRef] [PubMed]
18. Terg, R.; Coronel, E.; Sordá, J.; Muñoz, A.E.; Findor, J. Efficacy and Safety of Oral Naltrexone Treatment for Pruritus of Cholestasis, a Crossover, Double Blind, Placebo-Controlled Study. *J. Hepatol.* **2002**, *37*, 717–722. [CrossRef]
19. Wolfhagen, F.H.J.; Sternieri, E.; Hop, W.C.J.; Vitale, G.; Bertolotti, M.; van Buuren, H.R. Oral Naltrexone Treatment for Cholestatic Pruritus: A Double-Blind, Placebo-Controlled Study. *Gastroenterology* **1997**, *113*, 1264–1269. [CrossRef]
20. Bergasa, N.V.; Ailing, D.W.; Talbot, T.L.; Swain, M.G.; Yurdaydin, C.; Turner, M.L.; Schmitt, J.M.; Walker, E.C.; Jones, E.A. Effects of Naloxone Infusions in Patients with the Pruritus of Cholestasis. A Double-Blind, Randomized, Controlled Trial. *Ann. Intern. Med.* **1995**, *123*, 161–167. [CrossRef]
21. Pauli-Magnus, C.; Mikus, G.; Alscher, D.M.; Kirschner, T.; Nagel, W.; Gugeler, N.; Risler, T.; Berger, E.D.; Kuhlmann, U.; Mettang, T. Naltrexone Does Not Relieve Uremic Pruritus: Results of a Randomized, Double-Blind, Placebo-Controlled Crossover Study. *J. Am. Soc. Nephrol.* **2000**, *11*, 514–519. [CrossRef] [PubMed]
22. Phan, N.Q.; Bernhard, J.D.; Luger, T.A.; Ständer, S. Antipruritic Treatment with Systemic μ-Opioid Receptor Antagonists: A Review. *J. Am. Soc. Nephrol.* **2010**, *63*, 680–688. [CrossRef]
23. Antal, A.S.; Bernhard, J.; Ständer, S. Systemic Kappa Opioid Receptor Agonists in the Treatment of Chronic Pruritus: A Literature Review. *Acta Derm. Venereol.* **2012**, *92*, 555–560. [CrossRef]
24. Lazenka, M.L.; Moerke, M.J.; Townsend, E.A.; Freeman, K.B.; Carroll, F.I.; Negus, S.S. Dissociable Effects of the Kappa Opioid Receptor Agonist Nalfurafine on Pain/Itch-Stimulated and Pain/Itch-Depressed Behaviors in Male Rats. *Psychopharmacology* **2017**, *235*, 203–213. [CrossRef]
25. Jain, M.R.; Patel, R.B.; Prajapati, K.D.; Vyas, P.; Bandyopadhyay, D.; Prajapati, V.; Bahekar, R.; Patel, P.N.; Kawade, H.M.; Kokare, D.M.; et al. ZYKR1, a Novel, Potent, and Peripherally Selective Kappa Opioid Receptor Agonist Reduces Visceral Pain and Pruritus in Animal Models. *Eur. J. Pharmacol.* **2022**, *924*, 174961. [CrossRef]
26. Inan, S.; Dun, N.J.; Cowan, A. Antipruritic Effect of Nalbuphine, a Kappa Opioid Receptor Agonist, in Mice: A Pan Antipruritic. *Molecules* **2021**, *26*, 5517. [CrossRef]
27. Togashi, Y.; Umeuchi, H.; Okano, K.; Ando, N.; Yoshizawa, Y.; Honda, T.; Kawamura, K.; Endoh, T.; Utsumi, J.; Kamei, J.; et al. Antipruritic Activity of the κ-Opioid Receptor Agonist, TRK-820. *Eur. J. Pharmacol.* **2002**, *435*, 259–264. [CrossRef]
28. Nakao, K.; Hirakata, M.; Miyamoto, Y.; Kainoh, M.; Wakasa, Y.; Yanagita, T. Nalfurafine Hydrochloride, a Selective κ Opioid Receptor Agonist, Has No Reinforcing Effect on Intravenous Self-Administration in Rhesus Monkeys. *J. Pharmacol. Sci.* **2016**, *130*, 8–14. [CrossRef]
29. Ueno, Y.; Mori, A.; Yanagita, T. One Year Long-Term Study on Abuse Liability of Nalfurafine in Hemodialysis Patients. *Int. J. Clin. Pharmacol. Ther.* **2013**, *51*, 823–831. [CrossRef] [PubMed]
30. Miyamoto, Y.; Oh, T.; Aihara, E.; Ando, A. Clinical Profiles of Nalfurafine Hydrochloride for the Treatment of Pruritus Patients. *Handb. Exp. Pharmacol.* **2022**, *271*, 455–472. [CrossRef]
31. Weisshaar, E.; Szepietowski, J.C.; Bernhard, J.D.; Hait, H.; Legat, F.J.; Nattkemper, L.; Reich, A.; Sadoghi, B.; Sciascia, T.R.; Zeidler, C.; et al. Efficacy and Safety of Oral Nalbuphine Extended Release in Prurigo Nodularis: Results of a Phase 2 Randomized Controlled Trial with an Open-Label Extension Phase. *J. Eur. Acad. Dermatol. Venereol.* **2022**, *36*, 453–461. [CrossRef]
32. Kumagai, H.; Ebata, T.; Takamori, K.; Muramatsu, T.; Nakamoto, H.; Suzuki, H. Effect of a Novel Kappa-Receptor Agonist, Nalfurafine Hydrochloride, on Severe Itch in 337 Haemodialysis Patients: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study. *Nephrol. Dial. Transplant.* **2010**, *25*, 1251–1257. [CrossRef]
33. Pilla, J.E.; Devulapally, P. *Difelikefalin*; StatPearls: Treasure Island, FL, USA, 2021.
34. Shirazian, S.; Spencer, R.; Kilfeather, S. Reduction of Pruritus by Difelikefalin Correlates With Reductions in Markers for Pruritus and Inflammation in Subjects Undergoing Hemodialysis. *Am. J. Kidney Dis.* **2022**, *79*, S42.
35. Viscusi, E.R.; Torjman, M.C.; Munera, C.L.; Stauffer, J.W.; Setnik, B.S.; Bagal, S.N. Effect of Difelikefalin, a Selective Kappa Opioid Receptor Agonist, on Respiratory Depression: A Randomized, Double-Blind, Placebo-Controlled Trial. *J. Clin. Transl. Sci.* **2021**, *14*, 1886–1893. [CrossRef]

36. Shram, M.J.; Spencer, R.H.; Qian, J.; Munera, C.L.; Lewis, M.E.; Henningfield, J.E.; Webster, L.; Menzaghi, F. Evaluation of the Abuse Potential of Difelikefalin, a Selective Kappa-Opioid Receptor Agonist, in Recreational Polydrug Users. *J. Clin. Transl. Sci.* **2022**, *15*, 535–547. [CrossRef]
37. Deeks, E.D. Difelikefalin: First Approval. *Drugs* **2021**, *81*, 1937–1944. [CrossRef] [PubMed]
38. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. *BMJ* **2021**, *372*, 89. [CrossRef]
39. Fishbane, S.; Mathur, V.; Germain, M.J.; Shirazian, S.; Bhaduri, S.; Munera, C.; Spencer, R.H.; Menzaghi, F.; Aaronson, M.; Alford, K.; et al. Randomized Controlled Trial of Difelikefalin for Chronic Pruritus in Hemodialysis Patients. *Kidney Int. Rep.* **2020**, *5*, 600–610. [CrossRef]
40. Fishbane, S.; Jamal, A.; Munera, C.; Wen, W.; Menzaghi, F. A Phase 3 Trial of Difelikefalin in Hemodialysis Patients with Pruritus. *N. Engl. J. Med.* **2020**, *382*, 222–232. [CrossRef] [PubMed]
41. Narita, I.; Tsubakihara, Y.; Uchiyama, T.; Okamura, S.; Oya, N.; Takahashi, N.; Gejyo, F.; Yamamoto, A.; Ichikawa, A.; Ohishi, A.; et al. Efficacy and Safety of Difelikefalin in Japanese Patients With Moderate to Severe Pruritus Receiving Hemodialysis: A Randomized Clinical Trial. *JAMA Netw. Open* **2022**, *5*, e2210339. [CrossRef]
42. McGuinness, L.A.; Higgins, J.P.T. Risk-of-bias VISualization (Robvis): An R Package and Shiny Web App for Visualizing Risk-of-bias Assessments. *Res. Syn. Meth.* **2020**, *12*, 55–61. [CrossRef] [PubMed]
43. Hashimoto, T.; Yosipovitch, G. Itching as a Systemic Disease. *J. Allergy Clin. Immunol.* **2019**, *144*, 375–380. [CrossRef] [PubMed]
44. Kimata, N.; Fuller, D.S.; Saito, A.; Akizawa, T.; Fukuhara, S.; Pisoni, R.L.; Robinson, B.M.; Akiba, T. Pruritus in Hemodialysis Patients: Results from the Japanese Dialysis Outcomes and Practice Patterns Study (JDOPPS). *Hemodial. Int.* **2014**, *18*, 657–667. [CrossRef]
45. Rayner, H.C.; Larkina, M.; Wang, M.; Graham-Brown, M.; van der Veer, S.N.; Ecder, T.; Hasegawa, T.; Kleophas, W.; Bieber, B.A.; Tentori, F.; et al. International Comparisons of Prevalence, Awareness, and Treatment of Pruritus in People on Hemodialysis. *Clin. J. Am. Soc. Nephrol. CJASN* **2017**, *12*, 2000–2007. [CrossRef]
46. Lai, J.W.; Chen, H.C.; Chou, C.Y.; Yen, H.R.; Li, T.C.; Sun, M.F.; Chang, H.H.; Huang, C.C.; Tsai, F.J.; Tschen, J.; et al. Transformation of 5-D Itch Scale and Numerical Rating Scale in Chronic Hemodialysis Patients. *BMC Nephrol.* **2017**, *18*, 1–5. [CrossRef] [PubMed]
47. Vernon, M.K.; Swett, L.L.; Speck, R.M.; Munera, C.; Spencer, R.H.; Wen, W.; Menzaghi, F. Psychometric Validation and Meaningful Change Thresholds of the Worst Itching Intensity Numerical Rating Scale for Assessing Itch in Patients with Chronic Kidney Disease-Associated Pruritus. *J. Patient-Rep. Outcomes* **2021**, *5*, 1–12. [CrossRef]
48. Kimel, M.; Zeidler, C.; Kwon, P.; Revicki, D.; Ständer, S. Validation of Psychometric Properties of the Itch Numeric Rating Scale for Pruritus Associated With Prurigo Nodularis: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Dermatol.* **2020**, *156*, 1354–1358. [CrossRef]
49. Naegeli, A.N.; Flood, E.; Tucker, J.; Devlen, J.; Edson-Heredia, E. The Worst Itch Numeric Rating Scale for Patients with Moderate to Severe Plaque Psoriasis or Psoriatic Arthritis. *Int. J. Dermatol.* **2015**, *54*, 715–722. [CrossRef]
50. Elman, S.; Hynan, L.S.; Gabriel, V.; Mayo, M.J. The 5-D Itch Scale: A New Measure of Pruritus. *Br. J. Dermatol.* **2010**, *162*, 587–593. [CrossRef]
51. Mathur, V.S.; Lindberg, J.; Germain, M.; Block, G.; Tumlin, J.; Smith, M.; Grewal, M.; McGuire, D. A Longitudinal Study of Uremic Pruritus in Hemodialysis Patients. *Clin. J. Am. Soc. Nephrol. CJASN* **2010**, *5*, 1410. [CrossRef]
52. Cheung, H.N.; Chan, Y.S.; Hsiung, N.H. Validation of the 5-D Itch Scale in Three Ethnic Groups and Exploring Optimal Cutoff Values Using the Itch Numerical Rating Scale. *Biomed. Res. Int.* **2021**, *2021*, 7640314. [CrossRef] [PubMed]
53. A Phase III Clinical Study of MR13A9 in Hemodialysis Patients with Pruritus. Available online: https://www.clinicaltrials.gov/ct2/show/NCT04711603?term=mr13a9&draw=2&rank=1 (accessed on 22 May 2022).
54. A Clinical Study of MR13A9 in Hemodialysis Patients with Pruritus. Available online: https://www.clinicaltrials.gov/ct2/show/NCT03802617?term=mr13a9&draw=2&rank=2 (accessed on 22 May 2022).
55. CR845-CLIN3103: A Global Study to Evaluate the Safety and Efficacy of CR845 in Hemodialysis Patients with Moderate-to-Severe Pruritus. Available online: https://www.clinicaltrials.gov/ct2/show/NCT03636269?term=difelikefalin&draw=2&rank=10 (accessed on 22 May 2022).
56. Extension Study to Evaluate IV CR845 in Hemodialysis Patients with Moderate-to-Severe Pruritus. Available online: https://www.clinicaltrials.gov/ct2/show/NCT03281538?term=difelikefalin&draw=2&rank=14 (accessed on 22 May 2022).
57. Study to Evaluate IV CR845 in Hemodialysis Patients with Moderate-to-Severe Pruritus. Available online: https://www.clinicaltrials.gov/ct2/show/NCT02858726?term=difelikefalin&draw=2&rank=13 (accessed on 22 May 2022).
58. A Study to Evaluate the Safety and Efficacy of CR845 in Hemodialysis Patients with Moderate-to-Severe Pruritus (KALM-1). Available online: https://www.clinicaltrials.gov/ct2/show/NCT03422653?term=difelikefalin&draw=2&rank=12 (accessed on 22 May 2022).
59. CR845-CLIN3105: A Study to Evaluate the Safety and Effectiveness of CR845 in Hemodialysis Patients with Moderate-to-Severe Pruritus. Available online: https://www.clinicaltrials.gov/ct2/show/NCT03998163?term=difelikefalin&draw=2&rank=11 (accessed on 22 May 2022).

60. A Study to Evaluate the Safety and Efficacy of CR845 in Chronic Kidney Disease Patients with Moderate-to-Severe Pruritus. Available online: https://www.clinicaltrials.gov/ct2/show/NCT03617536?term=difelikefalin&draw=2&rank=9 (accessed on 22 May 2022).
61. Study to Evaluate the Pharmacokinetics and Metabolism of [14C] CR845 (Difelikefalin) in Patients with End Stage Renal Disease on Hemodialysis and in Healthy Subjects. Available online: https://www.clinicaltrials.gov/ct2/show/NCT03947970?term=difelikefalin&draw=2&rank=8 (accessed on 22 May 2022).
62. Intermediate-Size Patient Population Expanded Access Program for Intravenous Difelikefalin. Available online: https://www.clinicaltrials.gov/ct2/show/NCT05031546?term=difelikefalin&draw=2&rank=4 (accessed on 22 May 2022).
63. A Study to Evaluate the Safety and Efficacy of Difelikefalin in Advanced Chronic Kidney Disease Patients with Moderate-to-Severe Pruritus and Not on Dialysis. Available online: https://www.clinicaltrials.gov/ct2/show/NCT05342623?term=difelikefalin&draw=2&rank=2 (accessed on 22 May 2022).
64. Study to Evaluate the Efficacy and Safety of Oral Difelikefalin (CR845) for Moderate to Severe Pruritus in Subjects with Notalgia Paresthetica (KOMFORT). Available online: https://www.clinicaltrials.gov/ct2/show/NCT04706975?term=difelikefalin&draw=2&rank=1 (accessed on 22 May 2022).
65. Study to Evaluate the Safety and Efficacy of Oral CR845 (Difelikefalin) in Patients with Primary Biliary Cholangitis (PBC) and Moderate-to-Severe Pruritus. Available online: https://www.clinicaltrials.gov/ct2/show/NCT03995212?term=difelikefalin&draw=2&rank=7 (accessed on 22 May 2022).
66. Study to Evaluate the Efficacy and Safety of Oral Difelikefalin (CR845) for Moderate to Severe Pruritus in Subjects with Atopic Dermatitis. Available online: https://www.clinicaltrials.gov/ct2/show/NCT04018027?term=difelikefalin&draw=2&rank=5 (accessed on 22 May 2022).
67. Home-ClinicalTrials.Gov. Available online: https://www.clinicaltrials.gov/ (accessed on 22 May 2022).
68. Little, P.J. Peripherally Restricted Opioid Analgesics. *ACS Symp. Ser.* **2013**, *1131*, 201–222. [CrossRef]
69. Fishbane, S.; Wen, W.; Munera, C.; Menzaghi, F. Long-Term Safety and Efficacy of Difelikefalin in Patients With Chronic Kidney Disease–Associated Pruritus: Analysis From KALM-1 and KALM-2. *Am. J. Kidney Dis.* **2021**, *77*, 593–594. [CrossRef]
70. Kapruvia | European Medicines Agency. Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/kapruvia (accessed on 22 May 2022).
71. Harden, R.; Burns, J.; Connolly, S.; Kirsling, A.; Abousaad, E.; Khoury, A.; Walega, D. (422) CR845, a Peripheral Kappa Opioid, Provides Better Pain Relief with Less Nausea and Vomiting than Placebo in Patients after Bunionectomy. *J. Pain* **2015**, *16*, S81. [CrossRef]

5. ARTYKUŁ DRUGI

Elevated level of serum neurotrophin-4, but not of brain-derived neurotrophic factor, in patients with chronic kidney disease-associated pruritus

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Elevated Level of Serum Neurotrophin-4, but Not of Brain-Derived Neurotrophic Factor, in Patients with Chronic Kidney Disease-Associated Pruritus

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Abstract: Chronic kidney disease-associated pruritus (CKD-aP) is a bothersome condition that occurs in patients with advanced chronic kidney disease (CKD) and severely reduces their quality of life. Recently, much research has focused on the search for markers that are involved in the pathogenesis of CKD-aP and may become a therapeutic target. One of the suggested hypotheses is the increased activation of sensory neurons by molecules such as neurotrophins (NTs). An increased serum concentration of NTs has been demonstrated in pruritic patients, which may suggest their involvement in the pathogenesis of itch. The purpose of this study is to assess the serum concentration of neurotrophin-4 (NT-4) and brain-derived neurotrophic factor (BDNF) in hemodialysis patients. The study enrolled 126 patients undergoing dialysis. Participants were divided into 2 groups: with and without CKD-aP. NRS scale was used to evaluate itch severity. Serum levels of NT-4 and BDNF have been assessed using ELISA. The results showed a significantly higher level of NT-4 in the group with pruritus. No significant difference was reported in the serum level of BDNF between the two groups of patients. There was also no correlation between serum NT-4 nor BDNF levels and the severity of pruritus. In summary, NT-4 may play an important role in the pathophysiology of pruritus in dialysis patients. More research is needed to understand the exact mechanism by which NTs influence the pathogenesis of CKD-aP.

Keywords: neurotrophin-4; brain-derived neurotrophic factor; pruritus; chronic itch; chronic kidney disease; chronic kidney disease-associated pruritus

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1. Introduction

Chronic itch (CI) is an inconvenient sensation on the skin causing a constant urge to scratch, that lasts more than 6 weeks and remains a serious therapeutic problem for both patients and physicians [1]. It is one of the primary symptoms in dermatological diseases, but it can also accompany systemic disorders such as cholestasis, hematological neoplasms, and advanced chronic kidney disease [1,2]. Depending on the underlying disease, the mechanism responsible for the perception of pruritus is different, but most often the etiology is multifactorial [2]. Chronic kidney disease-associated pruritus (CKD-aP) is defined as a burdensome condition affecting mainly patients with advanced stages of kidney disease, the occurrence of which is associated with worse medical outcomes and higher mortality [3]. According to the Dialysis Outcomes and Practice Patterns Study report, the prevalence of at least moderate CKD-aP in hemodialysis patients is 37% [4]. Despite the growing awareness of CKD-aP, the condition is still often underdiagnosed [5]. The literature mentions numerous hypotheses concerning the pathogenesis of CI in this group of patients, however, its etiology remains unclear. The suggested causes include the influence of uremic toxins, disbalance in calcium and phosphorous metabolism, hyperparathyroidism, xerosis, imbalance of opioid transmission as well as dysfunction of the neuronal and immune

systems [5–9]. It is supposed that the interaction between the skin and the peripheral nervous system, which conducts afferent impulses to the central nervous system, is of great importance [10]. More and more itch mediators are known that can stimulate the nerve endings in the dermis. This mechanism involves skin cells, which actively participate in the synthesis and release of neurotransmitters, cytokines, cannabinoids, endogenous opioids, and other factors that activate receptors on peripheral nerve endings [2]. Importantly, the pathophysiology of CI most often involves multiple interacting mediators rather than a single disease-specific stimulant [2]. Due to the unknown cause of CKD-aP, effective therapy for this condition is a major challenge. Moreover, antihistamines commonly used in the treatment of chronic itch do not bring significant improvement in patients with CKD-aP [11]. Current methods include UVB phototherapy, topical treatment with capsaicin, 10% urea, or tacrolimus, as well as moisturizing therapy to maintain proper skin hydration. Systemic drugs such as pregabalin, gabapentin, sertraline, and opioid agonists, including recently approved difelikefalin have also been shown to be effective [1,6,12,13]. However, considering the fact that dialysis patients often suffer from moderate to severe pruritus, current treatment options for CKD-aP are still insufficient [11].

Neurotrophins (NTs) are growth factors that ensure the proper functioning of neurons. Both neurotrophin-4 (NT-4) and brain-derived neurotrophic factor (BDNF) are proteins belonging to the NTs family, responsible for the proliferation, maturation, and differentiation of nerve cells [14]. They also provide increased plasticity of neurons and their resistance to damage, and inhibit pathways that promote apoptosis, thus allowing nerve cells to survive under conditions of increased oxidative stress [14,15]. NT-4 and BDNF share common receptors and act on the tyrosine kinase B receptor (TrkB) with low affinity on the p75 neurotrophin receptor [16]. Reduced BDNF concentration in the central nervous system has been observed in neurodegenerative diseases such as Parkinson's disease and multiple sclerosis [17]. In addition to the central and peripheral nervous systems, receptors for these proteins are expressed and have important functions in other tissues and organs such as the heart, lungs, kidneys, muscles, and skin [18]. The role of neurotrophins in the proper functioning of the skin and the pathophysiology of skin diseases is being constantly studied. It has been found that the nerve growth factors found in the skin promote the proliferation of keratinocytes, regulate hair growth, and the survival of melanocytes [10]. The involvement of these factors has also been noticed in pathological conditions of the skin with inflammation, such as psoriasis or atopic dermatitis as well as in melanoma [10,19]. Moreover, reports are suggesting the involvement of NTs in the pathogenesis of pruritus [20,21]. NTs are suspected to be involved in the interactions between keratinocytes, cells of the immune system, mainly eosinophils, and non-myelinated C-type sensory neurons responsible for the conduction of impulses that trigger the itching sensation [22,23]. In a study by Guseva et al. [24] stimulated eosinophils and neuronal projections have been observed to secrete NTs. Similarly, the neurotrophin receptor, TrkB, is expressed by both eosinophils and sensory nerve fibers [24]. Although functional TrkB has not been demonstrated on keratinocytes, NTs most likely act on these cells through the p75 neurotrophin receptor [16]. Moreover, it has been shown that NTs, such as BDNF, lead to the branching of dorsal root ganglion neurons and increase the skin density of the sensory fibers [24]. Nerve endings also release neuropeptides, which in turn bind to specific receptors on the surface of non-neuronal skin cells and lead to their activation. A branched network of interactions is formed, which further enhances the production of pruritogens [24,25]. Subsequently, neuronal projections activated by various mediators such as cytokines, NTs, kinins, and proteases, secreted by intracutaneous cells, conduct impulses through the posterior roots to the spinal cord. Then, via the spinothalamicus tract, they reach the thalamus, from where impulses are transmitted to specific areas of the brain [22]. The suggested mechanism of action of NTs in the pathogenesis of pruritus is illustrated in Figure 1.

Agarwal et al. [5] suggested that CKD-aP associated with nervous system dysfunction could be triggered in various ways, either by cortical activation by centrally acting mediators, by a nerve impulse inhibition defect, or by hyperactivation of peripheral sen-

sory neurons [5]. Interestingly, indirect immunohistochemistry has revealed an abnormal pattern of skin innervation in patients undergoing hemodialysis. In addition, increased growth of nerve fibers throughout the epidermis was noticed [26]. Taking into account the above-mentioned research results, the most likely mechanism of action of NTs in CKD-aP seems to be related to the hypersensitivity of sensory neurons, however, further research is required to confirm this hypothesis.

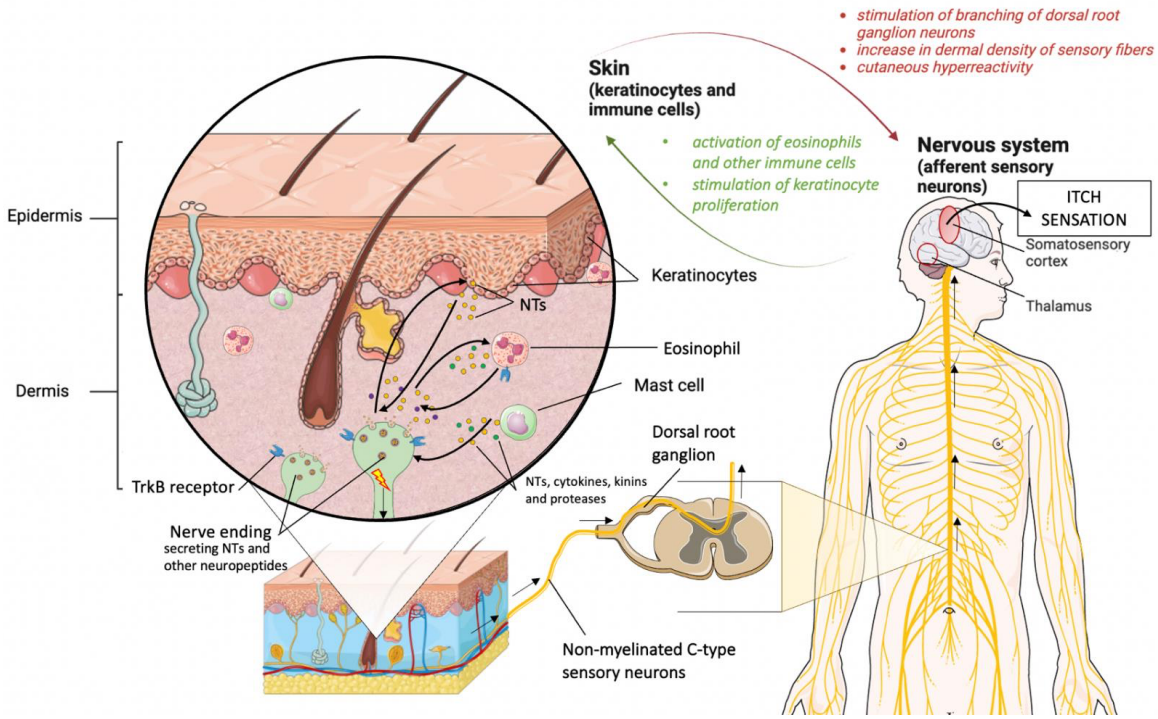

Figure 1. Possible pathomechanism of pruritus involving neurotrophins (NTs). Keratinocytes and skin immune cells produce NTs that activate receptors located on the cell membrane of nerve endings. The stimulated sensory neurons conduct impulses through the dorsal root ganglion to the somatosensory cortex, leading to an itching sensation. Simultaneously, the same molecules produced by non-neuronal skin cells lead also to an increase in skin density of sensory fibers and skin hyperreactivity. Moreover, nerve cells located in the skin have the ability to produce neuropeptides, including NTs, which in turn influence the proliferation of keratinocytes and the activation of immune cells, and further enhance mutual stimulation between neurons and non-neuronal skin cells. This figure was created using Servier Medical Art under a CC 3.0 license (https://smart.servier.com/, accessed on 23 September 2022) [27].

The aim of the study was to assess the concentration of NT-4 and BDNF in the serum of patients undergoing hemodialysis, with and without pruritus, and to verify whether there is a difference in the level of neurotrophins between these two groups of patients. Furthermore, correlations between the concentration of NT-4 or BDNF and the severity of pruritus were determined.

2. Materials and Methods

2.1. Participants and Study Design

The study was conducted between November 2020 and April 2021. 126 hemodialysis patients from the Department of Nephrology and Transplantation Medicine at the University Hospital in Wroclaw, Poland, and the Dialysis Unit at the University Hospital in

Opole, Poland were enrolled in the study. Inclusion criteria were as follows: patients over 18 years of age receiving hemodialysis 2 or 3 times a week for at least 3 months, who signed the patient's informed consent. Dialysis patients with other chronic conditions that may cause itching were not included in the study. Moreover, additional exclusion criteria were antipruritic therapy, mental disorders, and lack of informed consent.

Basic demographic and clinical data (gender, age, cause of renal failure, duration of hemodialysis, type of vascular access, and presence of pruritus) was collected. This research received ethical approval from the Wroclaw Medical University Ethics Committee (Consent no. 26/202, date: 29 January 2021). All patients enrolled in this study have provided their informed consent.

2.2. Laboratory Tests

A total of 126 blood samples were taken from patients immediately (5–10 min) prior to the dialysis session. The time of blood sampling was the same for all participants. The blood samples were then centrifuged at 3000 rpm for 15 min, and the serum was stored at −80 °C until further tests were performed. Subsequently, the samples were spread out in 96-well plates. An enzyme-linked immunosorbent assay was performed according to the manufacturer's instructions using the ELISA Kits to assess the serum level of NT-4 (Nori Human Neurotrophin 4 ELISA Kit, GR111502, Genorise Scientific, Inc., Pennsylvania, PA, USA) and BDNF (Nori Human BDNF ELISA Kit, GR111085, Genorise Scientific, Inc., Pennsylvania, PA, USA). Absorbance was measured using an EPOCH multiplate reader (BioTEK® Instruments, Inc., Winooski, VT, USA) at a wavelength of 450 nm. Serum levels of NT-4 and BDNF were expressed in pg/mL.

2.3. Pruritus Assessment

In this study, the numerical rating scale (NRS) was used to assess the severity of pruritus in patients with CKD-aP, which is considered an easy and reliable tool for assessing the severity of pruritus. Patients were asked to rate the intensity of itching they experienced in the past 3 days on a scale of 0 to 10 points. Depending on the results, the severity of pruritus was divided into mild (NRS score < 3 points), moderate (NRS score ≥3–7 points), severe (NRS score ≥7–9 points), and very severe (NRS score ≥9-10 points) [28]. Patients also completed the validated Polish version of the UP-Dial questionnaire [29]. This scale, dedicated to patients with CKD-aP undergoing dialysis, consists of 14 items assessing the severity of pruritus, but also its impact on various spheres of life, including skin changes caused by itching, the severity, frequency and distribution of pruritus, and the impact on psychosocial life and sleep quality [29]. Additionally, the quality of life was assessed using the ItchyQoL questionnaire. It is a tool designed for patients with pruritus, assessing 3 domains: symptoms, functions, and emotions. The questionnaire consists of 22 items, each scored from 1 to 5 points [30].

2.4. Statistical Analysis

The IBM SPSS Statistics v. 26 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis of the results obtained in the study. Initially, all data was checked for normal or abnormal distribution. For quantitative data analysis, the Mann–Whitney U test and Pearson's or Spearman's correlations were used. Differences in NT-4 and BDNF between various pruritus severity groups were assessed using the Kruskal-Wallis test with Bonferroni correction. Assessment of qualitative results was evaluated with the use of the chi-squared test. Data were expressed as a minimum, maximum, mean ± SD, median, first and third quantiles with $p < 0.05$ being considered statistically significant.

3. Results

3.1. Baseline Characteristics of the Subjects

There were 61 (48.4%) men and 65 (51.6%) women among the respondents. The average age of the patients was 62.5 ± 15.8 years. The most common causes of renal

failure among all participants were glomerulonephritis in 25 patients (19.8%) and diabetic nephropathy in 24 patients (19.0%).

Based on the presence of pruritus, participants were divided into 2 groups. The pruritic group (group A) included 62 participants and the non-pruritic group (group B) had 64 participants. The groups were similar in terms of gender and age, with a mean age of 61.1 ± 15.9 years and 63.9 ± 15.6 years, respectively.

The baseline characteristics of the groups analyzed in this study are presented in Table 1.

Table 1. Characteristics of the study participants.

Parameter	Group A–Itchy	Group B–Non-Itchy	*p*-Value
All participants, n (%)	62 (100.0)	64 (100.0)	
-men/women	30 (48.4)/32 (51.6)	31 (48.4)/33 (51.6)	NS
Age, mean ± SD	61.1 ± 15.9	63.9 ± 15.6	NS
Duration of dialysis (months), mean ± SD	51.4 ± 44.5	46.3 ± 58.4	NS
Cause of CKD, n (%)			NS
-glomerulonephritis	8 (12.9)	17 (26.6)	
-diabetic nephropathy	11 (17.8)	13 (20.3)	
-ischaemic nephropathy	9 (14.5)	8 (12.5)	
-others	34 (54.8)	26 (40.6)	
Access, n (%)			$p < 0.005$
-tunneled internal jugular central venous catheter	30 (48.4)	14 (21.9)	
-arterio-venous fistulae	32 (51.6)	50 (78.1)	

NS—not statistically significant, SD—standard deviation.

3.2. Serum Levels of NT-4 and BDNF in Itchy and Non-Itchy Patients

The study has shown that patients undergoing dialysis with CKD-aP have statistically significantly higher levels of NT-4 compared to the non-pruritic group. The determined concentrations were 224.4 ± 128.8 pg/mL and 159.1 ± 90.0 pg/mL, respectively ($p = 0.003$). A comparison of NT-4 serum levels in both groups of patients is presented in Figure 2.

The serum level of BDNF in the pruritic group was 55.3 ± 66.0 pg/mL, while in the non-pruritic group it was 64.2 ± 62.7 pg/mL. The difference was not statistically significant. Moreover, no statistically significant differences and correlations were found between NT-4 nor BDNF concentrations and demographic data, including age, gender, duration of dialysis, type of access, or the cause of renal failure (detailed data not shown). The results of neurotrophin concentrations are summarized in Table 2.

Table 2. Plasma concentrations of NT-4 and BDNF in dialysis patients with (group A) and without (group B) pruritus.

Parameter.	Group A–Itchy			Group B–Non-Itchy			*p*-Value
	Mean ± SD	Median	Q1; Q3	Mean ± SD	Median	Q1; Q3	
NT-4 (pg/mL)	224.4 ± 128.8	197.7	144.5; 260.5	159.1 ± 90.0	133.0	95.4; 210.0	0.003
BDNF (pg/mL)	55.3 ± 66.0	31.2	13.1; 65.8	64.2 ± 62.7	52.9	16.3; 85.5	NS

N/A—not applicable, NS—not statistically significant, SD—standard deviation, Q1—first quartile (25th percentile), Q3—third quartile (75th percentile).

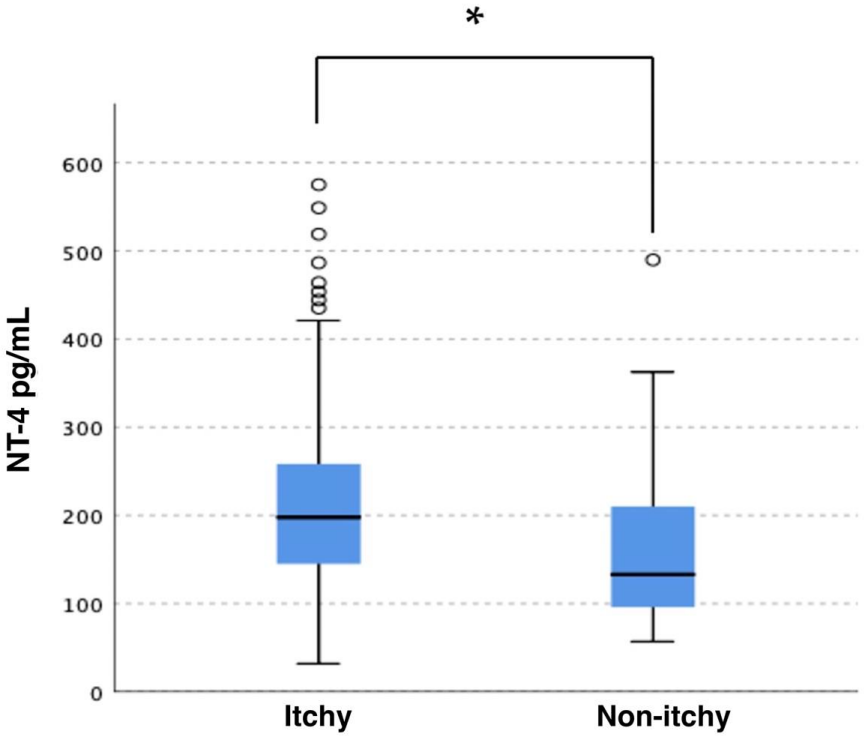

Figure 2. Serum level of NT-4 in groups of patients with pruritus and without pruritus. * $p = 0.003$.

3.3. Pruritus Assessment and Serum Levels of NT-4 and BDNF

In the group of patients undergoing dialysis with CKD-aP, the mean severity of pruritus on the 1–10 NRS scale was 4.9 ± 2.2 points. Most often, patients experienced moderate pruritus (48.4%). In turn, moderate to severe pruritus was reported by 70% of participants (Table 3). No statistically significant differences in NT-4 and BDNF serum concentrations were found between the four pruritus severity groups. Despite the higher concentration of NT-4 in this group of patients compared to the non-pruritic group, no correlation was found between the level of NT-4 nor BDNF and the severity of pruritus on the NRS (detailed data not shown). The mean UP-dial total score of itch in the studied group was assessed as 14.2 ± 9.8 points and did not correlate with both NT-4 and BDNF serum levels. Additionally, no significant relationships between ItchyQoL and serum concentrations of studied NTs were found (detailed data not shown).

Table 3. Data on the severity of pruritus and quality of life in patients with CKD-aP.

Parameters	Result
NRS, mean ± SD, points	4.9 ± 2.2
Severity group based on NRS score, n (%)	
mild pruritus	16 (25.8)
moderate pruritus	30 (48.4)
severe pruritus	14 (22.6)
very severe pruritus	2 (3.2)
UP-Dial total, mean ± SD, points	14.2 ± 9.8
signs and symptoms domain	9.1 ± 4.5
sleep domain	2.8 ± 3.8
psychosocial domain	2.3 ± 2.9
ItchyQoL, mean ± SD, points	36.7 ± 13.7

NRS—numerical rating scale; SD—standard deviation.

4. Discussion

The role of neurotrophins in the proper functioning of the skin and maintaining its homeostasis has long been the subject of many studies. It has been known that NTs in the skin act as transmitters between skin cells and nerve endings in the dermis [31]. They are released by activated mast cells and eosinophils, as well as by keratinocytes and neuronal projections [20,32]. As previously mentioned, both BDNF and NT-4 bind to the TrkB receptor belonging to the tyrosine kinase family and the p75 neurotrophin receptor. In vivo studies in mice have shown that TrkB is present on the neurons innervating Ruffini and Meissner corpuscles, which are mechanoreceptors responsible for touch and stretching sensation. Furthermore, it has been noticed that increased TrkB expression leads to greater innervation of the skin and may be involved in the pathophysiology of some skin diseases [33].

The mechanism of action of NTs in the pathogenesis of skin diseases is still not fully understood. However, there are many studies investigating the contribution of these molecules to various, mainly pruritic skin conditions. In a clinical study by Raap et al. [34] performed in patients with atopic dermatitis (AD), the level of BDNF and the expression of the TrkB were measured. It has been noticed that AD patients have an increase in serum BDNF concentration and higher TrkB expression on eosinophils compared to people without atopic diseases. In addition, BDNF has been shown to inhibit eosinophil apoptosis and modulate eosinophil function, suggesting BDNF involvement in the pathophysiology of pruritic inflammatory skin diseases such as AD [34]. In several studies, it has also been observed that serum levels of BDNF correlate with the severity of AD in both children and adults [35,36]. A strong correlation was demonstrated between the BDNF concentration in the serum of children with AD and nocturnal scratching of the skin, which additionally confirms the role of this neurotrophin in the pathomechanism of pruritus [37]. Moreover, a significantly increased level of BDNF in the serum and altered skin was noticed in patients with chronic spontaneous urticaria [38]. Interestingly, in skin diseases such as vitiligo, psoriasis or acne vulgaris the level of BDNF is significantly lower compared to the control group [39–42]. However, the cause of this phenomenon has not been elucidated. A suggested hypothesis is chronic intense stress, often associated with the pathophysiology of certain dermatological conditions, which significantly reduces BDNF levels [43]. Interestingly, in another study on pruritus in psoriasis patients, no statistically significant differences in BDNF expression were observed between pruritic and non-pruritic patients [44].

The literature shows a large discrepancy in BDNF concentration in patients with CKD. It has been shown in numerous studies that the expression of BDNF is enhanced in patients with CKD or undergoing hemodialysis [9,45–47]. This may be related to the fact that this neurotrophin has been found to have a significant effect on glomerular development and function and is also involved in the repair of podocyte damage [45,46]. However, completely opposite results were obtained in the studies by Ortíz et al. [48] and Żołądź et al. [49] where the level of BDNF in CKD patients requiring hemodialysis was significantly lower compared to the healthy control group. In turn, Lee et al. [50] assessed the plasma level of BDNF and depressive symptoms in patients with CKD, but no differences in the concentration of BDNF were observed between patients with CKD and healthy subjects. Several studies have focused on studying BDNF levels in patients with CKD due to diabetic nephropathy. It has been found that in diabetic patients the plasma level of BDNF is significantly higher compared to patients with CKD but without diabetes [46]. However, our study did not show any correlation between BDNF levels and the cause of renal failure, including diabetic nephropathy. There is also no clear data on the association between BDNF level and gender. Our study did not show any difference between the concentration of this neutrophin and the gender of the patients. In the study by Marchelek-Myśliwiec et al. [51], in patients with chronic kidney disease, a higher concentration of this neutrophin was found in men, while in the study by Endlich et al. [46] BDNF concentration was almost twice as high in female as in male patients. Despite studies confirming the participation

of BDNF in the pathogenesis of pruritic dermatological diseases and data suggesting an increased expression of this factor in patients with CKD, there is currently insufficient evidence in the literature to acknowledge the role of BDNF in the pathogenesis of CKD-aP. As in our study, Sorour et al. [9] did not show a statistically significant difference in BDNF concentration between the group of patients undergoing dialysis accompanied by pruritus compared to the group of patients undergoing dialysis without pruritus. There was also no correlation between the concentration of BDNF and the severity of itching [9].

In the case of NT-4, there are fewer publications assessing the level of this neurotrophin in dermatological diseases and conditions associated with pruritus. In vitro study by Grewe et al. [52] showed that activation of keratinocytes with interferon-gamma leads to an increase in NT-4 production. In turn, immunohistochemistry of human skin showed increased expression of NT-4 in irritated skin injected with gamma interferon. In addition, intense NT-4 staining in the biopsy of itchy lesions of AD patients was observed [52]. However, in a study by Chang et al. [53] in patients with psoriasis, NT-4 serum levels did not differ statistically between pruritic and non-pruritic patients [53]. So far, there is only a single publication examining the influence of NT-4 on the occurrence of CKD-aP. Sorour et al. [9] showed a significant statistical difference in NT-4 concentration between the groups of patients undergoing hemodialysis with and without pruritus. Moreover, it has been proved that the dependence on NT-4 concentration correlates positively with the severity of pruritus [9]. In our study, we also showed that the concentration of NT-4 is significantly higher in the group of dialysis patients with pruritus compared to those without pruritus. However, no positive correlation was found between the severity of the itch and the concentration of this neurotrophin in the patient's serum.

Treatment of CKD-aP is a great challenge and despite many therapeutic options, including local and systemic treatments, many of them show insufficient anti-itching effects. A promising drug seems to be difelikefalin, which has recently been approved for the treatment of CKD-aP. However, as it is a new drug, data on its long-term effectiveness is limited [54]. Therefore, new possibilities are constantly searched for. Considering the possible involvement of NT-4 and BDNF in the pathomechanism of CKD-aP, further studies on the inhibition of neurotrophin-dependent activation of neuronal sensory pathways leading to pruritus are required. So far, no TrkB receptor antagonist has been identified that could be used in clinical trials in pruritic patients. In contrast, molecules that function as TrkB agonists that may be effective in the treatment of neurological and psychiatric diseases are currently being sought [55]. However, clinical trials with Pegkantratinib (CT327, SNA-120)—antagonist of other neutrophin receptors—TrkA in patients with pruritic skin disorders such as AD or psoriasis are ongoing or have already been completed [56,57]. A randomized phase II clinical trial has shown the efficacy of Pegkantratinib in reducing pruritus in patients with psoriasis [56]. Given the important role of neurotrophins in the proper functioning of the nervous system, inhibition of TrkB could be associated with numerous side effects. Therefore, studies on a TrkB antagonist that, like Pegcantratinib, would be applied topically seem to be the most warranted.

The limitation of the study is the assessment of only selected neurotrophins. The concentration of e.g., nerve growth factor was not evaluated in the study. Moreover, patients with CKD and other kidney replacement therapy, such as peritoneal dialysis, were not included in the study.

5. Conclusions

The results of the presented study indicate that in patients with end-stage renal disease undergoing hemodialysis, the occurrence of chronic pruritus correlates with elevated serum levels of NT-4. NT-4 may play an important role in the pathophysiology of pruritus in dialysis patients. More research is needed to understand the exact mechanism by which neurotrophins influence the occurrence of CKD-aP. The results of the study further confirm the importance of looking for substances that would inhibit neurotrophin-dependent

interactions between the skin and the nervous system and could be used in the treatment of CKD-aP.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11216292/s1, Figure S1: Polish version of the ItchyQoL questionnaire.

Author Contributions: Conceptualization: K.W.-Z., P.K.K., K.Ś.-M., M.K., and J.C.S.; methodology: K.W.-Z., P.K.K., K.Ś.-M., D.N.-S., M.K., and J.C.S.; formal analysis: K.W.-Z., P.K.K., D.N.-S., K.Ś.-M., M.K., and J.C.S.; investigation: K.W.-Z., P.K.K., K.Ś.-M., D.N.-S., M.K., and J.C.S.; writing—original draft preparation: K.W.-Z. and J.C.S.; writing—review and editing, K.W.-Z., P.K.K., K.Ś.-M., M.K., and J.C.S.; visualization: K.W.-Z. and P.K.K.; supervision: K.W.-Z., P.K.K., K.Ś.-M., 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 study participants.

Data Availability Statement: The datasets generated and analyzed in the current study are available from the corresponding author upon reasonable request. Acknowledgments: The authors would like to thank Marzena Lesik, a chair of the Dialysis Unit at the University Clinical Hospital in Opole, for their valuable help in collecting patients' blood samples.

Conflicts of Interest: J.C.S. has served as an advisor for AbbVie, LEO Pharma, Menlo Therapeutics, Novartis, Pierre Fabre, Sienna Biopharmaceuticals, and Trevi; has received speaker honoraria from AbbVie, Eli Lilly, Janssen, LEO Pharma, Novartis, Sanofi-Genzyme, Sun Pharma and Berlin-Chemie Mennarini; has served as an investigator and has received funding from AbbVie, Amgen, Galapagos, Holm, Incyte Corporation, InflaRX, Janssen, Menlo Therapeutics, Merck, Boehringer Ingelheim, Novartis, Pfizer, Regeneron, Trevi, and UCB. Other authors reported no conflict of interest.

References

1. Reszke, R.; Krajewski, P.; Szepietowski, J.C. Emerging Therapeutic Options for Chronic Pruritus. *Am. J. Clin. Dermatol.* **2020**, *21*, 601–618. [CrossRef]
2. Steinhoff, M.; Bienenstock, J.; Schmelz, M.; Maurer, M.; Wei, E.; Bíró, T. Neurophysiological, Neuroimmunological, and Neuroendocrine Basis of Pruritus. *J. Investig. Dermatol.* **2006**, *126*, 1705–1718. [CrossRef] [PubMed]
3. Hu, X.; Sang, Y.; Yang, M.; Chen, X.; Tang, W. Prevalence of Chronic Kidney Disease-Associated Pruritus among Adult Dialysis Patients: A Meta-Analysis of Cross-Sectional Studies. *Medicine* **2018**, *97*, e10633. [CrossRef]
4. Sukul, N.; Karaboyas, A.; Csomor, P.A.; Schaufler, T.; Wen, W.; Ed Erique Menzaghi, F.; Rayner, H.C.; Hasegawa, T.; al Salmi, I.; Al-Ghamdi, S.M.G.; et al. Self-Reported Pruritus and Clinical, Dialysis-Related, and Patient-Reported Outcomes in Hemodialysis Patients. *Kidney Med.* **2021**, *3*, 42–53. [CrossRef]
5. Agarwal, P.; Garg, V.; Karagaiah, P.; Szepietowski, J.C.; Grabbe, S.; Goldust, M. Chronic Kidney Disease-Associated Pruritus. *Toxins* **2021**, *13*, 527. [CrossRef]
6. Mettang, T.; Kremer, A.E. Uremic Pruritus. *Kidney Int.* **2015**, *87*, 685–691. [CrossRef] [PubMed]
7. Reszke, R.; Szepietowski, J.C. End-Stage Renal Disease Chronic Itch and Its Management. *Dermatol. Clin.* **2018**, *36*, 277–292. [CrossRef] [PubMed]
8. Fallahzadeh, M.K.; Roozbeh, J.; Geramizadeh, B.; Namazi, M.R. Interleukin-2 Serum Levels Are Elevated in Patients with Uremic Pruritus: A Novel Finding with Practical Implications. *Nephrol. Dial. Transplant.* **2011**, *26*, 3338–3344. [CrossRef] [PubMed]
9. Sorour, N.E.; Elesawy, F.M.; Tabl, H.A.; Ibrahim, M.E.; Akl, E.M. Evaluation of Serum Levels of Neurotrophin 4 and Brain-Derived Nerve Growth Factor in Uremic Pruritus Patients. *Clin. Cosmet. Investig. Dermatol.* **2019**, *12*, 109–114. [CrossRef]
10. Botchkarev, V.A.; Yaar, M.; Peters, E.M.J.; Raychaudhuri, S.P.; Botchkareva, N.V.; Marconi, A.; Raychaudhuri, S.K.; Paus, R.; Pincelli, C. Neurotrophins in Skin Biology and Pathology. *J. Investig. Dermatol.* **2006**, *126*, 1719–1727. [CrossRef]
11. Verduzco, H.A.; Shirazian, S. CKD-Associated Pruritus: New Insights Into Diagnosis, Pathogenesis, and Management. *Kidney Int. Rep.* **2020**, *5*, 1387. [CrossRef] [PubMed]
12. Simonsen, E.; Komenda, P.; Lerner, B.; Askin, N.; Bohm, C.; Shaw, J.; Tangri, N.; Rigatto, C. Treatment of Uremic Pruritus: A Systematic Review. *Am. J. Kidney Dis.* **2017**, *70*, 638–655. [CrossRef]
13. Urbonas, A.; Schwartz, R.A.; Szepietowski, J.C. Uremic Pruritus—An Update. *Am. J. Nephrol.* **2001**, *21*, 343–350. [CrossRef]

14. Huang, E.J.; Reichardt, L.F. Neurotrophins: Roles in Neuronal Development and Function. *Annu. Rev. Neurosci.* **2001**, *24*, 677–736. [CrossRef]
15. Dechant, G.; Neumann, H. Neurotrophins. *Adva. Exp. Med. Biol.* **2002**, *513*, 303–334. [CrossRef]
16. Marconi, A.; Terracina, M.; Fila, C.; Franchi, J.; Bonté, F.; Romagnoli, G.; Maurelli, R.; Failla, C.M.; Dumas, M.; Pincelli, C. Expression and Function of Neurotrophins and Their Receptors in Cultured Human Keratinocytes. *J. Investig. Dermatol.* **2003**, *121*, 1515–1521. [CrossRef]
17. Bathina, S.; Das, U.N. Brain-Derived Neurotrophic Factor and Its Clinical Implications. *Arch. Med. Sci.* **2015**, *11*, 1164–1178. [CrossRef]
18. Sariola, H. The Neurotrophic Factors in Non-Neuronal Tissues. *Cell. Mol. Life Sci.* **2001**, *58*, 1061–1066. [CrossRef] [PubMed]
19. Truzzi, F.; Marconi, A.; Pincelli, C. Neurotrophins in Healthy and Diseased Skin. *Dermato-Endocrinology* **2011**, *3*, 32–36. [CrossRef]
20. Ständer, S.; Raap, U.; Weisshaar, E.; Schmelz, M.; Mettang, T.; Handwerker, H.; Luger, T.A. Pathogenesis of Pruritus. *J. Dtsch. Dermatol. Ges.* **2011**, *9*, 456–463. [CrossRef]
21. Raap, U.; Papakonstantinou, E.; Metz, M.; Lippert, U.; Schmelz, M. Update on the Cutaneous Neurobiology of Pruritus. *Hautarzt* **2016**, *67*, 595–600. [CrossRef] [PubMed]
22. Roosterman, D.; Goerge, T.; Schneider, S.W.; Bunnett, N.W.; Steinhoff, M. Neuronal Control of Skin Function: The Skin as a Neuroimmunoendocrine Organ. *Physiol. Rev.* **2006**, *86*, 1309–1379. [CrossRef]
23. Raap, U.; Ständer, S.; Metz, M. Pathophysiology of Itch and New Treatments. *Curr. Opin. Allergy Clin. Immunol.* **2011**, *11*, 420–427. [CrossRef] [PubMed]
24. Guseva, D.; Rüdrich, U.; Kotnik, N.; Gehring, M.; Patsinakidis, N.; Agelopoulos, K.; Ständer, S.; Homey, B.; Kapp, A.; Gibbs, B.F.; et al. Neuronal Branching of Sensory Neurons Is Associated with BDNF-Positive Eosinophils in Atopic Dermatitis. *Clin. Exp. Allergy* **2020**, *50*, 577–584. [CrossRef]
25. Bíró, T.; Tóth, B.I.; Marincsák, R.; Dobrosi, N.; Géczy, T.; Paus, R. TRP Channels as Novel Players in the Pathogenesis and Therapy of Itch. *Biochim. Biophys. Acta-Mol. Basis Dis.* **2007**, *1772*, 1004–1021. [CrossRef] [PubMed]
26. Ståhle-Bäckdahl, M. Uremic Pruritus. Clinical and Experimental Studies. *Acta Derm. Venereol.* **1989**, *145*, 1–38.
27. SMART—Servier Medical ART. Available online: https://smart.servier.com/ (accessed on 14 August 2022).
28. Reich, A.; Mcglone, F. Tailoring the Cut-off Values of the Visual Analogue Scale and Numeric Rating Scale in Itch Assessment. *Acta Derm. Venereol.* **2017**, *97*, 759–760. [CrossRef]
29. Świerczyńska, K.; Krajewski, P.; Reszke, R.; Krajewska, M.; Nochaiwong, S.; Białynicki-Birula, R.; Szepietowski, J.C.; Dermatol Allergol, A. Uraemic Pruritus in Dialysis Patient (UP-Dial) Questionnaire: Creation and validation of the Polish Language Version. *Adv. Dermatol. Allergol.* **2021**, *39*, 538–544. [CrossRef]
30. Stumpf, A.; Pfleiderer, B.; Fritz, F.; Osada, N.; Chen, S.C.; Ständer, S. Assessment of Quality of Life in Chronic Pruritus: Relationship between ItchyQol and Dermatological Life Quality Index in 1,150 Patients. *Acta Derm. Venereol.* **2018**, *98*, 142–143. [CrossRef]
31. Kremer, A.E.; Feramisco, J.; Reeh, P.W.; Beuers, U.; Oude Elferink, R.P.J. Receptors, Cells and Circuits Involved in Pruritus of Systemic Disorders. *Biochim. Biophys. Acta-Mol. Basis Dis.* **2014**, *1842*, 869–892. [CrossRef]
32. Botchkarev, V.A.; Metz, M.; Botchkareva, N.V.; Welker, P.; Lommatzsch, M.; Renz, H.; Paus, R. Brain-Derived Neurotrophic Factor, Neurotrophin-3, and Neurotrophin-4 Act as "Epitheliotrophins" in Murine Skin. *Lab. Investig.* **1999**, *79*, 557–572.
33. MontañO, J.A.; Pérez-Piñera, P.; GarcíA-Suá Rez, O.; Cobo, J.; Vega, J.A. Development and Neuronal Dependence of Cutaneous Sensory Nerve Formations: Lessons from Neurotrophins. *Microsc. Res. Tech.* **2010**, *73*, 513–529. [CrossRef] [PubMed]
34. Raap, U.; Goltz, C.; Deneka, N.; Bruder, M.; Renz, H.; Kapp, A.; Wedi, B. Brain-Derived Neurotrophic Factor Is Increased in Atopic Dermatitis and Modulates Eosinophil Functions Compared with That Seen in Nonatopic Subjects. *J. Allergy Clin. Immunol.* **2005**, *115*, 1268–1275. [CrossRef] [PubMed]
35. Fölster-Holst, R.; Papakonstantinou, E.; Rüdrich, U.; Buchner, M.; Pite, H.; Gehring, M.; Kapp, A.; Weidinger, S.; Raap, U. Childhood Atopic Dermatitis—Brain-Derived Neurotrophic Factor Correlates with Serum Eosinophil Cationic Protein and Disease Severity. *Allergy* **2016**, *71*, 1062–1065. [CrossRef] [PubMed]
36. Ma, L.; Gao, X.H.; Zhao, L.P.; Di, Z.H.; McHepange, U.; Zhang, L.; Chen, H.D.; Wei, H.C. Brain-Derived Neurotrophic Factor Gene Polymorphisms and Serum Levels in Chinese Atopic Dermatitis Patients. *J. Eur. Acad. Dermatol. Venereol.* **2009**, *23*, 1277–1281. [CrossRef]
37. Hon, K.L.E.; Lam, M.C.A.; Wong, K.Y.; Leung, T.F.; Ng, P.C. Pathophysiology of Nocturnal Scratching in Childhood Atopic Dermatitis: The Role of Brain-Derived Neurotrophic Factor and Substance P. *Br. J. Dermatol.* **2007**, *157*, 922–925. [CrossRef]
38. Rössing, K.; Novak, N.; Mommert, S.; Pfab, F.; Gehring, M.; Wedi, B.; Kapp, A.; Raap, U. Brain-Derived Neurotrophic Factor Is Increased in Serum and Skin Levels of Patients with Chronic Spontaneous Urticaria. *Clin. Exp. Allergy* **2011**, *41*, 1392–1399. [CrossRef]
39. Yanik, M.E.; Erfan, G.; Albayrak, Y.; Aydin, M.; Kulac, M.; Kuloglu, M. Reduced Serum Brain-Derived Neurotrophic Factor in Patients with First Onset Vitiligo. *Neuropsychiatr. Dis. Treat.* **2014**, *10*, 2361–2367. [CrossRef]
40. Sjahrir, M.; Roesyanto-Mahadi, I.D.; Effendy, E. Correlation between Serum Brain-Derived Neurotrophic Factor Level and Depression Severity in Psoriasis Vulgaris Patients. *Open Access Maced. J. Med. Sci.* **2019**, *7*, 583–586. [CrossRef]
41. Brunoni, A.R.; Lotufo, P.A.; Sabbag, C.; Goulart, A.C.; Santos, I.S.; Benseñor, I.M. Decreased Brain-Derived Neurotrophic Factor Plasma Levels in Psoriasis Patients. *Braz. J. Med. Biol.* **2015**, *48*, 711–714. [CrossRef]

42. Mikhael, N.W.; Hamed, A.M.; Mansour, A.I.; Abdelrahman, E.S. Serum Levels of Brain-Derived Neurotrophic Factor in Patients with Acne Vulgaris. *J. Cosmet. Dermatol.* **2019**, *18*, 1998–2003. [CrossRef]
43. Smith, M.A.; Makino, S.; Kvetnansky, R.; Post, R.M. Stress and Glucocorticoids Affect the Expression of Brain-Derived Neurotrophic Factor and Neurotrophin-3 MRNAs in the Hippocampus. *J. Neurosci.* **1995**, *15*, 1768–1777. [CrossRef] [PubMed]
44. Nakamura, M.; Toyoda, M.; Morohashi, M. Pruritogenic Mediators in Psoriasis Vulgaris: Comparative Evaluation of Itch-Associated Cutaneous Factors. *Br. J. Dermatol.* **2003**, *149*, 718–730. [CrossRef] [PubMed]
45. Li, M.; Armelloni, S.; Zennaro, C.; Wei, C.; Corbelli, A.; Ikehata, M.; Berra, S.; Giardino, L.; Mattinzoli, D.; Watanabe, S.; et al. BDNF Repairs Podocyte Damage by MicroRNA-Mediated Increase of Actin Polymerization. *J. Pathol.* **2015**, *235*, 731–744. [CrossRef]
46. Endlich, N.; Lange, T.; Kuhn, J.; Klemm, P.; Kotb, A.M.; Siegerist, F.; Kindt, F.; Lindenmeyer, M.T.; Cohen, C.D.; Kuss, A.W.; et al. BDNF: MRNA Expression in Urine Cells of Patients with Chronic Kidney Disease and Its Role in Kidney Function. *J. Cell. Mol. Med.* **2018**, *22*, 5265–5277. [CrossRef]
47. Shin, S.J.; Yoon, H.E.; Chung, S.; Kim, Y.G.; Kim, D.J. Plasma Brain-Derived Neurotrophic Factor in Hemodialysis Patients. *Int. J. Med. Sci.* **2012**, *9*, 772. [CrossRef]
48. Ortíz, B.M.; Emiliano, J.R.; Ramos-Rodríguez, E.; Martínez-Garza, S.; Macías-Cervantes, H.; Solorio-Meza, S.; Pereyra-Nobara, T.A. Brain-Derived Neurotrophic Factor Plasma Levels and Premature Cognitive Impairment/Dementia in Type 2 Diabetes. *World J. Diabetes* **2016**, *7*, 615–620. [CrossRef]
49. Zoladz, J.A.; Śmigielski, M.; Majerczak, J.; Nowak, L.R.; Zapart-Bukowska, J.; Smoleński, O.; Kulpa, J.; Duda, K.; Drzewińska, J.; Bartosz, G. Hemodialysis Decreases Serum Brain-Derived Neurotrophic Factor Concentration in Humans. *Neurochem. Res.* **2012**, *37*, 2715–2724. [CrossRef]
50. Lee, J.G.; Park, M.K.; Kim, Y.H.; Kim, Y.W.; Jin, K.; Park, S.W.; Seo, M.K.; Kim, Y.H. The Correlations among Depressive Symptoms, Cognitive Performance and Serum BDNF Levels in the Patients with Chronic Kidney Disease. *Psychiatry Investig.* **2018**, *15*, 186–192. [CrossRef]
51. Marchelek-Myśliwiec, M.; Cichocka, E.; Dziedziejko, V.; Dutkiewicz, G.; Stępniewska, J.; Safranow, K.; Budkowska, M.; Sałata, D.; Syrenicz, A.; Machaliński, B.; et al. Insulin Resistance and Brain-Derived Neurotrophic Factor Levels in Chronic Kidney Disease. *Ann. Clin. Biochem.* **2015**, *52*, 213–219. [CrossRef]
52. Grewe, M.; Vogelsang, K.; Ruzicka, T.; Stege, H.; Krutmann, J. Neurotrophin-4 Production by Human Epidermal Keratinocytes: Increased Expression in Atopic Dermatitis. *J. Investig. Dermatol.* **2000**, *114*, 1108–1112. [CrossRef] [PubMed]
53. Chang, S.E.; Han, S.S.; Jung, H.J.; Choi, J.H. Neuropeptides and Their Receptors in Psoriatic Skin in Relation to Pruritus. *Br. J. Dermatol.* **2007**, *156*, 1272–1277. [CrossRef] [PubMed]
54. Deeks, E.D. Difelikefalin: First Approval. *Drugs* **2021**, *81*, 1937–1944. [CrossRef] [PubMed]
55. Tejeda, G.S.; Díaz-Guerra, M. Integral Characterization of Defective BDNF/TrkB Signalling in Neurological and Psychiatric Disorders Leads the Way to New Therapies. *Int. J. Mol. Sci.* **2017**, *18*, 268. [CrossRef] [PubMed]
56. Roblin, D.; Yosipovitch, G.; Boyce, B.; Robinson, J.; Sandy, J.; Mainero, V.; Wickramasinghe, R.; Anand, U.; Anand, P. Topical TrkA Kinase Inhibitor CT327 Is an Effective, Novel Therapy for the Treatment of Pruritus Due to Psoriasis: Results from Experimental Studies, and Efficacy and Safety of CT327 in a Phase 2b Clinical Trial in Patients with Psoriasis. *Acta Derm. Venereol.* **2015**, *95*, 542–548. [CrossRef]
57. Clinical Trial on Atopic Dermatitis: CT327 Ointment, Placebo—Clinical Trials Registry—ICH GCP. Available online: https://ichgcp.net/clinical-trials-registry/NCT01808157 (accessed on 20 July 2022).

6. ARTYKUŁ TRZECI

Endogenous opioid imbalance as a potential factor involved in the pathogenesis of chronic kidney disease-associated pruritus in dialysis patients

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Endogenous Opioid Imbalance as a Potential Factor Involved in the Pathogenesis of Chronic Kidney Disease-Associated Pruritus in Dialysis Patients

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Abstract: Chronic pruritus is one of the most common symptoms of dermatological diseases. It may occur in the course of other disorders, such as kidney disease. Chronic kidney disease-associated pruritus (CKD-aP) most often affects people with end-stage renal disease. The etiology of this condition is still not fully understood, but researchers are currently focusing on a thorough analysis of the association between disturbed opioid balance and increased neuronal signaling leading to pruritus. The aim of this study is to assess the concentration of endogenous opioids in dialysis patients with and without pruritus and in the control group, and to determine the correlation between the concentration of these substances and the occurrence and severity of itching. The study involved 126 dialysis patients and 50 healthy controls. Patients were divided into groups with pruritus (n = 62) and without pruritus (n = 64). The severity of pruritus was assessed using the NRS scale. The concentration of endogenous opioids was determined using the ELISA. The concentration of met-enkephalin was higher in the group of patients with pruritus compared to the control group. Moreover, significantly lower levels of β-endorphin and dynorphin A were observed in the group of dialysis patients compared to the control group. In addition, a statistically significant difference was seen between the β-endorphin concentration in the group of dialysis patients with pruritus compared to the group without pruritus. The ratio of β-endorphin/dynorphin A concentrations was significantly lower in the group of patients with pruritus compared to patients without pruritus and the control group. No correlations were found between serum level of studied opioids and the severity of pruritus. The concentrations of the studied opioids did not correlate with the severity of pruritus. Observed opioid imbalance may affect the occurrence of CKD-aP in dialysis patients, but a thorough understanding of the mechanism of action of these substances in the sensation of pruritus is necessary to assess the possibility of finding a new therapeutic target.

Keywords: pruritus; chronic itch; enkephalins; dynorphins; endorphins; chronic kidney disease-associated pruritus; chronic kidney disease

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1. Introduction

Chronic itch (CI) is one of the most common symptoms of dermatological diseases and leads to significant impairment of daily functioning of patients [1]. CI may also occur in the course of other systemic conditions such as pregnancy, kidney and liver diseases, and lymphomas [2,3]. In chronic kidney disease, the incidence of CI, referred to as chronic kidney disease-associated pruritus (CKD-aP), depends on the severity of the disease and most often affects patients with end-stage renal disease requiring dialysis [4,5].

Importantly, it is emphasized that even half of patients with CI do not report their problem to a doctor. In addition, despite the use of currently available treatment methods,

some patients do not respond to therapy at all or do not achieve sufficient improvement [6]. This leads to a significant reduction in the quality of life, an increase in patient mortality, and disturbances in everyday functioning, which may also lead to socio-economic consequences [7]. Luigi Naldi et al. [6] draws attention to the need to educate patients and create interdisciplinary pruritus treatment clinics that provide CI treatment with psychosocial support and innovative therapeutic methods.

Although the etiology of CI remains unclear, many pruritic mediators have been described that may play an important role in the pathogenesis of pruritus [1,8]. In addition, an attempt was made to identify clinical factors that can be positively correlated with the occurrence and increased severity of pruritus. For instance, G. Damiani et al. [9] reported that in patients with psoriasis, in which CI is present in up to 64–98% of cases, factors such as female gender, psoriasis of the head, face and genital area, pustular psoriasis, or lack of previous treatment are associated with higher itch intensity. Recently, many researchers have focused on a thorough analysis of the association between disturbed opioid balance and increased neuronal signaling leading to itching sensation [10–12]. The significant role of opioids in the pathogenesis of pruritus is suggested by the occurrence of itching in patients treated with opioids. This is particularly evident with epidural and intrathecal administration [12,13]. In order to analyze the influence of opioid disorders on the pathogenesis of CI, our current knowledge about the opioid system should be considered. So far, three main opioid receptors have been precisely identified and described, the activation of which will lead to specific, diverse changes in neuronal signaling. These are the δ-opioid receptor (DOR), μ-opioid receptor (MOR) and κ-opioid receptor (KOR) [14]. These transmembrane G protein receptors have been shown to be present in the cells of the peripheral and central nervous systems but are also expressed in keratinocytes, fibroblasts, dermal nerve ending, cells of the immune system, and secretory organs such as the pituitary [15,16]. In addition to the transmission of pain and itch stimuli, endogenous opioids are also responsible for modulation of the immune and cardiovascular systems, drug tolerance occurrence and, through the reward center, affect behavioral domain such as addiction and mood regulation [17,18]. Each of the opioid receptors is subject to the physiological influence of endogenous substances, which leads to the activation or inhibition of signaling. It should be emphasized that endogenous agonists are not fully specific for one receptor and also act on other receptors, but to a lesser extent, leading to a complex clinical response. DOR is activated mainly by endogenous enkephalins, MOR by endorphins, and KOR by dynorphins (A and B) [15,19].

Furthermore, in experimental studies, administration of MOR agonists has been noted to cause scratching in mice. In turn, the use of KOR agonists or MOR antagonists suppresses these reflexes [20,21]. These results led to the conclusion that MOR-dependent stimulation causes pruritus and that KOR-dependent signaling inhibits pruritus. The literature emphasizes the role of KOR and MOR in the pathogenesis of itching. However, recent research suggests that DOR can be involved in the modulation of pruritus at the spinal cord level [22]. In the study of Smith et al. [22] intrathecal administration of DOR agonists reduced chloroquine-induced itching in mice, while DOR antagonists stimulated pruritus. Numerous studies using endogenous opioids also supported previous observations. For example, endorphins, affecting mainly the MOR, cause an analgesic effect and depression of the respiratory system. With morphine-like properties, endorphins have been shown to cause pruritus and increase histamine-induced itching [23]. On the contrary, the administration of dynorphins, in addition to an analgesic effect, alleviates the itching via KOR [24]. Met-enkephalin and leu-enkephalin show the greatest affinity to the DOR and to a slightly less extent to MOR [25,26]. This may explain their main analgesic effect with less influence on pruritus [26]. It was also noted that the role of endogenous opioids in the formation and modulation of pruritus occurs through receptors present in the skin at the spinal cord level and in the central nervous system [27].

In pathological conditions such as neurological diseases (Parkinson's disease, Alzheimer's disease, spinal cord injury, epilepsy) altered opioid system activity has been noted [28]. A

disturbed balance between the components of the opioid system has also been observed in dermatological diseases, including atopic dermatitis and psoriasis, which are often accompanied by pruritus [16,29,30]. The literature also suggests that alteration in opioid transmission may be important in the pathophysiology of CKD-aP. However, the number of clinical studies is insufficient to fully explain the mechanism of these disorders. It is assumed that, as in the case of other pruritic conditions, in CKD-aP there is an excessive activation of mu-opioid conduction with a decrease in KOR-dependent impulsation [5]. Therefore, in addition to determining the concentrations of individual substances, the ratio of the concentration of the MOR agonist (β-endorphin) to the KOR agonist (dynorphin A) is often calculated. The changed MOR/KOR ligand ratio indicates an increased activity and predominance of one of the elements of the opioid system [31]. However, the theory of an important role of opioids is mainly based on observations from clinical data demonstrating the efficacy of treatment of CKD-aP with KOR agonists and MOR antagonists. So far, there are only a few studies evaluating endogenous opioid concentrations and one study assessing the expression of opioid receptors in patients with end-stage renal disease [32–35].

Many patients with CI do not respond to standard therapy for pruritus, including antihistamines. Therefore, new therapeutic options for the treatment of CI of various origins are constantly sought [36]. Recently, aprepitant, a selective β/neurokinin 1 receptor antagonist, has been shown to be effective and significantly superior to antihistamines in the treatment of pruritus in patients with psoriasis [37]. Furthermore, clinical observations and animal studies have led to the discovery of new options for the treatment of CKD-aP with the use of opioid agonists or antagonists. For example, KOR agonists such as nalfurafine have been shown to reduce the severity of pruritus when administered to patients with CKD-aP [38]. KOR agonist—selective and peripherally acting difelikefalin is the first drug to have been approved by the FDA and EMA for the treatment of CKD-aP [39]. However, some dialysis patients do not respond to available therapies or their improvement is not sufficient. Therefore, taking into consideration the not fully explained pathogenesis of CKD-aP and the role of opioids in this disease, this area should be further explored in order to obtain new therapeutic options.

The aim of this study is to verify whether the concentration of endogenous opioids (Met-enkephalin, Leu-enkephalin, β-endorphin, and Dynorphin A) in the serum changes in dialysis patients with pruritus compared to dialysis patients without pruritus and a group of healthy people. In addition, it was also assessed whether there are correlations between the concentrations of these substances and the severity of pruritus.

2. Materials and Methods

2.1. Participants and Study Design

The study was conducted on a group of 126 patients from the Dialysis Unit at the University Hospital in Opole, Poland and the Department of Nephrology and Transplantation Medicine at the University Hospital in Wroclaw, Poland as well as 50 healthy subjects. All patients provided written, informed consent to participate in the study. Ethical approval was obtained from the Wroclaw Medical University Ethics Committee (Consent no. 26/2021, date: 29 January 2021). The study enrolled patients over 18 years of age who had been on dialysis 2 or 3 times a week for at least 3 months. Patients suffering from other diseases that may cause chronic pruritus, with psychiatric disorders and using antipruritic therapy were excluded from the study. Blood samples and basic demographic and clinical and data (age, gender, cause of CKD, duration of dialysis, type of vascular access) were collected from participants between November 2020 and April 2021.

2.2. Laboratory Tests

Initially, 9 mL blood samples were collected from 126 dialysis patients approximately 5–10 min before the next dialysis session and from 50 healthy study participants. Then, all samples (n = 176) were centrifuged for 15 min at 3000 rpm. Until further tests were performed, the research material was stored at −80 °C. The serum samples were dis-

tributed in 96-well plates and then, according to the manufacturer's protocol, the enzyme immunoassay was performed. ELISA kits were used to evaluate the concentrations of metenkephalin (S-1419 Met-Enkephalin ELISA Kit, BMA BIOMEDICALS, Augst, Switzerland), leu-enkephalin (Leu-Enkephalin EIA Kit, Phoenix Pharmaceuticals, Inc., Burlingame, CA, USA), β-endorphin (Nori® Human β-endorphin ELISA Kit, GR111460-1, Genorise Scientific, Inc., Pennsylvania, PA, USA) and dynorphin A (RayBio® Human Dynorphin A EIA Kit, Ray Biotech, Inc., Peachtree Corners, GA, USA), respectively. An EPOCH multiplate reader (BioTEK® Instruments, Inc., Winooski, VT, USA) was then used to measure the absorbance at 450 nm.

Concentration of met-enkefalin, leu-enkefalin, and dynorphin A in serum were expressed in ng/mL and beta-endorphin in pg/mL. The ratio of MOR agonists to KOR agonists was calculated and presented as the ratio of plasma beta-endorphin concentration to dynorphin A concentration.

2.3. Pruritus Assessment

The severity of pruritus in CKD-aP patients was assessed using the numerical rating scale (NRS). Participants rated the worst severity of itching over the last 3 days on a scale of 1 to 10 (10 being the worst itch imaginable). The scores were then grouped by severity of pruritus into mild pruritus (NRS <3 points), moderate pruritus (NRS ≥3–7 points), severe pruritus (NRS ≥7–9 points), and very severe pruritus (NRS ≥9 points) [40].

Patients were also asked to complete the Polish version of the UP-Dial questionnaire [41]. It is a validated scale that has been developed to assess the severity of pruritus and its impact on quality of life specifically in CKD-aP dialysis patients. Components such as the severity, frequency and distribution of pruritus, skin changes caused by pruritus, as well as the impact on the patient's sleep quality and psychosocial life are evaluated [41].

Moreover, the ItchyQoL questionnaire, a reliable, validated and designed for patients with CI instrument, was used to assess the quality of life of our patients. This questionnaire consists of 22 items (each item is scored from 1 to 5) evaluating 3 main domains: symptoms, functional limitation and emotions [42].

2.4. Statistical Analysis

All results were statistically analyzed using IBM SPSS Statistics v. 26.0 (SPSS Inc., Chicago, IL, USA). Initially, all the data were assessed for normal distribution. Qualitative results were subsequently assessed using the chi-square test. The T-Student and Mann-Whitney U tests were used for qualitative normally and abnormally distributed data. Pearson or Spearman correlations were used to analyze quantitative data based on normality. The differences in serum concentrations of the tested opioids between groups were analyzed using the Kruskal-Wallis test with the Bonferroni correction. All data are presented as mean ± SD. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of the Study Group

Among all participants, there were 91 (51.7%) women and 85 (48.3%) men. The mean age of the subjects was 63.9 ± 15.6 years in the non-pruritic patients, 61.1 ± 15.9 years in the pruritic patients, and 48.0 ± 10.2 years in the control group, respectively.

Patients underwent hemodialysis using arteriovenous fistulas (n = 82, 65.1%) or a tunneled internal jugular venous catheter (n = 44, 34.9%). In the group of patients with pruritus, patients with arteriovenous fistulas accounted for 51.6% (n = 32), patients with a central venous catheter—48.4% (n = 30). In the group without pruritus, 78.1% (n = 50) of patients had arteriovenous fistulas, 21.9% (n = 14) were patients with a central venous catheter. The difference in dialysis access was statistically significant ($p < 0.005$). The mean duration of dialysis was 48.8 ± 51.9 months, 46.3 ± 58.4 months in patients without CKD-aP, and 51.4 ± 44.5 months in the group with CKD-aP, respectively. The most common causes of renal failure in all groups were diabetic nephropathy, glomerulonephritis,

and ischemic nephropathy. Both the duration of dialysis therapy and the cause of renal failure are not significantly different in both groups of dialysis patients.

3.2. Serum Levels of Met-enkephalin, Leu-enkephalin, β-endorphin and Dynorphin A in Patients and in Control Group

Significantly lower β-endorphin concentrations ($p < 0.001$) were observed in dialysis patients compared to the control group and were 216.25 ± 171.21 pg/mL in patients with pruritus, 344.84 ± 268.3 pg/mL in patients without pruritus and 658.51 ± 377.66 pg/mL in control group. In addition, a statistically significant difference ($p = 0.005$) was observed between the concentration of β-endorphin in the group of dialysis patients with pruritus compared to the group without pruritus (Figure 1).

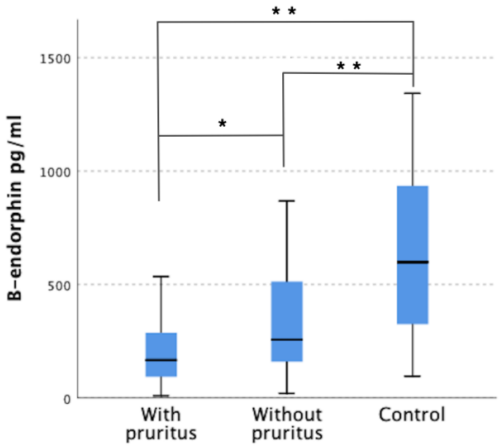

Figure 1. Serum level of β-endorphin in patients with pruritus, without pruritus, and control group. * $p = 0.005$; ** $p < 0.001$.

Similarly, serum level of dynorphin A was lower in both groups of dialysis patients compared to control group ($p < 0.001$). However, no significant difference in dynorphin A concentrations was shown between group with and without pruritus, which were 4.32 ± 3.95 ng/mL and 4.62 ± 3.87 ng/mL, respectively (Figure 2).

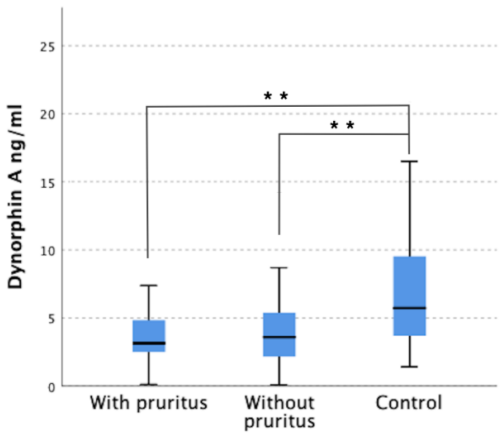

Figure 2. Serum level of Dynorphin A in patients with pruritus, without pruritus, and control group. ** $p < 0.001$.

Moreover, the ratio of β-endorphin to dynorphin A concentrations was 0.16 ± 0.64 in the group of patients with pruritus and was significantly lower compared to patients without pruritus ($p = 0.048$) and the control group ($p = 0.005$) (Figure 3).

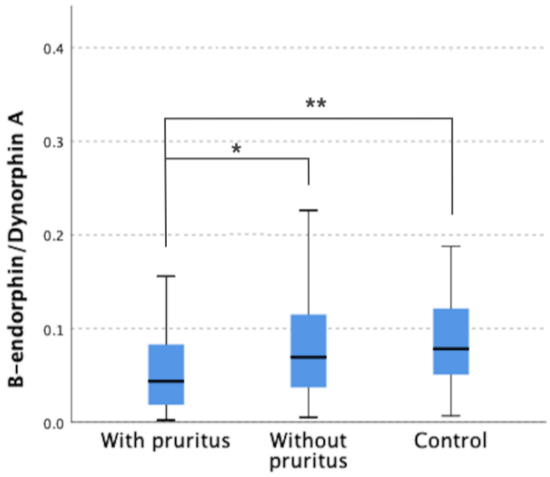

Figure 3. β-endorphin /Dynorphin A concentrations ratio in all study groups. * $p < 0.05$; ** $p = 0.005$.

In turn, in the group of patients with pruritus the concentration of met-enkephalin was significantly higher compared to the control group (75.98 ± 65.48 ng/mL versus 48.06 ± 92.09 ng/mL) ($p = 0.009$). The concentration of met-enkephalin in pruritis patients also differed compared to the group without pruritus (61.37 ± 44.92 ng/mL), but in this case no statistically significant difference was obtained (Figure 4). There were no significant differences in leu-enkephalin serum levels between the study groups (Figure 5). Table 1 summarizes the results of opioid concentrations in the serum of study participants.

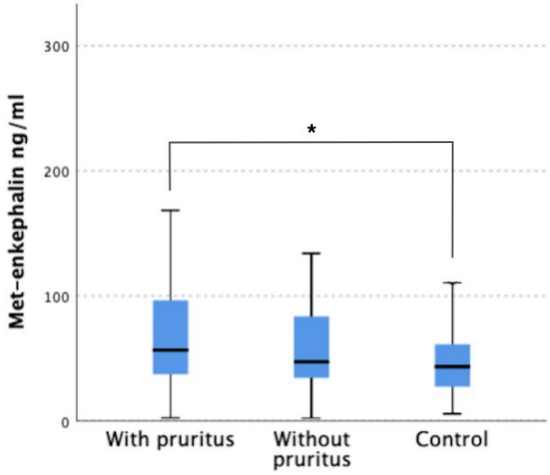

Figure 4. Serum level of Met-enkephalin in patients with pruritus, without pruritus, and control group. * $p = 0.009$.

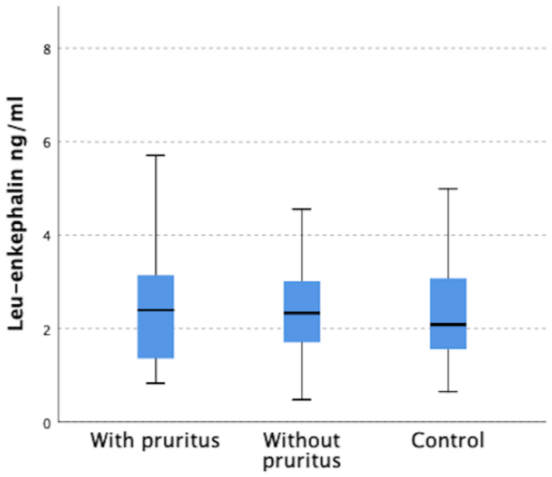

Figure 5. Leu-enkephalin concentrations in all study groups.

Table 1. Concentrations of Met-enkephalin, Leu-enkephalin, β-endorphin, and Dynorphin A in serum in the studied group.

Parameter	Group 1—With Pruritus		Group 2—Without Pruritus		Group 3—Controls		*p*-Value
	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	
Met-enkephalin (ng/mL)	75.98 ± 65.48	58.6	61.37 ± 44.92	47.3	48.06 ± 92.09	43.3	0.033
Leu-enkephalin (ng/mL)	2.9 ± 2.15	2.5	2.79 ± 2.1	2.3	2.42 ± 1.22	2.1	NS
β-endorphin (pg/mL)	216.25 ± 171.21	166.4	344.84 ± 268.3	256.6	658.51 ± 377.66	596.2	<0.001
Dynorphin A (ng/mL)	4.32 ± 3.95	3.1	4.62 ± 3.87	3.6	8.1 ± 6.2	5.8	<0.001
β-endorphin/Dynorphin A	0.16 ± 0.64	0.047	0.16 ± 0.34	0.076	0.13 ± 0.14	0.086	0.004

NS—not statistically significant, SD—standard deviation.

3.3. Correlations of Opioids Serum Concentration with Itch Intensity and Other Clinical and Demographic Data

The mean pruritic NRS score in dialysis patients with CI was 4.9 ± 2.2 points. Mild pruritus was reported by 16 (25.8%) CKD-aP patients, moderate pruritus by 30 (48.4%) and severe pruritus by 14 (22.6%) patients. Very severe pruritus (NRS 9–10 points) was observed in 2 (3.2%) patients. The concentrations of met-enkephalin, leu-enkephalin, B-endorphin and dynorphin A did not correlate with the severity of pruritus. The quality of life assessed by the participants (ItchyQoL scale) was on average 36.7 ± 13.7 points. Mean Up-dial total score was 14.2 ± 9.8 points. The concentration of the tested opioids did not correlate with the ItchyQoL score and the Up-Dial score.

The concentration of dynorphin A differed significantly in dialysis patients depending on the dialysis access and was lower in patients with a venous catheter ($p = 0.026$). In the case of other opioids, no similar correlations were observed. There were also no significant differences in serum concentrations of all tested opioids depending on data such as age, duration of dialysis and cause of renal failure.

4. Discussion

Undoubtedly, changes in the opioid system are involved in the pathogenesis of CKD-aP. This claim is supported both by the results of studies evaluating the concentration of endogenous opioids in CKD patients and clinical trials evaluating the effectiveness of drugs acting on opioid receptors, such as KOR agonists—difelikefalin, in reducing pruritus [14,31,35,38,43,44]. It is still not fully understood how opioid disturbances may

affect the onset of pruritus in dialysis patients. The literature data published so far are inconsistent and refer to patients with pruritus caused by various diseases, such as cholestasis, psoriasis or atopic dermatitis [16,29,30,45–47].

According to Komiya et al. [48], an imbalance in the opioid system is one of the important factors in the pathogenesis of psoriatic pruritus. Clinical studies have shown a significant reduction in dynorphin A levels in psoriatic patients who complained of itching. However, in the mu-opioid system, both B-endorphin concentration and MOR expression remained unchanged in psoriasis patients compared to controls [48]. In contrast, other studies have shown elevated B-endorphin levels in inflammatory dermatological conditions such as atopic dermatitis, psoriasis and systemic sclerosis [49,50]. Furthermore, in experimental studies on mouse models, it was observed that in mice with imiquimod-induced psoriasis-like dermatitis and in atopic dermatitis Japanese mice, the administration of a MOR antagonist and a KOR agonist leads to the reduction of scratching, which additionally confirms the role of opioids in the sensation of itching in inflammatory dermatoses [51,52].

In our study, significantly lower B-endorphin and dynorphin A concentrations were obtained in dialysis patients compared to controls. However, only in the case of B-endorphin was a significant difference observed between pruritic and non-pruritic patients, with lower concentrations in the pruritic group. As studies emphasize the role of opioid balance in the pathogenesis of pruritus (and not just concentrations alone), the ratio of MOR agonists to KOR agonists is often evaluated. Such agonists include B-endorphin and dynorphin A, respectively. We have shown that this ratio is significantly lower in pruritic patients compared to non-pruritic patients and controls. In the study by Moniaga et al. [53] patients with chronic liver disease showed a lower concentration of dynorphin A but higher concentrations of β-endorphin in the group with cholestatic pruritus compared to the group without pruritus. In addition, a significantly higher β-endorphin/dynorphin A ratio was found in the pruritic group compared to non-pruritic patients and this ratio positively correlated with the severity of pruritus on the VAS scale, which is the complete opposite of our results [53]. In turn, in a study of Düll et al. [54] in patients with hepatic pruritus, a decreased concentration of dynorphin A was observed compared to patients without pruritus, however, the concentration of β-endorphin was also reduced, and thus no significant differences in the ratio of β-endorphin to dynorphin A concentrations between the study groups were observed [54]. To date, there have been only a few studies evaluating endorphin levels in CKD patients. Moreover, they were carried out in the last century. In a study conducted in the 1980s by Hwang et al. [33] dialysis patients showed elevated B-endorphin levels compared to healthy participants [33]. However, in a subsequent study in dialysis patients, in which the subjects were divided into pruritic and non-pruritic groups, no statistically significant differences in the concentration of B-endorphin were observed. In addition, no correlation was found between the serum concentration of this opioid and the severity of pruritus [34].

A little more research can be found on the concentration of enkephalins in patients with kidney diseases, including those on dialysis. Studies conducted in hemodialysis patients show that the concentration of met-enkephalin is higher in patients compared to healthy controls [55,56]. However, Danno et al. [56] reported no significant differences between the pruritic and non-pruritic groups. In turn, another clinical study showed a significant difference between patients undergoing dialysis with and without pruritus, however, it is worth noting that the study groups consisted of four patients each [35]. Data on leu-enkephalin levels in the serum of dialysis patients vary widely. The concentrations of this opioid described in the literature are both higher and lower in nephrological patients compared to the control group [55,57]. The studies did not assess the relationship between leu-enkephalin levels and the occurrence of pruritus [55,57]. In the case of hepatic pruritus, despite higher met-enkephalin and leu-enkephalin levels in patients with cholestatic diseases compared to controls, no statistically significant difference was observed between pruritic and non-pruritic patients [54,58].

Another important element in the pathogenesis of CKD-aP is the alteration in the expression of opioid receptors. A study in pruritic and non-pruritic dialysis patients assessed the expression of MOR and KOR in the skin and showed that KOR expression is downregulated in CKD-aP patients and correlates negatively with pruritus severity [32]. Similar results were obtained by Taneda et al. [59] in patients with pruritic psoriasis who had significantly reduced KOR levels in the epidermis compared to healthy controls [59]. Furthermore, in another study, biopsies of skin lesions in patients with psoriasis showed a reduced amount of KOR. A positive correlation was found between the downregulation of KOR expression and the severity of pruritus [60]. In all of these studies, there was no difference in the expression of MOR in keratinocytes among all study groups [32,59,60]. However, it should be emphasized that the modulation of pruritus also takes place at various levels of the nervous system (e.g., in the dorsal horns of the spinal cord) [24]. Receptor expression in the nervous system of CKD-aP patients has not yet been studied.

The results presented in this study do not provide a simple explanation for the pathogenesis of pruritus in CKD patients. It is worth noting that patients with liver disease or CKD have impaired metabolism or excretion of substances, which may lead to variations in the concentrations of the tested opioids [61]. For example, exogenous opioids such as morphine, oxycodone, and codeine accumulate in patients with renal impairment [62,63]. The increased effect of opioids may therefore not be due to increased synthesis but to impaired excretion. Therefore, it may be beneficial to measure opioid concentrations and also intensity of pruritus in patients both before and immediately after a dialysis session. Furthermore, the results obtained in this study raise the question of whether primary disturbances in the opioid system lead to pruritus or are secondary to pruritus, and the imbalance between KOR and MOR-mediated transmission in favor of KOR was intended to inhibit the impulses leading to itching. The differences in the concentrations of individual opioids in patients with CKD-aP demonstrated in the study, although they do not fully explain the pathogenesis of CKD-aP, confirm the role of the opioid system in the formation of pruritus in this group of patients. Therefore, it is reasonable to search for further therapeutic options focusing on the modulation of opioid transmission in the treatment of CKD-aP.

Our study is the first to evaluate the concentrations of multiple endogenous opioids (agonists of each of the three major receptors) in patients with CKD-aP. In addition, the study was conducted on the largest group of patients so far. However, the limitation of the study is the assessment of the concentration of endogenous opioids in the patient's serum only before the dialysis session. It has not been evaluated whether these concentrations change after dialysis. In addition, expression of the opioid receptors (MOR, KOR and DOR) as well as production of opioids in the skin of patients was not assessed in this study.

5. Conclusions

Disturbances in the balance between the concentrations of the individual components of the opioid system may contribute to pruritus or modulate itching sensation in dialysis patients. Further studies, including determination of the expression of opioid receptors, may help researchers to understand the exact mechanism of action of these substances in the pathogenesis of CKD-aP.

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Informed Consent Statement: Informed consent was obtained from all study participants.

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: J.C.S. has served as an advisor for AbbVie, LEO Pharma, Menlo Therapeutics, Novartis, Pierre Fabre, Sienna Biopharmaceuticals and Trevi; has received speaker honoraria from AbbVie, Eli Lilly, Janssen, LEO Pharma, Novartis, Sanofi-Genzyme, Sun Pharma and Berlin-Chemie Mennarini; has served as an investigator and has received funding from AbbVie, Amgen, Galapagos, Holm, Incyte Corporation, InflaRX, Janssen, Menlo Therapeutics, Merck, Boehringer Ingelheim, Novartis, Pfizer, Regeneron, Trevi, and UCB. Other authors reported no conflicts of interests.

References

1. Grundmann, S.; Ständer, S. Chronic Pruritus: Clinics and Treatment. *Ann. Dermatol.* **2011**, *23*, 1–11. [CrossRef] [PubMed]
2. Reszke, R.; Krajewski, P.; Szepietowski, J.C. Emerging Therapeutic Options for Chronic Pruritus. *Am. J. Clin. Derm.* **2020**, *21*, 601–618. [CrossRef] [PubMed]
3. Yosipovitch, G.; Bernhard, J.D. Clinical Practice. Chronic Pruritus Item Type Journal Article. *N. Engl. J. Med.* **2013**, *368*, 1625–1659. [CrossRef] [PubMed]
4. Kim, D.; Pollock, C. Epidemiology and Burden of Chronic Kidney Disease-Associated Pruritus. *Clin. Kidney J.* **2021**, *14*, i1–i7. [CrossRef]
5. Verduzco, H.A.; Shirazian, S. CKD-Associated Pruritus: New Insights Into Diagnosis, Pathogenesis, and Management. *Kidney Int. Rep.* **2020**, *5*, 1387. [CrossRef]
6. Naldi, L.; Mercuri, S.R. Chronic Pruritus Management: A Plea for Improvement—Can Itch Clinics Be an Option? *Dermatology* **2010**, *221*, 216–218. [CrossRef]
7. Weisshaar, E. Itch: A Global Problem? *Front. Med.* **2021**, *8*, 680. [CrossRef]
8. Ständer, S.; Raap, U.; Weisshaar, E.; Schmelz, M.; Mettang, T.; Handwerker, H.; Luger, T.A. Pathogenesis of Pruritus. *J. Dtsch. Dermatol. Ges.* **2011**, *9*, 456–463. [CrossRef]
9. Damiani, G.; Cazzaniga, S.; Conic, R.R.Z.; Naldi, L.; Griseta, V.; Miracapillo, A.; Azzini, M.; Mocci, L.; Michelini, M.; Offidani, A.; et al. Pruritus Characteristics in a Large Italian Cohort of Psoriatic Patients. *J. Eur. Acad. Dermatol. Venereol.* **2019**, *33*, 1316–1324. [CrossRef]
10. Jaiswal, D.; Uzans, D.; Hayden, J.; Kiberd, B.A.; Tennankore, K.K. Targeting the Opioid Pathway for Uremic Pruritus: A Systematic Review and Meta-Analysis. *Can. J. Kidney Health Dis.* **2016**, *3*, 2054358116675345. [CrossRef]
11. Reich, A.; Szepietowski, J.C. Opioid-Induced Pruritus: An Update. *Clin. Exp. Dermatol.* **2010**, *35*, 2–6. [CrossRef] [PubMed]
12. Benson, J.L.; Campbell, H.E.; Phillips, C.N. Opioid-Induced Pruritus. *Consult. Pharm.* **2015**, *30*, 221–227. [CrossRef] [PubMed]
13. Kumar, K.; Singh, S.I. Neuraxial Opioid-Induced Pruritus: An Update. *J. Anaesthesiol. Clin. Pharmacol.* **2013**, *29*, 303. [CrossRef]
14. Schricker, S.; Kimmel, M. Unravelling the Pathophysiology of Chronic Kidney Disease-Associated Pruritus. *Clin. Kidney J.* **2021**, *14*, i23–i31. [CrossRef] [PubMed]
15. Stein, C. Opioid Receptors. *Annu. Rev. Med.* **2016**, *67*, 433–451. [CrossRef]
16. Tominaga, M.; Takamori, K. Peripheral Itch Sensitization in Atopic Dermatitis. *Allergol. Int.* **2022**, *71*, 265–277. [CrossRef]
17. Liang, X.; Liu, R.; Chen, C.; Ji, F.; Li, T. Opioid System Modulates the Immune Function: A Review. *Transl. Perioper. Pain Med.* **2016**, *1*, 5.
18. Toubia, T.; Khalife, T. The Endogenous Opioid System: Role and Dysfunction Caused by Opioid Therapy. *Clin. Obstet. Gynecol.* **2019**, *62*, 3–10. [CrossRef]
19. Reszke, R.; Kiliś-Pstrusińska, K.; Szepietowski, J.C. Chronic Kidney Disease-Associated Itch (CKD-AI) in Children—A Narrative Review. *Toxins* **2021**, *13*, 450. [CrossRef]
20. Umeuchi, H.; Togashi, Y.; Honda, T.; Nakao, K.; Okano, K.; Tanaka, T.; Nagase, H. Involvement of Central μ-Opioid System in the Scratching Behavior in Mice, and the Suppression of It by the Activation of κ-Opioid System. *Eur. J. Pharmacol.* **2003**, *477*, 29–35. [CrossRef]
21. Sakakihara, M.; Imamachi, N.; Saito, Y. Effects of Intrathecal κ-Opioid Receptor Agonist on Morphine-Induced Itch and Antinociception in Mice. *Reg. Anesth. Pain Med.* **2016**, *41*, 69–74. [CrossRef] [PubMed]
22. Smith, K.M.; Nguyen, E.; Ross, S.E. The Delta-Opioid Receptor Bidirectionally Modulates Itch. *Reg. Anesth. Pain Med.* **2023**, *24*, 264–272. [CrossRef] [PubMed]
23. Hägermark, Ö. Itch and Endorphins. In *New Trends in Allergy*; Ring, J., Burg, G., Eds.; Springer: Berlin/Heidelberg, Germany, 1986; pp. 128–134.

24. Kardon, A.P.; Polgár, E.; Hachisuka, J.; Snyder, L.M.; Cameron, D.; Savage, S.; Cai, X.; Karnup, S.; Fan, C.R.; Hemenway, G.M.; et al. Dynorphin Acts as a Neuromodulator to Inhibit Itch in the Dorsal Horn of the Spinal Cord. *Neuron* **2014**, *82*, 573–586. [CrossRef] [PubMed]
25. Takahashi, A. Enkephalin. In *Handbook of Hormones: Comparative Endocrinology for Basic and Clinical Research*; Ando, H., Ukena, K., Nagata, S., Eds.; Academic Press: London, UK, 2021; Volume 1, pp. 91–94. ISBN 9780128206492.
26. Lee, H.; Ko, M.-C. Distinct Functions of Opioid-Related Peptides and Gastrin-Releasing Peptide in Regulating Itch and Pain in the Spinal Cord of Primates OPEN. *Sci. Rep.* **2015**, *5*, 11676. [CrossRef]
27. Hägermark, Ö. Peripheral and Central Mediators of Itch. *Skin Pharmacol. Physiol.* **1992**, *5*, 1–8. [CrossRef]
28. Sandyk, R. The Endogenous Opioid System in Neurological Disorders of the Basal Ganglia. *Life Sci.* **1985**, *37*, 1655–1663. [CrossRef]
29. Szepietowski, J.C.; Reich, A. Pruritus in Psoriasis: An Update. *Eur. J. Pain* **2016**, *20*, 41–46. [CrossRef]
30. Umehara, Y.; Kiatsurayanon, C.; Trujillo-Paez, J.V.; Chieosilapatham, P.; Peng, G.; Yue, H.; Le, H.; Nguyen, T.; Song, P.; Okumura, K.; et al. Intractable Itch in Atopic Dermatitis: Causes and Treatments. *Biomedicines* **2021**, *9*, 229. [CrossRef]
31. Lipman, Z.M.; Yosipovitch, G. An Evaluation of Difelikefalin as a Treatment Option for Moderate-to-Severe Pruritus in End Stage Renal Disease. *Expert Opin. Pharmacother.* **2021**, *22*, 549–555. [CrossRef]
32. Wieczorek, A.; Krajewski, P.; Kozioł-Gałczyńska, M.; Szepietowski, J.C. Opioid Receptors Expression in the Skin of Haemodialysis Patients Suffering from Uraemic Pruritus. *J. Eur. Acad. Dermatol. Venereol.* **2020**, *34*, 2368–2372. [CrossRef]
33. Hwang, J.C.; Hsu, K.T.; Tsai, H.C.; Lam, K.K.; Wang, P.W. Serum Endorphin Levels in Uremic Patients under Maintenance Hemodialysis. *Taiwan Yi Xue Hui Za Zhi JFMA* **1989**, *88*, 360–365.
34. Mettang, T.; Fischer, F.P.; Dollenbacher, U.; Kuhlman, U. Uraemic Pruritus Is Not Related to β-Endorphin Serum Levels in Haemodialysis Patients. *Nephrol. Dial. Transplant.* **1998**, *13*, 231–232. [CrossRef] [PubMed]
35. Odou, P.; Azar, R.; Luyckx, M.; Brunet, C.; Dine, T. A Hypothesis for Endogenous Opioid Peptides in Uraemic Pruritus: Role of Enkephalin. *Nephrol. Dial. Transplant.* **2001**, *16*, 1953–1954. [CrossRef]
36. Fowler, E.; Yosipovitch, G. A New Generation of Treatments for Itch. *Acta Derm. Venereol.* **2020**, *100*, 37–45. [CrossRef]
37. Damiani, G.; Kridin, K.; Pacifico, A.; Malagoli, P.; Pigatto, P.D.M.; Finelli, R.; Taccone, F.S.; Peluso, L.; Conic, R.R.Z.; Bragazzi, N.L.; et al. Antihistamines-Refractory Chronic Pruritus in Psoriatic Patients Undergoing Biologics: Aprepitant vs Antihistamine Double Dosage, a Real-World Data. *J. Dermatol. Treat.* **2022**, *33*, 1554–1557. [CrossRef] [PubMed]
38. Kumagai, H.; Ebata, T.; Takamori, K.; Muramatsu, T.; Nakamoto, H.; Suzuki, H. Effect of a Novel Kappa-Receptor Agonist, Nalfurafine Hydrochloride, on Severe Itch in 337 Haemodialysis Patients: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study. *Nephrol. Dial. Transpl.* **2010**, *25*, 1251–1257. [CrossRef]
39. Wala, K.; Szepietowski, J. Difelikefalin in the Treatment of Chronic Kidney Disease-Associated Pruritus: A Systematic Review. *Pharmaceuticals* **2022**, *15*, 934.
40. Reich, A.; Mcglone, F. Tailoring the Cut-off Values of the Visual Analogue Scale and Numeric Rating Scale in Itch Assessment. *Acta Derm. Venereol.* **2017**, *97*, 759–760. [CrossRef]
41. Świerczyńska, K.; Krajewski, P.; Reszke, R.; Krajewska, M.; Nochaiwong, S.; Białynicki-Birula, R.; Szepietowski, J.C.; Dermatol Allergol, A. Uraemic Pruritus in Dialysis Patient (UP-Dial) Questionnaire: Creation and validation of the Polish Language Version. *Adv. Dermatol. Allergol.* **2021**, *39*, 538–544. [CrossRef]
42. Jang, Y.H.; Kim, S.M.; Eun, D.H.; Park, K.D.; Park, G.H.; Kim, B.S.; Li, K.; Park, C.O.; Kim, H.O.; Kim, H.S.; et al. Validity and Reliability of Itch Assessment Scales for Chronic Pruritus in Adults: A Prospective Multicenter Study. *J. Am. Acad. Dermatol.* **2020**, *82*, 80–86. [CrossRef]
43. Narita, I.; Tsubakihara, Y.; Uchiyama, T.; Okamura, S.; Oya, N.; Takahashi, N.; Gejyo, F.; Yamamoto, A.; Ichikawa, A.; Ohishi, A.; et al. Efficacy and Safety of Difelikefalin in Japanese Patients With Moderate to Severe Pruritus Receiving Hemodialysis: A Randomized Clinical Trial. *JAMA Netw. Open* **2022**, *5*, e2210339. [CrossRef] [PubMed]
44. Fishbane, S.; Wen, W.; Munera, C.; Menzaghi, F.; McCafferty, K. Long-Term Safety and Efficacy of Difelikefalin in Subjects With Chronic Kidney Disease–Associated Pruritus: Analysis From KALM-1 and KALM-2. *SKIN J. Cutan. Med.* **2021**, *5*, s75. [CrossRef]
45. Sutaria, N.; Adawi, W.; Goldberg, R.; Roh, Y.S.; Choi, J.; Kwatra, S.G. Itch: Pathogenesis and Treatment. *J. Am. Acad. Dermatol.* **2022**, *86*, 17–34. [CrossRef] [PubMed]
46. Langedijk, J.A.G.M.; Beuers, U.H.; Oude Elferink, R.P.J. Cholestasis-Associated Pruritus and Its Pruritogens. *Front. Med.* **2021**, *8*, 224. [CrossRef]
47. Bailey, A.J.M.; Li, H.O.Y.; Kirchhof, M.G. Novel Kappa-Opioid Receptor Agonist for the Treatment of Cholestatic Pruritus: Systematic Review. *JMIR Dermatol.* **2022**, *5*, e30737. [CrossRef]
48. Komiya, E.; Tominaga, M.; Kamata, Y.; Suga, Y.; Takamori, K. Molecular and Cellular Mechanisms of Itch in Psoriasis. *Int. J. Mol. Sci.* **2020**, *21*, 8406. [CrossRef]
49. Georgala, S.; Schulpis, K.H.; Papaconstantinou, E.D.; Stratigos, J. Raised β-Endorphin Serum Levels in Children with Atopic Dermatitis and Pruritus. *J. Dermatol. Sci.* **1994**, *8*, 125–128. [CrossRef]
50. Glinski, W.; Brodecka, H.; Glinska-Ferenz, M.; Kowalski, D. Increased Concentration of Beta-endorphin in Sera of Patients with Psoriasis and Other Inflammatory Dermatoses. *Br. J. Dermatol.* **1994**, *131*, 260–264. [CrossRef]

51. Takahashi, N.; Tominaga, M.; Kosaka, R.; Kamata, Y.; Umehara, Y.; Matsuda, H.; Sakaguchi, A.; Ogawa, H.; Takamori, K. Involvement of M-Opioid Receptors and κ-Opioid Receptors in Itch-Related Scratching Behaviour of Imiquimod-Induced Psoriasis-like Dermatitis in Mice. *Acta Derm. Venereol.* **2017**, *97*, 928–933. [CrossRef]
52. Nakasone, T.; Sato, T.; Matsushima, Y.; Inoue, T.; Kamei, C. Characteristics of Scratching Behavior in ADJM Mice (Atopic Dermatitis from Japanese Mice). *Immunopharmacol. Immunotoxicol.* **2015**, *37*, 202–206. [CrossRef]
53. Sagita Moniaga, C.; Iwamoto, S.; Kitamura, T.; Fujishiro, M.; Takahashi, N.; Kina, K.; Ogawa, H.; Tominaga, M.; Takamori, K. Plasma Dynorphin A Concentration Reflects the Degree of Pruritus in Chronic Liver Disease: A Preliminary Report. *Acta Derm. Venereol.* **2019**, *99*, 442–443. [CrossRef] [PubMed]
54. Düll, M.M.; Wolf, K.; Vetter, M.; Dietrich, P.; Neurath, M.F.; Kremer, A.E. Endogenous Opioid Levels Do Not Correlate With Itch Intensity and Therapeutic Interventions in Hepatic Pruritus. *Front. Med.* **2021**, *8*, 454. [CrossRef] [PubMed]
55. Zoccali, C.; Ciccarelli, M.; Mallamaci, F.; Maggiore, Q.; Lotti, M.; Zucchelli, G.C. Plasma Met-Enkephalin and Leu-Enkephalin in Chronic Renal Failure. *Nephrol. Dial. Transplant.* **1987**, *1*, 219–222. [CrossRef] [PubMed]
56. Danno, K.; Nishiura, K.; Tanaka, M. Increased Met-Enkephalin Plasma Levels in Hemodialysis Patients with or without Pruritus. *J. Dermatol. Sci.* **1995**, *10*, 238–240. [CrossRef]
57. Klin, M.; Waluga, M.; Rudka, R.; Madej, A.; Janiszewska, M.; Grzebieniak, E.; Wesolowsky, A. Plasma Catecholamines, Neuropeptide Y and Leucine-Enkephalin in Uremic Patients before and after Dialysis during Rest and Handgrip. *Boll. Chim. Farm.* **1998**, *137*, 306–313. [PubMed]
58. Spivey, J.R.; Jorgensen, R.A.; Gores, G.J.; Lindor, K.D. Methionine-Enkephalin Concentrations Correlate with Stage of Disease but Not Pruritus in Patients with Primary Biliary Cirrhosis. *Am. J. Gastroenterol. Suppl.* **1994**, *89*, 2028–2032. [CrossRef]
59. Taneda, K.; Tominaga, M.; Negi, O.; Tengara, S.; Kamo, A.; Ogawa, H.; Takamori, K. Evaluation of Epidermal Nerve Density and Opioid Receptor Levels in Psoriatic Itch. *Br. J. Dermatol.* **2011**, *165*, 277–284. [CrossRef]
60. Kupczyk, P.; Reich, A.; Hołysz, M.; Gajda, M.; Wysokińska, E.; Kobuszewska, A.; Nevozhay, D.; Nowakowska, B.; Strządała, L.; Jagodziński, P.P.; et al. Opioid Receptors in Psoriatic Skin: Relationship with Itch. *Acta Derm. Venereol.* **2017**, *97*, 564–570. [CrossRef]
61. Velenosi, T.J.; Urquhart, B.L. Pharmacokinetic Considerations in Chronic Kidney Disease and Patients Requiring Dialysis. *Expert Opin. Drug Metab. Toxicol.* **2014**, *10*, 1131–1143. [CrossRef]
62. Böger, R.H. Renal Impairment: A Challenge for Opioid Treatment? The Role of Buprenorphine. *Palliat. Med.* **2016**, *20*, 17–23. [CrossRef]
63. Mercadante, S. Opioid Metabolism and Clinical Aspects. *Eur. J. Pharmacol.* **2015**, *769*, 71–78. [CrossRef] [PubMed]

7. STRESZCZENIE W JĘZYKU POLSKIM

Rozprawa doktorska oparta jest o cykl trzech monotematycznych artykułów opublikowanych w międzynarodowych czasopismach naukowych indeksowanych w bazie PubMed i uwzględnionych na liście Journal Citation Reports oraz znajdujących się w wykazie czasopism naukowych Ministerstwa Edukacji i Nauki (MEiN). Artykuły wchodzące w skład rozprawy doktorskiej zostały zaakceptowane do publikacji w międzynarodowych czasopismach o łącznym współczynniku wpływu (Impact Factor – IF) 15,143 oraz punktacji MEiN 380 punktów.

Pierwszą pracą spośród cyklu jest przegląd systematyczny piśmiennictwa dotyczący zastosowania difelikefaliny w leczeniu świądu u pacjentów dializowanych. Stanowi ona podsumowanie aktualnej wiedzy na temat klinicznej efektywności oraz bezpieczeństwa stosowania nowego agonisty receptora kappa-opioidowego – difelikefaliny w leczeniu świądu mocznicowego. Przeglądu dokonano zgodnie z wytycznymi protokołu PRISMA w maju 2022r.

Następnie, w badaniach będących podstawą drugiej i trzeciej publikacji cyklu oceniono stężenia neurotrofin oraz endogennych opioidów w surowicy pacjentów dializowanych. Badania prowadzono w latach 2020-2023. Do badań włączono grupę liczącą 126 pacjentów przewlekle hemodializowanych, z których prawie połowa (62 pacjentów) cierpiała na świąd skóry. Od wszystkich pacjentów zostały zebrane dane demograficzne oraz kliniczne, a następnie została pobrana próbka krwi. Stężenia neuroprzekaźników – neurotrofin (NT4 i BDNF) oraz endogennych opioidów (met-enkefaliny, leu-enkefaliny, dynorfiny A oraz beta-endorfiny) oceniono metodą ELISA z wykorzystaniem komercyjne dostępnych kitów. Nasilenie świądu (największe nasilenie świądu w ciągu ostatnich trzech dni) oceniano z użyciem skali numerycznej (ang. Numerical Rating Scale, NRS). Ponadto, pacjenci byli również proszeni o wypełnienie kwestionariusza UP-Dial, który ocenia nasilenie świądu i jego wpływu na jakość życia pacjentów dializowanych oraz ItchyQoL, stworzonego do oceny jakości życia u pacjentów ze świądem. Następnie, przeanalizowano różnicę stężeń neuroprzekaźników między poszczególnymi grupami oraz zbadano korelację stężenia badanych substancji z nasileniem świądu i jakością życia pacjentów.

W badaniach przeprowadzonych wśród pacjentów dializowanych wykazano, że pacjenci ze świądem mają istotnie wyższe stężenie NT-4 ($p=0.003$) w porównaniu do grupy bez świądu. Nie odnotowano znaczącej różnicy w poziomie BDNF w surowicy między badanymi grupami pacjentów.

W kolejnym etapie pracy badawczej wykazano istotnie niższe stężenie beta-endorfiny w grupie pacjentów dializowanych w porównaniu z pacjentami bez świądu oraz grupą kontrolną ($p<0.001$). Ponadto, zaobserwowano istotną statystycznie różnicę pomiędzy stężeniem dynorfiny A w grupie pacjentów dializowanych ze świądem i bez świądu w porównaniu do grupy kontrolnej ($p<0.001$). Stosunek stężeń beta-endorfiny do dynorfiny A był istotnie niższy w grupie pacjentów ze świądem w porównaniu z pacjentami bez świądu i grupą kontrolną ($p=0.005$). Zaobserwowano też wyższe stężenie met-enkefaliny w grupie chorych ze świądem w porównaniu z grupą kontrolną ($p=0.009$).

Średnie maksymalne nasilenie świądu zgłaszane przed pacjentów wynosiło 4.9 ± 2.2 punktów w skali NRS. Świąd w stopniu co najmniej umiarkowanym występował u 46 (74.2%) pacjentów. Jakość życia pacjentów ze świądem została oceniona na 14.2 ± 9.8 punktów według kwestionariusza UP-Dial oraz 36.7 ± 13.7 według kwestionariusza ItchyQoL. Stężenia badanych opioidów oraz neurotrofin nie korelowały z nasileniem świądu ani jakością życia pacjentów.

Analizowane w przeglądzie systematycznym badania kliniczne wykazały, że difelikefalina stosowana w dawce 0.5 μg/kg przez 8-12 tygodni skutecznie zmniejsza świąd u pacjentów dializowanych z redukcją średnio o 3.65 – 3.8 punktów w skali NRS. Zmniejszenie nasilenia świądu o minimum 3 punkty w skali NRS uzyskano u 49.1 - 64% pacjentów, a o 4 punkty u 40.5 – 51% badanych. Odnotowano również poprawę jakości życia ocenianej na podstawie m.in. skali Skindex oraz 5-D itch scale. Najczęściej zgłaszane działania niepożądane były łagodne i obejmowały nudności, wymioty, zawroty głowy i biegunkę.

Podsumowując, wyniki prac zawartych w rozprawie doktorskiej potwierdzają możliwą rolę neuroprzekaźników w patogenezie przewlekłego świądu u pacjentów dializowanych. Ponadto, wskazują potencjalny kierunek dalszych badań mających na celu poszukiwania nowych substancji, które hamując lub modulując impulsy nerwowe prowadzące do występowania świądu, mogłyby stać się nową, efektywną metodą terapeutyczną leczenia przewlekłego świądu u pacjentów ze schyłkową niewydolnością nerek, co przełoży się na poprawę jakości ich życia.

8. STRESZCZENIE W JĘZYKU ANGIELSKIM

The doctoral dissertation is based on a series of three monothematic articles published in international scientific journals indexed in the PubMed database and included in the Journal Citation Reports list, as well as in the list of scientific journals of the Ministry of Education and Science (MEiN). The articles included in the doctoral dissertation have been accepted for publication in international journals with a total Impact Factor (IF) of 15.143 and a MEiN score of 380 points.

The first work in the series is a systematic review of the literature on the use of difelikefalin in the treatment of pruritus in dialysis patients. It is a summary of the current knowledge on the clinical effectiveness and safety of the use of a novel kappa-opioid receptor agonist - difelikefalin in the treatment of uremic pruritus. The review was carried out in accordance with the PRISMA protocol guidelines in May 2022.

In the studies being the basis for the second and third publications of the series, the concentrations of neurotrophins and endogenous opioids in the serum of dialysis patients were assessed. The research was conducted in 2020-2023. A group of 126 patients on chronic hemodialysis was included in the study, almost half of whom (62 patients) suffered from pruritus. Demographic and clinical data, as well as a blood sample were collected from all patients. Concentrations of neurotransmitters – neurotrophins (NT4 and BDNF) and endogenous opioids (met-enkephalin, leu-enkephalin, dynorphin A and beta-endorphin) were assessed by ELISA using commercially available kits. The severity of pruritus (the worst severity of pruritus in the last three days) was assessed using a Numerical Rating Scale (NRS). In addition, patients were also asked to complete the UP-Dial questionnaire, which assesses the severity of itching and its impact on the quality of life of dialysis patients, and the ItchyQoL, designed to assess the quality of life in patients with pruritus. Then, the difference in the concentration of neurotransmitters between the groups was analyzed and the correlation of the concentration of the tested substances with the severity of itching and the quality of life of patients was examined.

In studies conducted among dialysis patients, it was shown that patients with pruritus have significantly higher NT-4 concentrations ($p=0.003$) compared to the group without pruritus. There was no significant difference in serum BDNF levels between the study groups.

In the next stage of the research, a significantly lower concentration of beta-endorphin was found in the group of dialysis patients compared to patients without pruritus and the control

group ($p<0.001$). In addition, a statistically significant difference was observed between the concentration of dynorphin A in the group of dialysis patients with and without pruritus compared to the control group ($p<0.001$). The beta-endorphin to dynorphin A ratio was significantly lower in the pruritic group than in the non-pruritic group and the control group ($p=0.005$). A higher concentration of met-enkephalin was also observed in the group of patients with pruritus compared to the control group ($p=0.009$).

The mean maximum severity of pruritus reported by the patients was 4.9 ± 2.2 points in the NRS score. Pruritus was at least moderate in 46 (74.2%) patients. The quality of life of patients with pruritus was assessed at 14.2 ± 9.8 points according to the UP-Dial questionnaire and 36.7 ± 13.7 according to the ItchyQoL questionnaire. The concentrations of the studied opioids and neurotrophins did not correlate with the severity of pruritus or the patients' quality of life.

Clinical trials analyzed in a systematic review showed that difelikefalin used at a dose of 0.5 μg/kg for 8-12 weeks was effective in reducing pruritus in dialysis patients with an average reduction of 3.65 - 3.8 points in the NRS score. Reduction in the severity of pruritus by at least 3 points was obtained in 49.1 - 64% of patients, and by 4 points in 40.5 - 51% of the subjects. There was also an improvement in the quality of life assessed using e.g. Skindex scale and 5-D itch scale. The most commonly reported adverse reactions were mild and included nausea, vomiting, dizziness and diarrhoea.

In conclusion, the results of the work included in the doctoral dissertation confirm the possible role of neurotransmitters in the pathogenesis of chronic pruritus in dialysis patients. In addition, they indicate the possible direction of further research aimed at searching for new substances that, by inhibiting or modulating nerve impulses leading to the occurrence of pruritus, could become a new, effective therapeutic method in the treatment of chronic pruritus in patients with end-stage renal disease, which will lead to an improvement in their quality of life.

9. OPINIA KOMISJI BIOETYCZNEJ

KOMISJA BIOETYCZNA
przy
Uniwersytecie Medycznym
we Wrocławiu

OPINIA KOMISJI BIOETYCZNEJ Nr KB – 253/2023

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)
prof. dr hab. Krzysztof Kaliszewski (chirurgia endokrynologiczna)
dr prawa Andrzej Malicki (prawo)
dr hab. Marcin Mączyński, prof.UMW (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.

„Badania nad neuroprzekaźnikami w patogenezie świądu mocznicowego"

zgłoszonym przez lek. Kamilę Wala-Zielińską, zatrudnioną w Katedrze i Klinice Dermatologii, Wenerologii i Alergologii Uniwersytetu Medycznego we Wrocławiu oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła **wyrazić zgodę** na przeprowadzenie badania w Katedrze i Klinice Dermatologii, Wenerologii i Alergologii Uniwersytetu Medycznego we Wrocławiu oraz Klinice Nefrologii i Medycyny Transplantacyjnej Uniwersytetu Medycznego we Wrocławiu pod nadzorem prof. dr hab.

Jacka Szepietowskiego, **pod warunkiem zachowania anonimowości zgromadzonych danych.**

UWAGA: Jeśli projekt/badanie wymaga ubezpieczenia na podstawie Rozporządzenia Ministra Finansów, Funduszy i Polityki Regionalnej z dnia 23.12.2020r. w sprawie obowiązkowego ubezpieczenia odpowiedzialności cywilnej podmiotu przeprowadzającego eksperyment medyczny, Wnioskodawca zobowiązany jest do złożenia wniosku o zawarcie umowy ubezpieczenia odpowiedzialności cywilnej zgodnie z procedurą przyjętą w Uniwersytecie Medycznym we Wrocławiu. W takim przypadku pozytywna opinia Komisji Bioetycznej ma charakter warunkowy i będzie uprawniała do prowadzenia Badania pod warunkiem zawarcia przez Uniwersytet umowy ubezpieczenia OC zgodnie z Rozporządzeniem wskazanym w zdaniu poprzednim.

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 9.03.2023

10. CURRICULUM VITAE

CURRICULUM VITAE

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Edukacja:

Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu — 10.2014 – 06.2020

Kierunek Lekarski, Wydział lekarski

Technische Universität - Faculty of Medicine Carl Gustav Carus — 10.2018 – 06.2019

Drezno, Niemcy - ERASMUS + Exchange Scholarship

Doświadczenie:

Zawodowe:

Lekarz rezydent (w trakcie specjalizacji) — 01/12/2021 – obecnie
Klinika Dermatologii, Wenerologii i Alergologii, Uniwersytecki Szpital Kliniczny im. Mikulicza Radeckiego we Wrocławiu

Lekarz (stażysta) *Dolnośląskie Centrum Onkologii we Wrocławiu* — 01/10/2020 – 31/10/2021

Staże międzynarodowe:

Universitätsklinikum Carl Gustav Carus Dresden, Niemcy	07/2019 – 08/2019
Centro Hospitalar e Universitário de Coimbra, Portugalia	07/2018 – 08/2018

Naukowe:

Publikacje:

• 10 pełnotekstowych artykułów opublikowanych w międzynarodowych czasopismach indeksowanych w bazie PubMed, z czego 5 jako pierwszy autor

• Całkowity współczynnik wpływu (Impact Factor) opublikowanych prac = 59,152

• Punktacja ministerialna: 1352,0

Granty i Nagrody:

• Medal im. Ludwika Hirszfelda dla najlepszego absolwenta

• Grant naukowy dla studentów i doktorantów z Funduszu Aktywności Studenckiej w ramach projektu „Wpływ 6-Gingerolu na cykl komórkowy i apoptozę komórek raka piersi w monoterapii oraz w skojarzeniu z paklitakselem –badania in vitro”

• Wielokrotne stypendia rektora dla najlepszych studentów

Członkostwo w towarzystwach naukowych:

• Polskie Towarzystwo Dermatologiczne

• International Society of Dermatology

• European Academy of Dermatology and Venerology

• International Forum for the Study of Itch

11. DOROBEK NAUKOWY

I. Publikacje w czasopiśmie naukowym z IF

1. **Wala Kamila,** Szlasa Wojciech, Saczko Jolanta, Rudno-Rudzińska Julia, Kulbacka Julita: Modulation of blood-brain barrier permeability by activating adenosine A2 receptors in oncological treatment, Biomolecules, 2021, vol. 11, nr 5, art.633, DOI:10.3390/biom11050633

2. **Wala Kamila,** Szlasa Wojciech, Sauer Natalia, Kasperkiewicz-Wasilewska Paulina, Szewczyk Anna, Saczko Jolanta, Rembiałkowska Nina, Kulbacka Julita, Baczyńska Dagmara: Anticancer efficacy of 6-gingerol with paclitaxel against wild type of human breast adenocarcinoma, Molecules, 2022, vol. 27, nr 9, art.2693, DOI:10.3390/molecules27092693

3. Szlasa Wojciech, Gachowska Martyna, Kiszka Karolina, Rakoczy Katarzyna, Kiełbik Aleksander, **Wala Kamila,** Puchała Julia, Chorążykiewicz Katarzyna, Saczko Jolanta, Kulbacka Julita: Iron chelates in the anticancer therapy, Chemical Papers, 2022, vol. 76, nr 3, s. 1285-1294, DOI:10.1007/s11696-021-02001-2

4. Paluszkiewicz Patrycja, Martuszewski Adrian, Zaręba Natalia, **Wala Kamila,** Banasik Mirosław, Kepinska Marta: The application of nanoparticles in diagnosis and treatment of kidney diseases, International Journal of Molecular Sciences, 2022, vol. 23, nr 1, art.131, DOI:10.3390/ijms23010131

5. Szymonik Julia, **Wala Kamila,** Górnicki Tomasz, Saczko Jolanta, Pencakowski Bartosz, Kulbacka Julita: The impact of iron chelators on the biology of cancer stem cells, International Journal of Molecular Sciences, 2022, vol. 23, nr 1, art.89, DOI:10.3390/ijms23010089

6. **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, DOI:10.3390/jcm11216292

7. **Wala Kamila,** Szepietowski Jacek C.: Difelikefalin in the treatment of chronic kidney disease-associated pruritus: a systematic review, Pharmaceuticals, 2022, vol. 15, nr 8, art.934, DOI:10.3390/ph15080934

8. **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 disease-associated pruritus in dialysis patients, Journal of Clinical Medicine, 2023, vol. 12, nr 7, art.2474, DOI:10.3390/jcm12072474

9. Maj Joanna, **Wala Kamila,** Szepietowski Jacek C.: Monkeypox with exclusive genital lesions [letter to the editor], Journal of the European Academy of Dermatology and Venereology, 2023, vol. 37, nr 4, e522-e523, DOI:10.1111/jdv.18621

10. Chernyshov Pavel V., **Wala Kamila**, Wójcik Ewa, Szepietowski Jacek C.: Improvement of the attitude of students to persons with skin diseases after a single presentation of patients stories: A pilot study [letter to the editor], Journal of the European Academy of Dermatology and Venereology, 2023, vol. 37, nr 4, e532-e534, DOI:10.1111/jdv.18744

II. Publikacje w czasopiśmie naukowym bez IF

1. **Wala Kamila,** Zieliński Karol, Zdrojewicz Zygmunt. Rola selenu w patogenezie chorób tarczycy. Medycyna Rodzinna, 2018, 21(2A), 46-50.

2. Szlasa Wojciech, **Wala Kamila,** Kiełbik Aleksander, Zalesińska Aleksandra, Saczko Jolanta, Kulbacka Julita: Connection between Warburg effect and oncometabolites biosynthesis with its clinical implications, Organic & Medicinal Chemistry International Journal, 2020, 9, 121-130.

III. Rozdziały w monografiach

1. Kuczyńska Martyna, **Wala Kamila,** Elnour Dominika Abdalla, Gajos Piotr, Cebulski Kamil, Paprocka-Borowicz Małgorzata, Gnus Jan: Dylematy etyczne i niejasności medyczne. Kiedy stwierdzić śmierć mózgu? W: W drodze do brzegu życia. T.15: praca zbiorowa, (red.) Elżbieta Krajewska-Kułak [i in.], Białystok 2017, Uniwersytet Medyczny w Białymstoku, s. 107-115, ISBN 978-83-944852-4-5

2. Cebulski Kamil, Gajos Piotr, Kuczyńska Martyna, **Wala Kamila**, Jaszczak Jakub, Dorna Krzysztof, Paprocka-Borowicz Małgorzata, Gnus Jan: Współczesna medycyna a życie społeczne pacjenta - brakujący element w drabinie terapeutycznej, W: W drodze do brzegu życia. T.15: praca zbiorowa, (red.) Elżbieta Krajewska-Kułak [i in.], Białystok 2017, Uniwersytet Medyczny w Białymstoku, s. 703-710, ISBN 978-83-944852-4-5

3. **Wala Kamila**, Kuczyńska Martyna, Makarewicz Olga, Drewniak Maciej, Kurzelewska-Sobczak Anna, Dorna Krzysztof, Gnus Jan: Problem i terapia bezsenności u osób cierpiących na choroby nowotworowe, W: W drodze do brzegu życia. T.16: praca zbiorowa, (red.) Elżbieta Krajewska-Kułak [i in.], Białystok 2018, Uniwersytet Medyczny w Białymstoku, s. 224-239, ISBN 978-83-946571-9-2

4. Gworys Martyna, Kolasa Wojciech, Gibasiewicz Marcin, **Wala Kamila**, Dorna Krzysztof, Paprocka-Borowicz Małgorzata, Gnus Jan: Wiedza studentów Wydziału Lekarskiego na temat hospicjów perinatalnych w Polsce, W: W drodze do brzegu życia. T.16: praca zbiorowa, (red.) Elżbieta Krajewska-Kułak [i in.], Białystok 2018, Uniwersytet Medyczny w Białymstoku, s. 362-369, ISBN 978-83-946571-9-2

5. Makarewicz Olga, Kuczyńska Martyna, **Wala Kamila**, Cebulski Kamil, Dorna Krzysztof, Ferenc Stanisław, Gnus Jan: Żałoba jako doświadczenie nieuniknione, W: W drodze do brzegu życia. T.16: praca zbiorowa, (red.) Elżbieta Krajewska-Kułak [i in.], Białystok 2018, Uniwersytet Medyczny w Białymstoku, s. 444-462, ISBN 978-83-946571-9-2

6. Kuczyńska Martyna, **Wala Kamila**, Makarewicz Olga, Jaszczak Jakub, Dorna Krzysztof, Gnus Jan: Jak współczesna medycyna podchodzi do tematu wielokulturowości? Wspólne szanse i zagrożenia, W: W drodze do brzegu życia. T.16: praca zbiorowa, (red.) Elżbieta Krajewska-Kułak [i in.], Białystok 2018, Uniwersytet Medyczny w Białymstoku, s. 602-610, ISBN 978-83-946571-9-2

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IV. Doniesienia zjazdowe

1. **Kamila Wala-Zielińska:** Neurotrofiny jako potencjalny czynnik biorący udział w patogenezie świądu związanego z przewlekłą chorobą nerek u pacjentów dializowanych. 32 Zjazd Polskiego Towarzystwa Dermatologicznego, Lublin, Polska, 31.05-03.06.2023.
2. **Kamila Wala-Zielińska:** Ocena stężenia endogennych opioidów w surowicy pacjentów dializowanych oraz analiza wpływu tych substancji na występowanie świądu związanego z przewlekłą chorobą nerek. 32 Zjazd Polskiego Towarzystwa Dermatologicznego, Lublin, Polska, 31.05-03.06.2023.

12. OŚWIADCZENIA WSPÓŁAUTORÓW

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Wala Kamila, Szepietowski Jacek C., 2022: Difelikefalin in the treatment of chronic kidney disease-associated pruritus: a systematic review, Pharmaceuticals, 15(8), 934.

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