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Wybrane aspekty kliniczne oraz patogenetyczne świądu w cukrzycy

ROZPRAWA DOKTORSKA

Cykl publikacji powiązanych tematycznie

PROMOTOR:

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Jeśli widzę dalej, to tylko dlatego, że stoję na ramionach olbrzymów.

- Isaac Newton

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1. CYKL PRAC STANOWIĄCYCH ROZPRAWĘ DOKTORSKĄ

1. **Aleksandra A Stefaniak**, Iwona Chlebicka, Jacek C Szepietowski. *Itch in diabetes: a common underestimated problem*. Adv. Dermatol. Allergol. 2021; 38(2): 177-183
   IF: 1,837; Punktacja Ministerialna: 70 punktów

2. **Aleksandra A Stefaniak**, Agnieszka Zubkiewicz-Kucharska, Łukasz Matusiak, Anna Noczyńska, Jacek C Szepietowski. *Itch in children with type 1 diabetes: a cross-sectional study.* Dermatol. Ther. *(Heidelberg)*. 2020; 10(4):745-756
   IF: 3,264; Punktacja Ministerialna: 100 punktów

3. **Aleksandra A Stefaniak**, Piotr K Krajewski, Dorota Bednarska-Chabowska, Marek Bolanowski, Grzegorz Mazur, Jacek C Szepietowski. *Itch in adult population with type 2 diabetes mellitus: clinical profile, pathogenesis and disease-related burden in a cross-sectional study.* Biology *(Basel)* 2021;10(12):1332
   IF: 5,079; Punktacja Ministerialna: 100 punktów

4. **Aleksandra A Stefaniak**, Konstantin Agelopoulos, Dorota Bednarska-Chabowska, Grzegorz Mazur, Sonja Ständer, Jacek C Szepietowski *Small-fibre Neuropathy in Patients with Type 2 Diabetes Mellitus and its Relationship with Diabetic Itch: Preliminary Results.* Acta Derm. Venereol. 2022; 102: adv00719
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2. WYKAZ SKRÓTÓW

WHO	Światowa Organizacja Zdrowia (ang. *World Health Organization*)
IFSI	Międzynarodowe Forum na rzecz Badania Świądu (ang. *International Forum for Study of Itch*)
HbA1c	hemoglobina glikowana
CRP	białko ostrej fazy
BMI	wskaźnik masy ciała (ang. *body mass index)*
NRS	Numeryczna Skala Oceny (ang. *Numerical Rating Scale*)
4IIQ	4-stopniowy Kwestionariusz Świądu (ang. *4-Item Itch Questionnaire*)
CDLQI	Pediatryczny Dermatologiczny Kwestionariusz Oceny Jakości Życia (ang. *Children's Dermatology Life Quality Index*)
ItchyQoL	Kwestionariusz jakości życia specyficzny dla świądu
6-ISS	Sześcioczynnikowa Skala Stygmatyzacji (ang. *6-Item Stigmatization Scale*)
HADS	Szpitalna Skala Lęku i Depresji (ang. *Hospital Anxiety and Depression Scale*)
IENFD	gęstość śródnaskórkowych włókien nerwowych (ang. *intraepidermal nerve fiber density*)

3. OMÓWIENIE ROZPRAWY DOKTORSKIEJ

2.1 Wstęp

Cukrzyca i jej powikłania stanowią poważny problem na całym świecie. Międzynarodowa Federacja Diabetologiczna (International Diabetes Federation) oszacowała, że w 2015 roku 1 na 11 dorosłych (415 milionów dorosłych) miał cukrzycę. Cukrzyca jest też problemem o rosnącym znaczeniu - szacuje się, że do 2040 r. liczba chorych wzrośnie aż do 642 milionów, a największy wzrost będzie pochodził z regionów, które przechodzą transformację gospodarczą z poziomu niskiego do średniego dochodu. Przyczyny nasilającej się epidemii cukrzycy są wielorakie, m.in. starzenie się społeczeństwa, rozwój gospodarczy, urbanizacja, niezdrowe nawyki żywieniowe i siedzący tryb życia. Cukrzycę opisuje się jako grupę zaburzeń metabolicznych charakteryzujących się wysokim poziomem glukozy we krwi z powodu wadliwego wydzielania i/lub działania insuliny. Objawy sugerujące obecność cukrzycy to: wielomocz, zwiększone pragnienie i utrata wagi, której nie można wyjaśnić zamierzoną redukcją masy ciała.

Cukrzycę dzieli się etiologicznie - według World Health Organization (WHO) - na główne grupy:

1. Cukrzyca typu 1, cukrzyca insulinozależna
2. Cukrzyca typu 2
3. Inne specyficzne formy cukrzycy i
4. Cukrzyca ciążowa.

Ponad 95% przypadków cukrzycy to cukrzyca typu 2 i 1.

Przewlekła hiperglikemia wiąże się z uszkodzeniem, dysfunkcją i niewydolnością różnych narządów, w szczególności oczu, nerek, nerwów, serca i naczyń krwionośnych. Choroby skóry występują u 79,2% pacjentów z cukrzycą i mogą się one pojawić zarówno jako jej pierwszy objaw lub rozwinąć się w dowolnym momencie w przebiegu tej choroby. Jako dermatologiczne manifestacje cukrzycy opisywano zarówno choroby nieinfekcyjne, jak i infekcyjne. W cukrzycy leżąca u podstaw patofizjologia, przebieg choroby, współistniejące choroby i leki - wszystko to predysponuje pacjentów do wystąpienia świądu.

Świąd definiuje się jako nieprzyjemne uczucie, które prowadzi do intensywnego drapania. Jest to częsty i niepokojący objaw występujący nie tylko w schorzeniach dermatologicznych, ale także w przewlekłych chorobach ogólnoustrojowych, stanowiący duże obciążenie

i obniżający jakość życia dotkniętej nim osoby. Według Międzynarodowego Forum Badania Świądu (International Forum for Study of Itch, IFSI), klasyfikacja etiologiczna przewlekłego świądu obejmuje 6 kategorii: (I) dermatologiczny, (II) układowy, (III) neurologiczny, (IV) psychogenny/psychosomatyczny, (V) mieszany i (VI) inny. Większość badaczy klasyfikuje świąd w cukrzycy jako świąd układowy, jednak niektórzy autorzy sugerują mieszaną etiologię świądu cukrzycowego z dodatkowym udziałem komponentów dermatologicznych i neurologicznych. Do tej pory tylko nieliczni badacze zajmowali się tematyką świądu w cukrzycy. W badaniach tych jednak zastosowano niespójne definicje i różne narzędzia do oceny świądu, a badane populacje były heterogenne.

2.2 Cel badań, problemy badawcze

Celem badania jest ocena częstości i nasilenia świądu u pacjentów z cukrzycą typu 1 oraz typu 2, opisanie jego klinicznej charakterystyki i eksploracja potencjalnych przyczyn, jak konsekwencji psychospołecznych.

Cele szczegółowe:

1. Przedstawienie klinicznej charakterystyki świądu skóry u pacjentów z cukrzycą typu 1.
2. Przedstawienie klinicznej charakterystyki świądu skóry u pacjentów z cukrzycą typu 2.
3. Analiza potencjalnych czynników etiopatogenetycznych świądu u pacjentów z cukrzycą typu 1 oraz cukrzycą typu 2.
4. Analiza aspektów psychospołecznych świądu w cukrzycy.
5. Podjęcie próby oceny czy neuropatia małych włókien może mieć wpływ na patogenezę świądu w cukrzycy.

2.3 Materiał i metody

2.3.1 Materiał i metody pierwszego artykułu

W pierwszej pracy przeprowadzono analizę dotychczasowych badań dotyczących świądu w cukrzycy. Analiza została przeprowadzona według wytycznych PRISMA. Włączono do niej pięć oryginalnych artykułów.

2.3.2 **Materiał i metody drugiego artykułu**

Badaniem dotyczącym oceny klinicznej świądu w populacji pediatrycznej z cukrzycą typu 1 zostało objętych 100 dzieci (7-18 lat).

Kryteria włączenia: rozpoznanie cukrzycy potwierdzone badaniami laboratoryjnymi, pisemna zgodą na udział podpisana przez rodziców.

Kryteria wyłączenia z analizy obejmowały: zaburzenia stanu psychicznego uniemożliwiające pacjentowi dokonanie szczegółowej oceny świądu; znane ciężkie choroby nerek lub wątroby; przewlekłe choroby dermatologiczne w wywiadzie.

Po włączeniu do badania zostały zebrane szczegółowe informacje dotyczące danych demograficznych, historii klinicznej, chorób współistniejących, poprzednich terapii i stosowanego leczenia. Sprawdzane były również parametry kliniczne, takie jak waga ciała, wzrost i BMI. Od pacjentów została pobrana krew w celu wykonania badań laboratoryjnych. Analiza próbek została przeprowadzona przy użyciu metod stosowanych w szpitalnym laboratorium (CRP, morfologia krwi obwodowej, testy biochemiczne), ze szczególnym uwzględnieniem parametrów wyrównania cukrzycy: hemoglobiny glikowanej (HbA1c) oraz glukozy na czczo. Nasilenie świądu oceniano za pomocą Numerycznej Skali Oceny (NRS, Numerical Rating Scale) i 4-stopniowego kwestionariusza świądu (4IIQ, 4-Item Itch Quastionnaire). Pacjenci zostali poproszeni o ocenę najgorszego świądu w ciągu ostatnich trzech dni i 24 godzin. Sprawdzane były także różne cechy kliniczne świądu, w tym dokładna lokalizacja, natężenie oraz deskryptory, jak również najczęstsze czynniki odpowiedzialne za jego nasilenie lub złagodzenie. Do oceny kwestii jakości życia zastosowano pediatryczny kwestionariusz oceny jakości życia (CDLQI, Children's Dermatology Life Quality Index). Zbadano również różne cechy kliniczne i czynniki wpływające na świąd. Suchość skóry została oceniona klinicznie oraz poprzez nieinwazyjną ocenę nawilżenia naskórka za pomocą korneometru CM825 (Courage & Khazaka, Koeln, Niemcy). Wizualna ocena suchości skóry została dokonana przy użyciu klinicznej skali suchości (skala 1-4 punktów, 1 punkt - brak suchości skóry, 2 punkty - suchość o niewielkim nasileniu, 3 punkty - suchość skóry, drobnoziarniste złuszczanie, 4 punkty - bardzo sucha skóra, widoczne gruboziarniste złuszczanie). Neuropatię oceniano według wytycznych WHO. Ocena czucia skórnego została przeprowadzona za pomocą testu monofilamentowego Semmesa-Weinsteina przy użyciu standaryzowanego monofilamentu 10 g. Czucie wibracyjne było sprawdzane za pomocą wystandaryzowanego stroika laryngologicznego 128 Hz. Za pomocą urządzenia Tip-Threm

(Thermo Feel) oceniane zostało odczuwanie temperatury. Odruch kolanowy był badany przy użycu neurologicznego młoteczka odruchowego.
Analizy statystyczne przeprowadzono przy użyciu oprogramowania Statistica 12 (StatSoft, Tulsa, OK, USA).

2.3.3 **Materiał i metody trzeciego artykułu**

Do badania dotyczącego klinicznej oceny świądu w populacji dorosłych z cukrzycą typu 2 zostało włączonych 104 pacjentów. Kryteria włączenia: rozpoznanie cukrzycy potwierdzone badaniami laboratoryjnymi.
Osoby z zaburzeniami stanu psychicznego uniemożliwiające pacjentowi dokonanie szczegółowej oceny świądu; znanymi ciężkimi choroby nerek lub wątroby; ze znanymi ciężkimi przewlekłymi chorobami dermatologicznymi w wywiadzie zostały wykluczone z badania. Tak jak i w populacji dziecięcej, w tym badaniu również zebrano dane dotyczące historii choroby, danych demograficznych, stosowanych leków przeciwcukrzycowych. Pobrana została także krew do badań laboratoryjnych. Zastosowano standaryzowane kwestionariusze w celu oceny intensywności świądu (NRS i 4IIQ). W celu oceny szerokiego spektrum obciążenia psychologicznego związanego ze świądem, wszyscy pacjenci ze świądem w przebiegu cukrzycy zostali poproszeni o wypełnienie zatwierdzonych polskich wersji językowych kwestionariusza jakości życia specyficznego dla świądu (ItchyQoL) oraz Sześcioczynnikowej Skali Stygmatyzacji (6-Item Stigmatization Scale, 6-ISS. Niezależnie od odczuwanego świądu, wszyscy pacjenci zostali poproszeni o wypełnienie Szpitalnej Skali Lęku i Depresji (Hospital Anxiety and Depression Scale, HADS).
ItchyQoL jest pierwszym kwestionariuszem pierwotnie poświęconym objawom świądowym i koncentruje się nie tylko na wpływie świądu na codzienne czynności, ale również na charakterystyce objawów i doświadczanego poziomu obciążenia psychologicznego. Ocenia on 3 wymiary świądu: objawy, funkcjonowanie i emocje. ItchyQoL nadaje się również do stosowania u pacjentów ze świądem bez pierwotnych zmian skórnych. Ocena ItchyQoL składa się z 22 pytań, ocenianych na 5-punktowej skali od 1 (nigdy) do 5 (cały czas), a suma tworzy ogólny wynik ItchyQoL (22-110 punktów). Ogólny wynik ItchyQoL odpowiada poziomowi upośledzenia jakości życia związanej ze zdrowiem, zależnej od świądu, w następujący sposób: 0-30 punktów (bardzo łagodne); 31-50 punktów (łagodne); 51-80 punktów (umiarkowane); i 81-110 punktów (ciężkie upośledzenie). Podskale (objawy, funkcjonowanie i emocje) są obliczane jako średnie wyniki odnoszące się do danej kategorii (zakres 1-5 punktów).

Do oceny poziomu stygmatyzacji (zakres punktów 0-18) opracowano 6-ISS. Im wyższa punktacja, tym większy odczuwany przez pacjenta poziom stygmatyzacji.
HADS jest używana jako skala samooceny składająca się z 14 pozycji przeznaczonych do pomiaru lęku i depresji. Obejmuje ona siedem pozycji oceniających lęk i siedem oceniających depresję, każda z punktacją od 0 do 3 punktów. Wyniki w zakresie od 0 do 7 punktów są uważane za nieodbiegające od normy, od 8 do 10 punktów za przypadek graniczny, a od 11 do 21 punktów za wymagające dalszych badań lub leczenia.
Suchość skóry oceniano klinicznie i za pomocą nieinwazyjnej oceny nawilżenia naskórka korneometru CM825 (Courage & Khazaka, Koeln, Niemcy). Wizualna ocena suchości skóry została dokonana przy użyciu klinicznej skali suchości (0-4 punkty). Neuropatię oceniano klinicznie, a następnie za pomocą klinicznej skali neuropatii Katzenwadela.
Analiza statystyczna uzyskanych wyników została przeprowadzona przy użyciu programu Statistica v. 12 (StatSoft, Kraków, Polska).

2.3.4 **Materiał i metody czwartego artykułu**

Do tego badania zostało włączonych dwunastu pacjentów ze świądem w cukrzycy typu 2, a jedenastu pacjentów bez dolegliwości świądowych stanowiło grupę kontrolną. Od każdego pacjenta została pobrana 4-mm biopsja sztancowa z dystalnej części podudzia w celu oceny gęstości śródnaskórkowych włókien nerwowych (intraepidermal nerve fiber density, IENFD), jak i krew do badań laboratoryjnych w celu oznaczenia stężenia HbA1c oraz glukozy na czczo. W celu oceny IENFD biopsje były natychmiast utrwalane w 4% paraformaldehydzie przez 2 godziny, a następnie przechowywane przez noc w 5% sacharozie, buforowane w 10% i 20% sacharozie, a po 6 godzinach przechowywane w ciekłym azocie. Z każdej biopsji wycięto trzy 40-µm krioplasty, które następne zostały rozmrożone na szkiełkach mikroskopowych (Dako Cytomation GmbH, Hamburg, Niemcy) i przygotowane do barwienia immunofluorescencyjnego. Sekcje były inkubowane przez noc z przeciwciałem pierwotnym, poliklonalnym przeciwciałem przeciwko produktowi genu specyficznego dla neuronów hydrolazy białkowej (PGP) 9.5 (przeciwciało królicze 1:200; Zytomed, Berlin, Niemcy) w temperaturze pokojowej. Wycinki były barwione przeciwciałem wtórnym - izotiocyjanianem fluoresceiny (FITC) (1:200; świńska przeciwkrólicza immunoglobulina FITC; Dako, Glostrup, Dania) przez 2 godziny. Próbki były odczytywane za pomocą mikroskopu fluorescencyjnego Zeiss Axioplan (Zeiss, Oberkochen, Niemcy) przez jednego przeszkolonego i zaślepionego badacza. Skanowanie w poszukiwaniu nerwów śródnaskórkowych odbywało się w dwóch płaszczyznach: poziomo wzdłuż granicy naskórkowo-skórnej i pionowo przez ogniskowanie

przez grubość przekroju w celu wykrycia każdego odgałęzienia nerwowego i jego przebiegu, zgodnie z wytycznymi.

Tak jak i we wcześniejszych manuskryptach i tu zastosowano standaryzowane kwestionariusze w celu oceny intensywności świądu (NRS i 4IIQ). Suchość skóry oceniano klinicznie i za pomocą nieinwazyjnej oceny nawilżenia naskórka (korneometru CM825 (Courage & Khazaka, Koeln, Niemcy). Neuropatię oceniano także za pomocą klinicznej skali neuropatii Katzenwadela.

Analizy statystyczne przeprowadzono przy użyciu programu IBM SPSS Statistics for Windows, wersja 25.0 (Armonk, NY, USA).

2.4 Podsumowanie wyników

2.4.1 **Wyniki pierwszego artykułu**

Wśród 5 uwzględnionych oryginalnych artykułów, częstość występowania świądu została oszacowana na 18,4% do 27,5%. Suchość skóry i polineuropatia cukrzycowa okazały się sugerowanymi dwoma głównymi czynnikami związanymi z patogenezą świądu w cukrzycy. Nadal nie jest dokładnie określone, w jaki sposób kontrola glikemii jest związana z uogólnionym świądem. Nie istnieje leczenie z wyboru, jednak terapia miejscowa (emolienty) przynosi znaczną ulgę u części pacjentów.

2.4.2 **Wyniki drugiego artykułu**

Świąd występował u 22% dzieci z cukrzycą typu 1 ze średnim maksymalnym nasileniem 5,9 ± 3,0 punktów w $NRSmax_{3dni}$ i 6,7 ± 3,5 punktów w 4IIQ (mediana 5,5 punktów). U większości pacjentów świąd był zlokalizowany oraz ograniczony do kilku obszarów ciała; najczęściej dotyczył on kończyn górnych (68,2%), następnie kończyn dolnych (50%) i tułowia (31,8%). Łagodny świąd zgłaszało 16,7% pacjentów, umiarkowany 41,7% pacjentów, a ciężki lub bardzo ciężki 41,7% pacjentów. Klinicznie oceniana suchość skóry była znacznie bardziej zaawansowana u dzieci ze świądem w porównaniu z dziećmi bez świądu ($p < 0,01$). Średni wynik CDLQI w grupie ze świądem wynosił 4,0 ± 4,7 punktów (mediana 2,5 punktów), co wskazuje na niewielkie pogorszenie jakości życia. Żaden z badanych pacjentów nie miał objawów neuropatii cukrzycowej. Nasilenie świądu (zarówno NRS z ostatnich 3 dni, jak i NRS z ostatnich 24 godzin) korelowało pozytywnie z pogorszeniem jakości życia (odpowiednio $R = 0,7$; $p = 0,015$ i $R = 0,8$, $p = 0,002$).

2.4.3 **Wyniki trzeciego artykułu**

Świąd występował u 35,8% dorosłych pacjentów z cukrzycą typu 2, z $NRSmax_{3dni}$ 6,3 ± 2,2 punktów oraz 8,1 ± 3,5 punktów w 4IIQ. Świąd najczęściej pojawiał się jednoczasowo w wielu lokalizacjach (51,3%). Dotyczył głównie kończyn dolnych i górnych (38,5% i 23,1%), tułowia (30,8%) i skóry głowy (23,1%). Na uogólniony świąd uskarżało się dziewięciu pacjentom (23,1%), podczas gdy świąd anogenitalny dotyczył tylko jednego uczestnika (26%). Spośród 24 pacjentów, u których wystąpił świąd w okolicy kończyn, ośmiu (40%) odczuwało świąd w okolicy dłoni i stóp. Około 70% pacjentów (69,3%) cierpiało z powodu świądu codziennie lub co najmniej kilka razy w tygodniu. Badani najczęściej opisywali odczucia związane ze świądem jako pieczenie (38,5%, n = 15) i szczypanie (30,8%, n = 12), następnie mrowienie (28,2%, n = 11), kłucie i łaskotanie (w każdym odczuciu 12,8%, n = 5). Pacjenci ze świądem mieli istotnie wyższe stężenie glukozy na czczo w porównaniu z populacją bez świądu (p = 0,01). Pacjenci ze świądem wykazywali także istotnie wyższe prawdopodobieństwo neuropatii w porównaniu z osobami bez świądu (p < 0,01). Suchość skóry była istotnie bardziej zaawansowana u pacjentów ze świądem w porównaniu z osobami bez świądu (p < 0,01). Średni wynik ItchyQol oceniono na 41,2 ± 13,4 punktów, co wskazuje na łagodne pogorszenie jakości życia. Intensywnością świądu korelowała z obniżeniem jakości życia. Osoby cierpiące na świąd miały znacząco wyższe wyniki w obu wymiarach lęku i depresji HADS (w każdym z nich p < 0.01).

2.4.4 **Wyniki czwartego artykułu**

Wszyscy pacjenci, niezależnie od odczuwanego świądu, mieli obniżoną IENFD w stosunku do wartości normatywnych (grupa ze świądem: 2,7 włókna/mm, grupa kontrolna: 3,7 włókna/mm). Osoby z bardziej suchą skórą miały tendencję do niższej IENFD (R = 0,32, p=0,088), podczas gdy pacjenci z grupy świądowej mieli istotnie bardziej suchą skórę (p = 0,02). Ponadto pacjenci z grupy świądowej istotnie częściej odczuwali mrowienie lub drętwienie, w porównaniu z grupą bez dolegliwości świądowych (odpowiednio p = 0,02 i p = 0,04).

2.2 **Etyka**

Projekt pracy doktorskiej opartej na poniższych publikacjach został zatwierdzony przez Komisję Bioetyczną Uniwersytetu Medycznego we Wrocławiu - Nr KB 440/2020. 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.

2.3 **Wnioski**

1. Świąd jest częstym objawem występującym zarówno u chorych na cukrzycę typu 1, jak i typu 2.
2. Świąd u chorych na cukrzycę zazwyczaj ma umiarkowane nasilenie.
3. Świąd uogólniony dotyczy około jednej czwartej populacji dorosłych cierpiących na ten objaw, przy czym praktycznie nie występuje w populacji dzieci z cukrzyca typu 1.
4. Świąd w cukrzycy wpływa negatywnie na funkcjonowanie psychospołeczne pacjentów.
5. W patogenezie świądu u chorych na cukrzycę najprawdopodobniej rolę odgrywa suchość skóry (cukrzyca typu 1 i 2), zła kontrola glikemii (cukrzyca typu 2) oraz neuropatia cukrzycowa (cukrzyca typu 2).
6. Neuropatia małych włókien nerwowych wydaje się być istotnym czynnikiem patogenetycznym świądu u pacjentów chorych na cukrzycę.

7. ARTYKUŁ PIERWSZY:

ITCH IN DIABETES: A COMMON UNDERESTIMATED PROBLEM

Review paper

Itch in diabetes: a common underestimated problem

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Abstract

Introduction: Diabetes mellitus is associated with several skin manifestations, however the association with itch remains unclear.
Aim: To present a detailed literature review in order to analyse the frequency, pathogenesis, and course of itch in diabetes mellitus.
Material and methods: Data were collected from the PubMed and Cochrane databases. Articles were excluded if the populations presented with comorbidities or received treatment with drugs affecting the skin. Also, animal studies, studies with poor methodology and pilot studies were excluded.
Results: Among the 5 original articles included, the epidemiology of itch in diabetes varies from 18.4% to 27.5%. Two main factors are associated with the pathogenesis of itch in diabetes, namely skin xerosis and diabetic polyneuropathy. It is still poorly defined how glycaemic control is associated with generalized itch. No treatment of choice is available; however, topical therapy (emollients) provides significant relief in varying percentages of patients.
Conclusions: The results indicate a benefit of diabetes screening in individuals presenting with chronic itch without primary skin lesions.

Key words: diabetes mellitus, itch, pruritus.

Introduction

Diabetes mellitus (DM) and its complications are a major problem worldwide. The International Diabetes Federation estimated that 1 in 11 adults aged 20–79 years (415 million adults) had diabetes mellitus globally in 2015 [1]. DM is a problem of growing importance, this estimation is projected to rise to 642 million by 2040, and the largest increases will come from the regions experiencing economic transitions from low-income to middle-income levels [1]. The reasons for the escalating epidemic of DM are multiple, including population aging, economic development, urbanization, unhealthy eating habits, and sedentary lifestyles. DM is a group of metabolic disorders characterized by high blood glucose levels due to defective secretion and/or action of insulin [1]. Symptoms suggesting the presence of diabetes include polyuria; increased thirst and weight loss that cannot be explained by intended weight reduction. There are also other, less typical symptoms and signs such as fatigue and somnolence, purulent skin lesions, and inflammatory conditions of the genitourinary tract. In the case of the onset of symptoms, a random venous plasma glucose level should be measured.

According to WHO, DM is divided etiologically to the following main groups:
1) Diabetes type 1, Insulin Dependent Diabetes Mellitus (IDDM),
2) Diabetes type 2 (DM2),
3) Other specific forms of diabetes and
4) Gestational diabetes [2].

Over 95% of diabetes mellitus cases are DM2 and IDDM [3].

Chronic hyperglycaemia is associated with damage, dysfunction, and failure of various organs, in particular eyes, kidneys, nerves, heart, and blood vessels [4]. Skin disorders are present in 79.2% of patients with DM, and cutaneous disease may appear as the first sign of DM or develop at any time in the course of the disease. Non-infectious and infectious diseases have been described as dermatologic manifestations of diabetes mellitus [5–7]. In diabetes, underlying pathophysiology, the course of the disease, coexisting comorbidities and medications – all tend to predispose patients to develop itch.

Itch is defined as an unpleasant sensation that leads to intensive scratching [8]. It is a common and distressing symptom occurring not only in dermatological conditions but also in chronic systemic diseases [8, 9], posing a high

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burden and decrease in quality of life (QoL) of an affected individual [10, 11]. According to the International Forum for the Study of Itch (IFSI), the etiologic classification of chronic itch comprises 6 categories: (I) dermatologic, (II) systemic, (III) neurologic, (IV) psychogenic/psychosomatic, (V) mixed, and (VI) others [12]. Most researchers classify itch in diabetes as systemic itch [13], however some authors suggest mixed aetiology of diabetic itch with the additional involvement of both dermatologic and neurologic components [14–16]. Diabetes mellitus appears in most lists of the causes of generalized itch but is not common. Localized itch, for example pruritus vulvae, is common and often associated with candidal infection [17]. Only a few studies investigated the occurrence of itch in diabetes; however, these research projects used inconsistent definitions and different tools for itch evaluation and included heterogeneous diabetic populations [18].

Here, we present a detailed literature review in order to analyse the frequency, pathogenesis, and the course of itch in diabetes mellitus. Moreover, basing on the literature review, the treatment modalities for diabetic itch have been proposed.

Methodology

The search was conducted following the PRISMA guidelines [19]. The final search date was 21 August 2019. Terms included in the search, adjusted to the different databases were: "(pruritus OR itching) AND (diabetes mellitus OR diabetes OR diabetic OR diabetics OR non-insulin dependent diabetes mellitus OR Type 2 diabetes mellitus OR Type 1 diabetes mellitus OR insulin dependent diabetes OR insulin resistance OR impaired carbohydrate metabolism OR hyperinsulinaemia)". Additionally, for each review part, additional search terms (epidemiology/pathophysiology/treatment) were used.

We excluded studies of populations with confounding conditions like malignancies, thyroiditis, gestational diabetes and treatment with drugs affecting the skin. Moreover, we excluded animal studies, studies with poor methodology and pilot studies. Initially we also did not include studies focusing on more than one cutaneous manifestation, however, because only very few original papers related to the topic were found, we decided to take those studies into consideration as well. In some of the oldest articles, both the full text and the abstract were missing. These were not included in the final analysis. The included articles were screened for relevant cross-references. The selection process resulted in a total of 5 articles focusing precisely on itch in diabetes and all together 28 original papers focusing on cutaneous changes in diabetes including itching. Some of the articles focused on more aspects of itch in diabetes, so they were included into different parts of the analysis. Details of the selection process are presented in Figure 1.

Epidemiology

Epidemiologic aspects of itch in diabetes vary according to data presented in the literature. Only a few studies focused on itch investigation in diabetes. While prior studies [20, 21] showed no discernible relationship, recent papers from Taiwan and Japan [16, 22] demonstrated a correlation between diabetes and itch.

At the beginning of the 1980s, Kantor and Lookingbill [20] described a group of 44 patients with generalized itch; in this group 9.09% of patients suffered from DM.

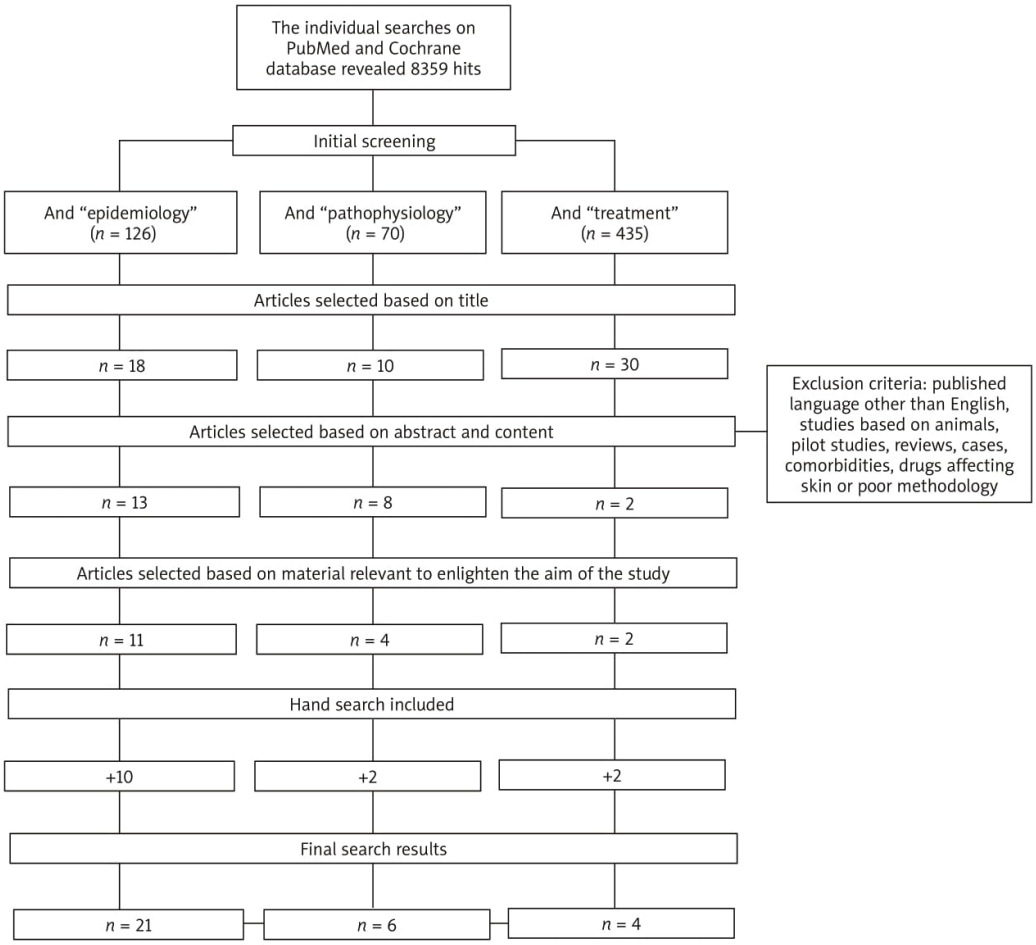
Neilly *et al.* [21] in 1986 assessed 300 DM and 100 non-DM hospital outpatients for the presence of generalized and localized itch. Pruritus vulvae was significantly more common in diabetic women (18.4%) than in controls (5.6%) and was significantly associated with poor diabetes control (mean glycosylated haemoglobin level lower than 12%). Generalized itch occurred in 8 diabetic patients only (2.7%) and was not significantly more common than in nondiabetic patients. Ko *et al.* [22] in 2013 analysed the data of 385 DM patients participating in the diabetes care program in Taiwan. Generalized itch was noted in 27.5% of the patients.

Patients classified to the group of DM type 2 with a higher postprandial glucose level had a higher probability of generalized itch (OR = 1.41, 95% CI: 1.05–1.90, $p = 0.02$).

A large multicentre study in Japan conducted by Yamaoka *et al.* [16] of 2,656 diabetic outpatients and 499 nondiabetic subjects revealed that the prevalence of truncal itch of unknown origin (TPUO) in diabetic subjects was significantly higher than in age-matched nondiabetic subjects (11.3 vs. 2.9%, $p = 0.0001$). The prevalence of total itch in diabetic subjects was significantly higher than in nondiabetic subjects (26.3 vs. 14.6%, $p < 0.001$). Interestingly, the prevalence of other forms of itch was not different between the two analysed groups. Table 1 shows details of the relevant epidemiological studies specifically dealing with itch in DM.

The other research projects were mostly examining cutaneous manifestations of diabetes, including itch. Historically, in late 1920s, Greenwood [23] was the first to show interests in itch in DM in his study of 500 DM cases. He showed that 6.6% of patients examined either had itch or had had it in the past. Out of these cases, 3.2% had generalized and 3.4% localized itch.

In a letter to the editor published in JAMA, Scribner [24] in the 1970s, attributes generalized itch and itch of the scalp to poorly controlled diabetes mellitus, but mostly he relied on his medical practice and general beliefs. However, a study done by Valdes-Rodriguez *et al.* [25] in 2015 on elderly patients, found that in the diabetic group, the presence of the disease correlated with scalp itch. In patients with DM2 ($n = 93$), 40% experienced itch on the scalp, in contrast with 17.5% of patients without DM ($p = 0.037$). Tseng *et al.* [15] who also studied the



*The amount of hits contains several duplicates.

Figure 1. Literature selection process according to PRISMA guidelines

elderly population, however, male-only, also claimed that itch was significantly associated with DM (AOR = 12.86, 95% CI: 4.40–37.59; $p < 0.001$). In another study based on female geriatric population [26] ($n = 36$), generalized itching (20%) and pruritus vulvae (33.3%) were commonly presenting complaints. In Poland [27], in a study conducted on 198 elderly subjects, no correlation between itch and diabetes mellitus has been found. In 1985, Hillson *et al.* [28] checked 235 newly diagnosed and untreated patients with DM2 and 20% of them had itch.

In the following studies, itch was reported in 4.5% of patients ($n = 200$) [29], 9.9% ($n = 106$) [30], 10% ($n = 100$) [31] and 13.33% ($n = 60$) [32]. In a study comprising 350 individuals, by Ahmed *et al.* [33], itch was reported in 7.1%. Another perspective was chosen by Alizadeh *et al.* [13] who examined 5 127 patients referred to the dermatologic clinic with chronic generalized itch without primary skin lesions – 12.5% of them had DM.

During the same time, among Egyptian diabetic patients [34], 11% had itch ($n = 100$). However, in this study, only patients with at least one skin manifestation of DM were selected. The same criteria were applied in the Indian study [31] in which the incidence was 30%, and also in the study done by Al-Mutairi *et al.* [35] in Kuwait. Al-Mutairi *et al.* [35] in their study showed the highest known incidence of itch – nearly half (49%) of the examined patients complained of the symptom.

Anogenital pruritus, commonly known in the case of women as pruritus vulvae, was also a subject of studies during the years. A large randomized controlled trial in Denmark by Drivsholm *et al.* [36] including patients aged ≥ 40 years with newly diagnosed DM2 ($n = 1,543$) re-

Table 1. Prevalence of itch in diabetes mellitus

Reference	Study design	Participants, *n*	Patients affected by itch	Prevalence of itch
Neilly *et al.*, 1986 [21]	Case-control	300 patients, 100 controls	18.4%	Point prevalence
Yamaoka *et al.*, 2010 [16]	Cross-sectional	2,656 outpatients, 499 inpatients	26.3%	No data
Ko *et al.*, 2013 [22]	Cross-sectional	385 patients	27.5%	Prevalence after the diagnosis of diabetes

vealed a prevalence of 27.2% of genital itching. In a study [37] comprising 100 individuals, localized anogenital itch was present in 19% of patients.

There are even fewer studies focusing on diabetes type 1. In Iran, Farshchian *et al.* [18] in their study examined patients for cutaneous manifestations of DM (n = 155). 17.4% of patients with IDDM had suffered from significant itching, comparing to 27% of patients with DM2. In Israel [38], 2% of IDDM (n = 238) patients were affected by itching sensations.

Summarizing, taking into account epidemiological data concerning itch in DM, one may draw a conclusion that there is a limited number of studies dealing specifically with itch in this group of patients. Most studies lack the information whether the point prevalence, life-time prevalence or incidence of itch was noted. It seems that 18.4% to 27.5% of patients with DM2 may suffer from itching. Studies on itch in IDDM, employing currently accepted methodology, are practically missing. Studies on itch prevalence, based on all clinical cutaneous manifestations analysed in DM patients, have given conflicting results and are difficult to be compared with each other due to non-homogenous methodology.

Pathogenesis

Pathogenesis of pruritus in DM is not fully understood and various factors are described as contributing to the development of this symptom. Currently, the researchers believe that there are two main factors associated with the itch in diabetes, namely skin xerosis and diabetic polyneuropathy.

Skin xerosis

It is well known that generalized itching may occur in clinically inconspicuous dry skin [16, 22]. Seité *et al.* [39] assessed 40 diabetic patients with regard to stratum corneum (SC) hydration (measured by a corneometer), the skin barrier function (transepidermal water loss – TEWL) (using a tewameter), skin elasticity (using a cutometer) and itching intensity. Emollient application induced a significant increase in skin hydration associated with a remarkable reduction in TEWL, and – consequently – alleviated itching.

Diabetes impairs wound healing [40–42]. Diabetes induces an increase in advanced glycosylation products in the collagen of the dermis. This glycosylation also favours oxidation, and it may be responsible for some of the skin changes associated with aging and this process is accelerated in persons with higher blood sugar levels [43, 44]. The significance of insulin as an essential growth factor for cultured keratinocytes and the substantial influence of insulin on keratinocyte proliferation [45], migration [46, 47] and differentiation [48] implies that the distorted keratinocyte phenotypes in patients with diabetes are an important factor in their impaired wound healing. Moreover, it is reasonable to presume that the abnormal proliferation and differentiation of keratinocytes in the epidermis of DM patients change the functions of the SC. Stratum corneum prevents excessive water loss and penetration of pathogens and allergens. All of the above mentioned factors may contribute to the pathogenesis of itching in DM. It was shown that diabetes influences the epidermal barrier quality. Sakai *et al.* [49, 50] put forward a hypothesis that patients with DM tend to develop a reduced hydration state of the SC together with decreased sebaceous gland activity. However, Seirafi *et al.* [51], in a case-control study, demonstrated no significant difference in SC hydration and TEWL in DM patients compared with age- and gender-matched healthy people. They additionally pointed to a lower acoustic wave propagation speed (related to skin elasticity) in DM subjects.

Neuropathy

Newer theories have suggested that itch in DM may be associated with polyneuropathy. Diabetes mellitus is the most common cause of small-fibre polyneuropathy in developed countries [52]. One of the theories suggested that diabetic polyneuropathy with correlated dysfunction of sweating due to impairment of the sympathetic nervous system may play a role in the pathogenesis of itch in DM [53].

Fluctuations in glucose levels seem to be the reason for dry skin in diabetes, however autonomic neuropathy may also play a significant role in skin dehydration in diabetic patients.

As a result of small-fibre polyneuropathy, diabetic patients can develop a neuropathic itch. A recent study in Ja-

pan [16] has mentioned truncal itch as a frequent clinical manifestation of neuropathy in diabetic patients. Multiple logistic regression analysis revealed that numbness of soles and palms and lack the Achilles tendon reflex (ATR) were independent risk factors for itch in age, sex, duration of diabetes, and glycolized haemoglobin (HbA_{1c}) levels. Autonomic nerve function was tested using the head-up tilt test and heart rate variability test. A fall of systolic blood pressure in diabetic subjects with itch was significantly impaired compared with that in subjects without it. In the patients with diabetic polyneuropathy judged by bilateral ATR areflexia, the prevalence of truncal pruritus of unknown origin was 20.5% compared to asymptomatic patients with polyneuropathy where itch was observed in 15.2%.

Other factors

Only a few studies focused on the itch and a blood glucose level. The limitations of these studies are the usage of different parameters, such as the fasting plasma glucose, postprandial glucose, and HbA_{1c} levels. The fasting plasma glucose (FPG) shows the hyperglycaemic state at the time of the measurements, while the HbA_{1c} reflects the average blood glucose levels in the past 7–8 weeks preceding the measurements. It seems that there is a correlation between postprandial glucose and generalized itch in patients with DM [22]. Ko *et al.* [22] found out that patients with a higher postprandial glucose level had a higher probability of generalized itch ($p = 0.02$). Hillson *et al.* [28] found out a correlation between the fasting plasma glucose and generalized pruritus in newly diagnosed and untreated patients with DM2.

When it comes to HbA_{1c} levels, different studies showed different results. In both studies mentioned above, no relationship between HbA_{1c} levels and generalized itching has been found [21, 22]. However, in a study designed by Afsar and Elsurer [54] on 75 patients (diabetic/nondiabetic, 29/46), the intensity of itching assessed with Visual Analog Scale (VAS) was higher in diabetic patients compared with nondiabetic patients (4.7 ±2.8 vs. 3.0 ±1.0, $p = 0.015$). Additionally, in diabetics, VAS itch score was independently related to HbA_{1c} ($\beta = +0.310$, $p = 0.027$). It is still poorly defined how glycaemic control is associated with generalized itch.

Unfortunately, most of the studies lack data showing whether the itch was followed by bacterial or fungal infections. In the study of Al-Mutairi *et al.* [35], diabetic patients hospitalized in the dermatologic ward were assessed for the presence of itch. Itch was one of the most common cutaneous signs of diabetes in 49% of ($n = 106$) patients, followed by fungal (78.8%) and bacterial (51.9%) infections.

Treatment

Only a few studies focused on treatment of itch in diabetes and most of them assessed topical therapy.

Seité *et al.* [39] performed a study on DM patients ($n = 40$), who were treated with the emollient (containing 5% urea associated with 0.2% hydroxyethylpiperazine ethane sulfonic acid) twice daily for 1 month on one arm and one leg, in normal conditions. The itch was also evaluated by 100-mm VAS starting from 2.0 ±2.91 at baseline, whereas on day 30 a marked reduction was noted (0.10 ±0.5, $p < 0.0001$). A significant improvement was also observed in skin hydration associated with a significant reduction in the desquamation index and TEWL.

There is a lack of research about the potential role of emollients in skin dryness prophylaxis in diabetes, as well. Also, the problem of dry skin in diabetes is often neglected by general practitioners. Narbutt *et al.* [55] proposed the application of an emollient with benfotiamine and Biolin prebiotic as prophylaxis of skin dryness and itch in skin care of DM patients, however there were no data supporting itch alleviation.

If emollients are contraindicated or less well tolerated, Ibrahim *et al.* [56] stated that topical treatment with clove oil may be also effective in chronic itch of systemic origin. He assessed topical clove oil use in 10 diabetic patients, comparing to 9 patients with diabetes treated with topical petrolatum as placebo for 2 weeks. Itch was assessed using 5-D itch scale. All the diabetic patients treated with topical clove oil showed a significant improvement in itch alleviation ($p = 0.02$) and comparing to the placebo group.

Diabetic neuropathy is often associated with oxidative stress. Therefore, an attempt was made to treat this disease with an antioxidant, lipoic acid, in Korean diabetic patients with distal symmetric polyneuropathy (DSP) [57]. Lipoic acid was administered orally using 600 mg once daily for 8 weeks to 61 diabetic patients with symptomatic polyneuropathy. Neuropathic symptoms (pain, burning sensation, paraesthesia, and numbness) were scored at baseline as well as at 4 and 8 weeks following treatment. Efficacy was evaluated in 38 patients who had completed the study according to the protocol. All the individual scores for neuropathic symptoms (pain, burning sensation, paraesthesia, and numbness) were also significantly reduced at 4 weeks and further decreased at 8 weeks ($p < 0.05$). As itch is commonly associated with the burning sensation and described by patients as numbness, lipoic acid seems to be a promising medication to alleviate neuropathic itch in patients with DM.

There is a lack of research on other treatment options for patients with itch and diabetes. However, basing on the treatment options for non-dermatological itch and other skin complications of diabetes, the treatment modalities for diabetic patients may be proposed.

Itch management begins with applying preventive measures to avoid factors that foster dryness of the skin, such as e.g. dry climate, heat (e.g. sauna), ice packs, frequent washing and bathing and contact with irritant substances [10]. It is recommended to use mild, non-alkaline

cleansers and to bath in lukewarm water for less than 20 min. Wearing loose-fitting, soft clothing permeable to the air, like cotton, is also beneficial. Patients may also appreciate wet, cooling or fat-moist-wrappings, black tea wrappings or relaxation techniques prescribed by the doctor.

The lifestyle changes, highly recommended by the American Diabetic Association, are mostly the use of emollients in the treatment of itch as a complication of diabetes [58]. Employment of emollients can restore physiological lipid levels in the skin, improves its barrier function, reduces itch and prevents infections related to scratching [58–60].

Therapy includes normalizing glucose levels accompanied by basic skin care with emollients such as urea-containing moisturizers, amended by topical antipruritics such as polidocanol, camphor, menthol or tannin preparations [10, 39, 61]. Emollient addition to standard diabetes therapy may reduce skin complications associated with elevated blood sugar level [39]. Although emollients represent a regular adjunct to other topical treatments for patients affected by dermatoses, studies evaluating their impact on skin improvement in DM are very few.

Despite relative effectiveness and safety of topical therapy, this method is often very difficult for patients to apply when they have a generalized itch and it also requires assistance of family members and/or caregivers.

Non-sedating antihistamines and selective serotonin reuptake inhibitor antidepressants may also reduce non-dermatological itch [62, 63]. However, there is a lack of the data assessing their usage in itch of patients with DM. The European Guideline on Chronic Pruritus [10] recommends from among systemic therapies the usage of corticosteroids with caution in patients with DM as they may cause hyperglycaemia.

Conflict of interest

The authors declare no conflict of interest.

References:

1. Cho NH, Shaw JE, Karuranga S, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 2018; 138: 271-81.
2. Araszkiewicz A, Bandurska-Stankiewicz E, Budzyński A, et al. 2019 Guidelines on the management of diabetic patients. A position of Diabetes Poland. Clin Diabetol 2019; 8: 1-95.
3. Bruno G, Runzo C, Cavallo-Perin P, et al. Incidence of type 1 and type 2 diabetes in adults aged 30-49 years: the population-based registry in the province of Turin, Italy. Diabetes Care 2005; 28: 2613-9.
4. Ezzati M, Hoorn SV, Lopez AD, et al. Comparative Quantification of Mortality and Burden of Disease Attributable to Selected Risk Factors. The International Bank for Reconstruction and Development/The World Bank 2006.
5. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA 2005; 293: 217.
6. Yancovitz M, Johnson H, Wang N, Pomeranz MK. Perforating collagenosis. Dermatol Online J 2008; 14: 14.
7. Wagner G, Sachse MM. Acquired reactive perforating dermatosis. J Der Dtsch Dermatologischen Gesellschaft 2013; 11: 723-9.
8. Ständer S, Streit M, Darsow U, et al. Diagnostic and therapeutic procedures in chronic pruritus. J Dtsch Dermatol Ges 2006; 4: 350-70.
9. Steinhoff M, Bienenstock J, Schmelz M, et al. Neurophysiological, neuroimmunological, and neuroendocrine basis of pruritus. J Invest Dermatol 2006; 126: 1705-18.
10. Weisshaar E, Szepietowski J, Darsow U, et al. European guideline on chronic pruritus. Acta Derm Venereol 2012; 92: 563-81.
11. Szepietowski JC, Reich A. Świąd. Patomechanizm, klinika, leczenie. Termedia, Poznań 2010.
12. Ständer S, Weisshaar E, Mettang T, et al. Clinical classification of itch: a position paper of the international forum for the study of itch. Acta Derm Venereol 2007; 87: 291-4.
13. Alizadeh N, Mirpour SH, Golmohamadi R, et al. Chronic generalized pruritus without primary skin lesions: a longitudinal prospective observational study. Int J Dermatol 2019; 58: 273-8.
14. Steinhoff M, Schmelz M, Szabó IL, Oaklander AL. Clinical presentation, management, and pathophysiology of neuropathic itch. Lancet Neurol 2018; 17: 709-20.
15. Tseng HW, Ger LP, Liang CK, et al. High prevalence of cutaneous manifestations in the elderly with diabetes mellitus: an institution-based cross-sectional study in Taiwan. J Eur Acad Dermatol Venereol 2015; 29: 1631-5.
16. Yamaoka H, Sasaki H, Yamasaki H, et al. Truncal pruritus of unknown origin may be a symptom of diabetic polyneuropathy. Diabetes Care 2010; 33: 150-5.
17. Lyell A. The itching patient. Scott Med J 1972; 17: 334-47.
18. Farshchian M, Farshchian M, Fereydoonnejad M, et al. Cutaneous manifestations of diabetes mellitus: a case series. Cutis 2010; 86: 31-5.
19. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.
20. Kantor GR, Lookingbill DP. Generalized pruritus and systemic disease. J Am Acad Dermatol 1983; 9: 375-82.
21. Neilly JB, Martin A, Simpson N, MacCuish AC. Pruritus in diabetes mellitus: investigation of prevalence and correlation with diabetes control. Diabetes Care 1986; 9: 273-5.
22. Ko MJ, Chiu HC, Jee SH, et al. Postprandial blood glucose is associated with generalized pruritus in patients with type 2 diabetes. Eur J Dermatol 2013; 23: 688-93.
23. Greenwood AM. A study of the skin in five hundred cases of diabetes. J Am Med Assoc 1927; 89: 774-7.
24. Scribner M. Diabetes and pruritus of the scalp. J Am Med Assoc 1977; 237: 1559.
25. Valdes-Rodriguez R, Mollanazar N, González-Muro J, et al. Itch prevalence and characteristics in a hispanic geriatric population: a comprehensive study using a standardized itch questionnaire. Acta Derm Venereol 2015; 95: 417-21.
26. Mishra VN, Mansharmani GG. Diabetes mellitus in geriatric females. J Indian Med Assoc 1989; 87: 138-9.
27. Reszke R, Pełka D, Walasek A, et al. Skin disorders in elderly subjects. Int J Dermatol 2015; 54: e332-8.
28. Hillson RM, Hockaday TD, Newton DJ, Pim B. Delayed diagnosis of non-insulin-dependent diabetes is associated with

greater metabolic and clinical abnormality. Diabet Med 1985; 2: 383-6.
29. Nigam PK, Pande S. Pattern of dermatoses in diabetics. Indian J Dermatol Venereol Leprol 2003; 69: 83-5.
30. Sasmaz S, Buyukbese M, Cetinkaya A, et al. The prevalence of skin disorders in type-2 diabetic patients. Internet J Dermatolol 2004; 3.
31. Raina S, Kaushal S, Mahajan V, et al. Pattern of cutaneous manifestations in diabetes mellitus. Indian J Dermatol 2010; 55: 39-41.
32. Ghosh K, Das K, Ghosh S, et al. Prevalence of skin changes in diabetes mellitus and its correlation with internal diseases: a single center observational study. Indian J Dermatol 2015; 60: 465-9.
33. Ahmed K, Muhammad Z, Qayum I. Prevalence of cutaneous manifestations of diabetes mellitus. J Ayub Med Coll Abbottabad 2009; 21: 76-9.
34. ElFangary M, ElNemisy N, Sanad E, Sorour N. Skin manifestations in Egyptian diabetic patients: a case series study. Egypt J Dermatology Venerol 2013; 33: 56-62.
35. Al-Mutairi N, Zaki A, Sharma AK, Al-Sheltawi M. Cutaneous manifestations of diabetes mellitus. Med Princ Pract 2006; 15: 427-30.
36. Drivsholm T, de Fine Olivarius N, Nielsen ABS, Siersma V. Symptoms, signs and complications in newly diagnosed type 2 diabetic patients, and their relationship to glycaemia, blood pressure and weight. Diabetologia 2005; 48: 210-4.
37. Wahid Z, Kanjee A. Cutaneous manifestations of diabetes mellitus. J Pak Med Assoc 1998; 48: 304-5.
38. Yosipovitch G, Hodak E, Vardi P, et al. The prevalence of cutaneous manifestations in IDDM patients and their association with diabetes risk factors and microvascular complications. Diabetes Care 1998; 21: 506-9.
39. Seité S, Khemis A, Rougier A, Ortonne J. Importance of treatment of skin xerosis in diabetes. J Eur Acad Dermatology Venereol 2011; 25: 607-9.
40. Franzén LE, Roberg K. Impaired connective tissue repair in streptozotocin-induced diabetes shows ultrastructural signs of impaired contraction. J Surg Res 1995; 58: 407-14.
41. Brown RL, Breeden MP, Greenhalgh DG. PDGF and TGF-alpha act synergistically to improve wound healing in the genetically diabetic mouse. J Surg Res 1994; 56: 562-70.
42. Bitar MS. Glucocorticoid dynamics and impaired wound healing in diabetes mellitus. Am J Pathol 1998; 152: 547-54.
43. Kennedy L, Baynes JW. Non-enzymatic glycosylation and the chronic complications of diabetes: an overview. Diabetologia 1984; 26: 93-8.
44. Sternberg M, Cohen-Forterre L, Peyroux J. Connective tissue in diabetes mellitus: biochemical alterations of the intercellular matrix with special reference to proteoglycans, collagens and basement membranes. Diabete Metab 1985; 11: 27-50.
45. Tsao MC, Walthall BJ, Ham RG. Clonal growth of normal human epidermal keratinocytes in a defined medium. J Cell Physiol 1982; 110: 219-29.
46. Ando Y, Jensen PJ. Epidermal growth factor and insulin-like growth factor I enhance keratinocyte migration. J Invest Dermatol 1993; 100: 633-9.
47. Benoliel AM, Kahn-Peries B, Imbert J, Verrando P. Insulin stimulates haptotactic migration of human epidermal keratinocytes through activation of NF-kappa B transcription factor. J Cell Sci 1997; 110: 2089-97.
48. Wertheimer E, Trebicz M, Eldar T, et al. Differential roles of insulin receptor and insulin-like growth factor-1 receptor in differentiation of murine skin keratinocytes. J Invest Dermatol 2000; 115: 24-9.
49. Sakai S, Kikuchi K, Satoh J, et al. Functional properties of the stratum corneum in patients with diabetes mellitus: similarities to senile xerosis. Br J Dermatol 2005; 153: 319-23.
50. Sakai S, Endo Y, Ozawa N, et al. Characteristics of the epidermis and stratum corneum of hairless mice with experimentally induced diabetes mellitus. J Invest Dermatol 2003; 120: 79-85.
51. Seirafi H, Farsinejad K, Firooz A, et al. Biophysical characteristics of skin in diabetes: a controlled study. J Eur Acad Dermatology Venereol 2009; 23: 146-9.
52. Young MJ, Boulton AJM, Macleod AF, et al. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia 1993; 36: 150-4.
53. Sun PC, Chen CS, Kuo CD, et al. Impaired microvascular flow motion in subclinical diabetic feet with sudomotor dysfunction. Microvasc Res 2012; 83: 243-8.
54. Afsar B, Elsurer Afsar R. HbA1c is related with uremic pruritus in diabetic and nondiabetic hemodialysis patients. Ren Fail 2012; 34: 1264-9.
55. Narbutt J, Bednarski IA, Lesiak A. The effect of an emollient with benfothiamine and Biolin prebiotic on the improvement of epidermal skin function. Adv Dermatol Allergol 2016; 33: 224-31.
56. Ibrahim IM, Elsaie ML, Almohsen AM, Mohey-Eddin MH. Effectiveness of topical clove oil on symptomatic treatment of chronic pruritus. J Cosmet Dermatol 2017; 16: 508-11.
57. Ryeal Hahm J, Kim BJ, Kim KW. Clinical experience with thioctacid (thioctic acid) in the treatment of distal symmetric polyneuropathy in Korean diabetic patients. J Diabetes Complications 2004; 18: 79-85.
58. Proksch E. The role of emollients in the management of diseases with chronic dry skin. Skin Pharmacol Physiol 2008; 21: 75-80.
59. Loden M. Role of topical emollients and moisturizers in the treatment of dry skin barrier disorders. Am J Clin Dermatol 2003; 4: 771-88.
60. Loden M. The clinical benefit of moisturizers. J Eur Acad Dermatology Venereol 2005; 19: 672-88.
61. Pham HT, Exelbert L, Segal-Owens AC, Veves A. A prospective, randomized, controlled double-blind study of a moisturizer for xerosis of the feet in patients with diabetes. Ostomy Wound Manage 2002; 48: 30-6.
62. O'Donoghue M, Tharp MD. Antihistamines and their role as antipruritics. Dermatol Ther 2005; 18: 333-40.
63. Zylicz Z, Krajnik M, van Sorge AA, Costantini M. Paroxetine in the treatment of severe non-dermatological pruritus: a randomized, controlled trial. J Pain Symptom Manage 2003; 26: 1105-12.

8. ARTYKUŁ DRUGI:

ITCH IN CHILDRN WITH TYPE 1 DIABETES:
A CROSS-SECTIONAL STUDY

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ORIGINAL RESEARCH

Itch in Children with Type 1 Diabetes: A Cross-Sectional Study

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ABSTRACT

Introduction: Type 1 diabetes (T1D) is reported to be one of the most common medical conditions in school-age youth and is ranked third in the prevalence of pediatric conditions. Only a few studies have investigated the occurrence of itch in diabetes mellitus, reporting conflicting data. The purpose of this study was to investigate the prevalence of itch in T1D to provide itch characteristics and to explore the potential underlying causes.

Methods: This prospective study evaluated itch among 100 children with T1D. Itch intensity was assessed with the Numerical Rating Scale (NRS) and the 4-Item Itch Questionnaire (4IIQ). The Children's Dermatology Life Quality Index (CDLQI) was implemented to assess the quality of life issues. Various clinical features and factors influencing itch were also examined. Skin dryness was evaluated clinically by non-invasive assessment of epidermis moisturizing.

Results: Itch occurred in 22% of children with T1D with the mean maximal intensity of 5.9 ± 3.0 points in NRS and 6.7 ± 3.5 points in 4IIQ (median, 5.5 points). In the majority of patients, the itch was limited to a few regions of the body; usually, the upper limbs (68.2%) were affected, followed by the lower limbs (50%) and the trunk (31.8%). Clinically examined skin xerosis was significantly more advanced in children with itch compared with those without itch ($p < 0.01$). The mean CDLQI score in the itchy group was 4.0 ± 4.7 points (median, 2.5 points), indicating a small impairment of quality of life. The intensity of itch (both NRS last 3 days and NRS last 24 h) correlated positively with life quality impairment ($R = 0.7$; $p = 0.015$ and $R = 0.8$, $p = 0.002$, respectively).

Conclusions: Our study found itch as a moderately frequent symptom in children with T1D; however, itch presence and intensity may relevantly debilitate quality of life among subjects. We suggest that dryness of the skin may play a role in the pathogenesis of itch in this population.

Keywords: Itch; Pruritus; Type 1 diabetes mellitus

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Key Summary Points

Type 1 diabetes (T1D) is reported to be one of the most common medical conditions in school-age youth, and it is ranked third in the prevalence of pediatric conditions.

However, only a few studies investigated the occurrence of itch in diabetes mellitus, reporting conflicting data. Studies on the child population with T1D are missing.

This study aimed to investigate the prevalence of itch in T1D to provide itch characteristics and to explore the potential underlying causes.

Itch is a moderately frequent symptom among children with T1D (22%). Dryness of the skin may play a role in the pathogenesis of itch in this population.

Itch presence and intensity may relevantly impair quality of life among the affected subjects.

INTRODUCTION

Diabetes mellitus (DM) and its complications are a growing problem worldwide. The International Diabetes Federation estimated that 1 in 11 adults aged 20–79 years (which amounts to 415 million adults) had DM globally in 2015 [1]. Type 1 diabetes (T1D) is reported to be one of the most common medical conditions in school-age youth, and it is ranked third in the prevalence of pediatric conditions [2]. More than 90% of patients with T1D are diagnosed before the age of 30 [3]. Approximately 2–3 teenagers per 1000 are currently diagnosed with this type of diabetes, and this ratio is rising by 3% per annum in European children, with an increasing number being diagnosed in early childhood [4].

Itch is defined as an unpleasant sensation that leads to intensive scratching [5]. It is a frequent and distressing symptom occurring not only in dermatologic conditions but also in chronic systemic diseases [5, 6], posing a high burden and decrease in quality of life (QoL) of patients [7, 8]. Most researchers classify itch in diabetes, according to the International Forum for the Study of Itch (IFSI), as systemic itch [9]; however, some authors suggested mixed etiology of diabetic itch with the additional involvement of both dermatologic and neurologic components [10–12]. Only a few studies investigated the occurrence of itch in DM, reporting a wide prevalence ranging from 18.4–27.5% [13]. However, these studies used inconsistent definitions and various tools for itch evaluation and included heterogeneous diabetic populations. Studies on itch in T1D, employing currently accepted methodology, are scarce.

Therefore, we set up a prospective study among pediatric patients with T1D, using standardized methods for itch assessment to investigate the prevalence of itch, to provide itch characteristics and to explore the potential underlying causes.

METHODS

Study Population and Design

This prospective cross-sectional study was performed between April 2019 and December 2019. The project was approved by the local Ethical Committee (ST.C260.18.019). The study procedures were carried out in agreement with the Helsinki Declaration of 1964 and its later amendments, and good clinical practice guidelines. Written informed consent to participate was obtained from all children and their carers before enrollment, they were also informed of their right to leave the study at any time. We approached 104 consecutive patients aged 6–18 years who were treated in the Department of Endocrinology and Diabetology for Children and Adolescents. The mother of one child refused participation in the study because of the severe course of T1D (hospitalization due to diabetic ketoacidosis); the mother of another child refused participation in the study without specifying the reasons (response rate: 98%). The inclusion criteria were diagnosis of T1D

Table 1 Basic demographics of the subjects

Sex (*n*)	100
Female	57
Male	43
Age (years), mean ± SD	13 ± 3.1
Range	(6–18)
Median	13
BMI (kg/m^2), mean ± SD	20.6 ± 3.9
Range	(12.8–33.1)
Median	20.7
Duration of diabetes (years), mean ± SD	4.6 ± 3.6
Range	(0–13)
Median	4

SD standard deviation, *BMI* body mass index

according to internationally accepted criteria [14] and an informed written participation agreement signed by the parent. Exclusion criteria included: mental status changes making the patient unable to make a detailed assessment of itch; known severe renal or liver disease; a history of chronic dermatologic disease. Among 102 patients, 2 subjects suffered from dermatologic disorders (one patient had atopic dermatitis and one suffered from psoriasis). Therefore, the final study group constituted 100 pediatric patients with T1D (Table 1).

After inclusion, detailed information on demographics, clinical history, comorbidities and physical findings was recorded. The results of routine laboratory blood tests were also noted with particular emphasis on glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG). If multiple laboratory tests were available, the results closest to the day of dermatologic examination would be chosen.

The main clinical parameter, the presence of chronic itch (CI), was documented, including the affected anatomical locations. A numerical rating scale (NRS; 0: no itch; 10 points: worst imaginable itch) was utilized to assess maximal values of itch intensity in both the last 3 days and last 24 h. NRS cutoff points are as follows: 1– < 3 points represent mild itch, 3–7 points moderate itch, ≥ 7–9 points severe itch and ≥ 9 points very severe itch [15].

Additionally, the 4-Item Itch Questionnaire (4IIQ), previously used by our group in many studies on different types of itch [16–19], was employed to assess CI extensity, severity, frequency and associated sleep impairment. Furthermore, the description of cutaneous sensations associated with itch, the emotional burden of itch, sleep impairment, certain factors influencing itch intensity and itch impact on psyche were noted.

The Children's Dermatology Life Quality Index (CDLQI) [20–22] was applied to assess relationships of itch with life quality impairment.

Skin dryness was assessed clinically using a graduated 4-point scale (range 0–3 points; 0 points – no symptoms of dry skin; 1, ashiness, but no discernible flakes; 2, small to medium flakes; 3, large flakes and a prominent "cracked glass pattern") [23, 24]. Subsequently, noninvasive corneometric assessment of epidermal hydration, using a Corneometer CM825 (Courage + Khazaka Electronic GmbH, Köln Germany) was carried out. All measurements were performed on four areas of the skin—forearm, lower leg, abdomen and chest—at stable room temperature (20–22 °C) and air humidity (40–50%) after a 10-min rest in the lying position.

Neurologic examination of the patients was done according to the guidelines of the American Diabetes Association [25]. Each patient was questioned as to the presence or absence of pain (characteristic of neuropathic pain such as burning, stabbing or shock-like); numbness, tingling and weakness in the feet; the presence or absence of similar upper-limb symptoms; and the presence or absence of unsteadiness on ambulation. Five sensory testings were evaluated: pain sensation with a pinprick, temperature sensation with the Tip-therm (Thermo Feel®) device, light touch sensation using the Semmes-Weinstein monofilament test with standardized 10 g monofilament, vibratory sensation with a 128-Hz standard tuning fork and the position sensation. All tests were

performed at the first toe and rated as normal or abnormal.

Statistical Analysis

All variables were assessed for normal or non-normal distribution to apply corresponding statistical tests. Differences between groups were determined using the Mann-Whitney U test with reference to the non-normal distribution of evaluated variables. Correlations were determined using Spearman's correlation analysis. The level of significance was set at $\alpha = 0.05$. The resulting p values were considered significant if $p < 0.05$. Statistical analyses were performed using Statistica 12 software (StatSoft, Tulsa, OK, USA).

The sample size of the study cohort was determined by sample size calculation using the principle of the anticipated response distribution of 50%, with a 95% confidence interval and 10% precision.

RESULTS

General Demographics, Laboratory Glycemic Control, Systemic Comorbidities and Diabetic Neuropathy

Among 100 studied patients, 22 subjects (22%) reported itch during the course of T1D. The recruited number of subjects fulfilled the above-mentioned sample size criterion, as 97 or more measurements/surveys were needed.

In 12 patients (12%), itch was present during the last 3 days. Clinical characteristics of the examined individuals displayed in different itch statuses (itch during the course of diabetes vs. itch during last 3 days vs. no itch) are shown in Table 2. There was no significant difference between the analyzed groups concerning sex, age, body mass index (BMI), duration of T1D and basic laboratory examinations (Table 2). No correlations were documented between any assessment of itch intensity and values of HbA1c and FPG (NRS during the last 3 days: with HbA1c-$R = 0.2$ $p = 0.6$, with FPG-$R = -0.4$ $p = 0.4$; NRS during the last 24 h: with HbA1C-$R = 0.5$ $p = 0.1$, with FPG-$R = 0.05$ $p = 0.9$; 4IIQ: with HbA1C-$R = 0.02$ $p = 0.9$ with FPG-$R = -0.02$ $p = 0.9$).

The most common systemic comorbidities encompassed thyroid disorders (11%), celiac disease (7%) and asthma (4%) without significant differences between itchy and non-itchy patients (detailed data not shown). All patients (100%) were euthyroid. Among the examined group, none of the subjects had signs of diabetic polyneuropathy in the basic neurologic examination.

Itch Characteristics

Twelve patients out of 22 itchy subjects (54.5%) had itch present during the last 3 days. In this group of subjects, the maximal NRS score for itch intensity during the last 3 days was 5.9 ± 3.0 points, while during the last 24 h it was assessed as 5.0 ± 3.8 points, indicating moderate itch intensity. Mild itch was observed in 16.7% of patients, moderate itch in 41.7% of patients, and severe or very severe itch in 41.7% of patients. The mean 4IIQ score was 6.7 ± 3.5 points (median, 5.5 points).

Notably, in all 22 itchy subjects, 25% of patients reported that itching occurs constantly every day. More than 40% of itchy patients (40.9%) reported a shorter duration of single itch episodes lasting < 1 min; however, 13.6% of patients reported feeling itch all the time without breaks.

In the majority of patients, itch was limited to a few regions of the body; most commonly, the upper limbs (68.2%) were affected, followed by the lower limbs (50%) and the trunk (31.8%). Not even a single subject reported generalized itch. Itch requiring scratching was found in 86.4% of itchy individuals.

Itch occurred most frequently during the evening and night (27.3%), very rarely in the morning and midday. Usually, itch was not accompanied by other unpleasant cutaneous sensations (81.8%). Less commonly, it was described as warming (13.6%), stinging (9.1%) or tingling (4.5%). Patients frequently described that itch did not affect their mood (51.9%);

Table 2 Basic demographics and laboratory glycemic control for the subsequent groups of subjects

	Itch during the course of diabetes	Itch during the last 3 days	No itch	*p*-value*
Sex (*n*)	22	12	78	NS
Women	12	6	35	
Men	10	6	33	
Age (years), mean ± SD	11.8 ± 3.5	12.6 ± 3.6	13.3 ± 3.1	NS
Range	(7–17)	(7–17)	(6–18)	
Median	11	13	14	
BMI (kg/m^2), mean ± SD	20.05 ± 4.2	21.1 ± 4.7	20.7 ± 3.8	NS
Range	(12.8–26.9)	(13.5–26.9)	(14.5–33.1)	
Median	21.6	21.7	20.7	
Duration of diabetes (years), mean ± SD	5.4 ± 2.7	5.75 ± 2.7	4.4 ± 3.8	NS
Range	(0–12)	(2–12)	(0–13)	
Median	5	5	3	
HbA1C (%), mean ± SD	8.6 ± 1.6	8.8 ± 1.6	9.3 ± 2.9	NS
Range	(6.5–12.9)	(6.9–12.9)	(5.6–19.3)	
Median	8.35	8.35	8.6	
FPG (mg/dl), mean ± SD	168.6 ± 72.2	181.2 ± 76.1	160.8 ± 63.8	NS
Range	(87–300)	(91–300)	(66–315)	
Median	153	167	147.5	

* For both comparisons, i.e., between the no itch group and itch during the last 3 days as well as between no itch and itch during the course of the disease

SD standard deviation, *NS* not significant, *BMI* body mass index, *HbA1C* glycated hemoglobin, *FPG* fasting plasma glucose

however, for some subjects itch was annoying (27.3%) and burdensome (18.2%).

Itch contributed to difficulties in falling asleep and sleep disturbances, described as "waking during the night sleep due to itching" in 18.2% of affected individuals, and one of them (4.5%) reported the use of soporifics.

The most common exacerbating factors included heat (18.2%) and hot water (13.6%), while diabetic diet and cold water were considered alleviating factors in 22.7% and 13.6% of patients, respectively. Most of the patients (54.5%) did not see any correlation between analyzed factors and itch; 31.8% of subjects regarded itch as a factor negatively influencing their mood with 27.3% finding it affected concentration, e.g., at school.

Itch and Skin Xerosis

Skin xerosis, examined clinically, was significantly more advanced in children with itch compared with those without itch ($p < 0.01$). The skin seemed to be even drier in patients with itch occurring during the last 3 days compared with all 22 subjects reporting itch during the course of T1D; however, the difference was

Table 3 Dry skin and itch in children with diabetes

	Itch during the course of diabetes	Itch during last 3 days	No itch	*P* value*
Skin xerosis (points), mean ± SD	0.8 ± 1.0	1.25 ± 0.6	0.3 ± 0.5	< 0.01
median	1	1	0	
Epidermal hydration (AU). mean ± SD (median)				
Forearm	25.6 ± 7.7 (27.1)	28.2 ± 8.6 (27.1)	25.0 ± 7.6 (23.7)	NS
Lower leg	27.7 ± 12.7 (28.0)	28.6 ± 9.7 (25.5)	30.0 ± 11.3 (28.1)	NS
Abdomen	24.2 ± 12.8 (23.7)	27.0 ± 13.9 (21.3)	25.6 ± 11.4 (22.3)	NS
Chest	38.2 ± 12.0 (39.0)	38.8 ± 11.4 (39.3)	40.0 ± 14.0 (38.3)	NS

SD standard deviation, *NS* not significant

* For both comparisons, i.e., between the no itch group and itch during the last 3 days as well as between no itch and itch during the course of the disease

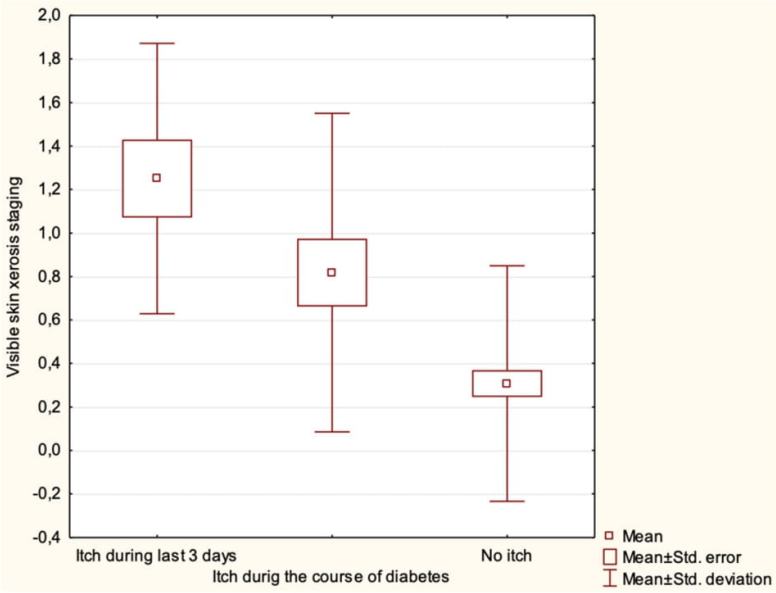

Fig. 1 Visible skin xerosis in children with itch during the last 3 days, during the course of the disease, compared with those without itch. Results are statistically significant

not statistically significant ($p > 0.05$) (Table 3, Fig. 1).

Using corneometry, there was no difference between the groups with and without itch with regard to the epidermal hydration values (Table 3).

However, there were significant correlations between itch intensity assessed by 4IIQ and

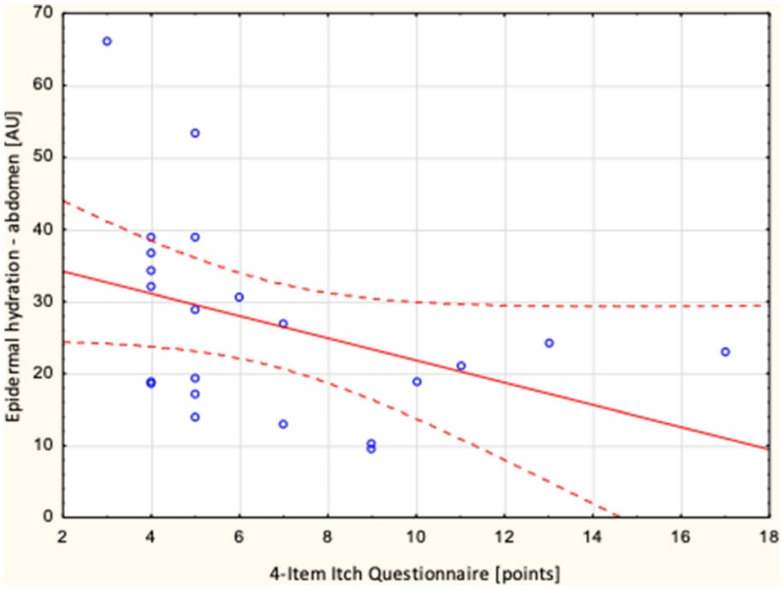

Fig. 2 Correlation between itch intensity measured with the 4-Item Itch Questionnaire and epidermal hydration on the abdomen ($R = -0{,}5$; $p = 0.032$)

Table 4 Correlations between itch intensity and epidermal hydration

Epidermal hydration (AU), mean ± SD	NRS during the last 3 days	4-Item Itch Questionnaire
Forearm	NS	NS
Lower leg	NS	NS
Abdomen	NS	$R = -0.5$ ($p = 0.032$)
Chest	NS	NS

SD standard deviation, *NS* not significant, *NRS* numerical rating scale

epidermal hydration on the abdomen ($R = -0.5$; $p = 0.032$) (Fig. 2). There were no relationships between itch severity evaluated with NRS and corneometric values (Table 4). Additionally, there were no significant correlations between itch intensity measured with the NRS and 4IIQ and skin xerosis, examined clinically (detailed data not shown).

Itch and Quality of Life

The mean CDLQI score in the itchy group was 4.0 ± 4.7 points (median 2.5, range 1–16 points), indicating small impairment of quality of life [26]. The intensity of itch (both NRS last 3 days and NRS last 24 h) correlated positively with life quality impairment ($R = 0.7$; $p = 0.015$ and $R = 0.8$, $p = 0.002$, respectively). Additionally, the abdominal epidermal hydration

correlated negatively with CDLQI ($R = -0.4$; $p < 0.045$).

DISCUSSION

To the best our knowledge, this is the first prospective study, investigating specifically the prevalence of itch among pediatric patients with T1D, in whom we obtained detailed characteristics and applied a comprehensive, validated methodology to characterize itch. We showed that itch occurred in more than 20% of children with T1D and those subjects who reported itch had more severe dry skin. These findings are in consistence with our previous study, where about 20% of children on dialysis treatment were suffering from uremic itch [18]. It was also clearly documented that diabetic itch markedly contributed to the impaired quality of life.

There are not many studies concerning cutaneous manifestations, including itch and dry skin, in children and adolescents with T1D. In 2007 Pavlovic et al. [27] studied the youngest population, comparable to ours. In the cross-sectional study, they examined 212 patients with T1D aged 2–22 years (mean age 12.5 ± 3.7 years) and compared the results with 196 healthy children and adolescents. The most common skin manifestation was xerosis, found in 22% of type 1 diabetic patients. In control subjects, dry skin was demonstrated only in 3% of the children and adolescents, the difference was highly significant. However, Pavlovic [27] did not exclude from their study group patients with other causes of xerosis, such as atopic dermatitis, etc. No patient with itch was reported. Romano et al. [28] in 1997 studied heterogeneous population of 477 patients with DM, of which 64 patients had T1D. Patients with T1D were mostly adolescents and young adults with mean age 22 ± 8 years, and mean diabetes duration of 10 ± 4 years. The studied population was older and with longer mean diabetes duration than our group. Skin xerosis was reported in 4 patients with T1D (6%), and itch in 1 patient (2%). Yosipovitch et al. [29] in 1998 performed a cross-sectional study with 238 T1D patients aged 12–44 years with a mean age of 23.5 ± 7.6 years, and mean diabetes course of 13 ± 2.5 years (range: 5–37 years). Only patients with disease onset at < 30 years of age and with diabetes duration > 5 years were qualified to the study. Skin xerosis was present in 48% of patients and only 0.4% of patients reported itching sensations. Khurdish et al. [30] studied older (above 15 years of age), mixed population of 350 diabetic patients, including 30 patients with T1D. Itch was not observed in the population of patients with T1D. In the study performed by Farshchian et al. [31] itch was reported by 17.4% of patients with T1D and this was no significant difference in comparison to their population of patients with type 2 DM (27% had itch).

Summarizing, taking into account available epidemiological data concerning itch in T1D, one may draw a conclusion that the studies on itch in T1D, employing currently accepted methodology, are practically missing. Studies on itch prevalence, based on all clinical cutaneous manifestations analyzed in T1D patients, have given conflicting results and are difficult to be compared with each other due to non-homogenous methodology. Most studies are based on the point prevalence of itch with no detailed data. It seems that 0% to 17.4% of patients with T1D may suffer from itch. Our study confirms this as itch during the course of DM was present in 22% of pediatric patients, while itch during the last three days was noted in 12% of studied subjects.

Pathogenesis of itch in DM is not fully understood and various factors have been suggested as contributing to the development of this symptom. Currently, it is believed that skin xerosis and diabetic polyneuropathy are the main factors influencing the occurrence and severity of itch in DM patients. In our cohort of patients, xerosis was more common in children with itch during the course of DM compared with those without itch. Moreover, epidermal hydration on the lower leg and abdomen correlated negatively the itch intensity. It is known that itching may occur in clinically inconspicuous dry skin [12, 32]. Seité et al. [33] assessed 40 diabetic patients, among them 32 (80%) were diagnosed with T1D, with regard to stratum corneum (SC) hydration, skin barrier

dysfunction (Trans Epidermal Water Loss—TEWL) and itching. The authors showed that emollient application induced a significant increase in skin hydration associated with a remarkable reduction in TEWL. This resulted in significant reduction of itch intensity. Sakai et al. [34, 35] proposed a thesis that patients with DM tend to develop a reduced hydration state of the SC together with decreased sebaceous gland activity. Unfortunately, data about the type of diabetes among their subjects, are missing. On the other hand, Seirafi et al. [36] provided a case–control study with 49 Japanese patients, among them 11 had T1D (22.5%). They demonstrated no significant difference in SC hydration and TEWL in DM patients compared with age- and gender-matched healthy people. Additionally, it was pointed out that patients with DM had a lower acoustic wave propagation speed (related to skin elasticity). As a result of long-lasting DM patients may develop a cutaneous neuropathy with subsequent neuropathic itch. In the current study population, no diabetic polyneuropathy was found, probably because of the short course of diabetes ranging from 0 to 13 years with a mean duration of 4.6 ± 3.6 years. The American Diabetes Association recommends screening for diabetic neuropathy five years after diagnosis for someone with type 1 diabetes [25]. Therefore, we suggest that cutaneous neuropathy most probably does not play an important role in the pathogenesis of itch in T1D pediatric population.

What is interesting, no correlation was found between parameters associated with glycemic control—FPG and HbA1c and the presence and severity of itch, skin dryness and quality of life among our subjects. Only a few studies focused on the itch and a parameter of glycemic control and all of them were performed on adult population with diabetes type 2. Ko et al. [32] claimed that patients with a higher postprandial glucose level had a higher probability of having generalized itch ($p = 0.02$). Moreover, in newly diagnosed and untreated patients with type 2 DM Hillson et al. [37] found out the correlation between the FPG and generalized itch. The mean FPG level in itching subjects was 239 ± 68 mg/dl, significantly higher comparing to non-itching population—200 ± 74 mg/dl ($p < 0.01$). The mean FPG levels in our cohort of itchy subjects were 168.6 ± 72.2 mg/dl, which represents much lower values than in the above-mentioned study. Nearly 1/4th of patients with itch during the course of diabetes (22.7%) considered diabetic diet (recommendation to consume products with a low glycemic index as well as carbohydrate counting in order to optimize prandial insulin dose) as itch alleviating, which, we can only speculate, may be consistent with the data presented by Hillson et al. [37].

In both above-mentioned studies, no relationship between HbA1c levels and itch has been found [32, 38].

In our group of pediatric patients with DM itch correlated with impairment of quality of life. This is in agreement with other studies on both cutaneous and systemic itch and quality of life assessment [16–18, 39–42]. It is generally accepted that chronic itch is the devastating symptom in the majority of itch patients.

This study has several limitations. Firstly, this was a single-centre study and the number of subjects with itch was relatively small, therefore, this study should be considered of an exploratory nature. The findings regarding the itch characteristics in pediatric population should be treated with caution. In addition, the descriptive nature of the study has to be taken into account. Secondly, concerning the neurological background of the itch, we did not consider the warmth detection thresholds. However, several other assessments were undertaken. Thirdly, the period of the study was relatively long starting in April and ending in December. Despite our efforts, additional factors such as change in the weather and connected to this, change in the patient's habits (different clothes, different sports) could affect the final results. Last but by no means least quality of life of our patients was measured with CLDQI. To the best of our knowledge there is no itch-specific instrument to evaluate influence of itch on quality of life in pediatric population, however the above-mentioned questionnaire was used to correlate the presence and intensity of itch with quality of life assessment in itchy adults [16, 17, 39–42].

CONCLUSIONS

In conclusion, our prospective study on children with T1D found itch as a moderately frequent symptom. We suggest that dryness of the skin may play a role in the pathogenesis of itch in this population. However, further multicenter studies, including a reasonable number of children with T1D, are necessary to confirm our findings.

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Compliance with Ethics Guidelines. The project was approved by the local ethics committee (ST.C260.18.019). The study procedures were carried out in agreement with the Helsinki Declaration of 1964 and its later amendments and good clinical practice guidelines. Written informed consent to participate was obtained from all children and their carers before enrollment; they were also informed of their right to leave the study at any time.

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

REFERENCES

1. Cho NH, Shaw JE, Karuranga S, et al. IDF diabetes atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018;138:271–81.
2. Pettitt DJ, Talton J, Dabelea D, et al. Prevalence of diabetes in US youth in 2009: the SEARCH for diabetes in youth study. Diabetes Care. 2014;37:402–8.
3. Williams G, Pickup J. Handbook of diabetes 2004.
4. Variation and trends in incidence of childhood diabetes in Europe. EURODIAB ACE Study Group. Lancet (London, England) 2000;355:873–6.
5. Ständer S, Streit M, Darsow U, et al. Diagnostic and therapeutic procedures in chronic pruritus. J Dtsch Dermatol Ges. 2006;4:350–70.
6. Steinhoff M, Bienenstock J, Schmelz M, Maurer M, Wei E, Bíró T. Neurophysiological, neuroimmunological, and neuroendocrine basis of pruritus. J Invest Dermatol. 2006;126:1705–18.

7. Weisshaar E, Szepietowski J, Darsow U, et al. European guideline on chronic pruritus. Acta Derm Venereol. 2012;92:563–81.

8. Szepietowski JC, Reich A. [Itch. Pathomechanism, clinic, treatment]. Poznań: Termedia; 2010.

9. Alizadeh N, Mirpour SH, Golmohamadi R, et al. Chronic generalized pruritus without primary skin lesions: a longitudinal prospective observational study. Int J Dermatol. 2019;58:273–8.

10. Steinhoff M, Schmelz M, Szabó IL, Oaklander AL. Clinical presentation, management, and pathophysiology of neuropathic itch. Lancet Neurol. 2018;17:709–20.

11. Tseng H-W, Ger L-P, Liang C-K, Liou H-H, Lam H-C. High prevalence of cutaneous manifestations in the elderly with diabetes mellitus: an institution-based cross-sectional study in Taiwan. J Eur Acad Dermatol Venereol. 2015;29:1631–5.

12. Yamaoka H, Sasaki H, Yamasaki H, et al. Truncal pruritus of unknown origin may be a symptom of diabetic polyneuropathy. Diabetes Care. 2010;33:150–5.

13. Stefaniak A, Chlebicka I, Szepietowski J. Itch in diabetes: a common underestimated problem. Adv Dermatology Allergol 2019;36.

14. Association AD. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. Diabetes Care 2020;43:S14–31.

15. Reich A, Chatzigeorkidis E, Zeidler C, et al. Tailoring the cut-off values of the visual analogue scale and numeric rating scale in itch assessment. Acta Derm Venereol. 2017;97:759–60.

16. Chrostowska-Plak D, Reich A, Szepietowski JC. Relationship between itch and psychological status of patients with atopic dermatitis. J Eur Acad Dermatol Venereol. 2013;27:e239–e242242.

17. Suseł J, Batycka-Baran A, Reich A, Szepietowski JC. Uraemic pruritus markedly affects the quality of life and depressive symptoms in haemodialysis patients with end-stage renal disease. Acta Derm Venereol. 2014;94:276–81.

18. Wojtowicz-Prus E, Kiliś-Pstrusińska K, et al. Chronic kidney disease-associated pruritus in children. Acta Derm Venereol. 2016;96:938–42.

19. Reich A, Mędrek K, Szepietowski J. Four-item itch questionnaire—validation of questionnaire. Przegl Dermatol. 2012;99:600–4.

20. Geel MJ, Maatkamp M, Oostveen AM, et al. Comparison of the dermatology life quality index and the children's dermatology life quality index in assessment of quality of life in patients with psoriasis aged 16–17 years. Br J Dermatol. 2016;174:152–7.

21. Olsen JR, Gallacher J, Finlay AY, Piguet V, Francis NA. Quality of life impact of childhood skin conditions measured using the Children's Dermatology Life Quality Index (CDLQI): a meta-analysis. Br J Dermatol. 2016;174:853–61.

22. Salek MS, Jung S, Brincat-Ruffini LA, et al. Clinical experience and psychometric properties of the Children's Dermatology Life Quality Index (CDLQI), 1995–2012. Br J Dermatol. 2013;169:734–59.

23. Eberlein-Ko B, Nig È, Scha È Fer T, et al. Skin Surface pH, stratum corneum hydration, trans-epidermal water loss and skin roughness related to atopic eczema and skin dryness in a population of primary school children. Acta Derm Venereol 2000;80(3):188–91.

24. Cook TH, Craft T. Topographics of dry skin, non-dry skin, and cosmetically treated dry skin as quantifed by skin profilometry. J Soc Cosmet Chem 1985:143–52.

25. Association AD. 11. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes-2020. Diabetes Care 2020;43:S135–51.

26. Waters A, Sandhu D, Beattie P, Ezughah FL-JS. Severity stratification of Children's Dermatology Life Quality Index (CDLQI) scores. Br J Dermatol 2010:121.

27. Pavlovi MD, Milenkovi T, Dini M, et al. The prevalence of cutaneous manifestations in young patients with type 1 diabetes. Diabetes Care. 2007;30(8):1964–7.

28. Romano G, Moretti G, Di Benedetto A, et al. Skin lesions in diabetes mellitus: prevalence and clinical correlations. Diabetes Res Clin Pract. 1998;39:101–6.

29. Yosipovitch G, Hodak E, Vardi P, et al. The prevalence of cutaneous manifestations in IDDM patients and their association with diabetes risk factors and microvascular complications. Diabetes Care. 1998;21:506–9.

30. Ahmed K, Muhammad Z, Qayum I. Prevalence of cutaneous manifestations of diabetes mellitus. J Ayub Med Coll Abbottabad;21:76–9.

31. Farshchian M, Farshchian M, Fereydoonnejad M, Yazdanfar A, Kimyai-Asadi A. Cutaneous manifestations of diabetes mellitus: a case series. Cutis. 2010;86:31–5.

32. Ko M-J, Chiu H-C, Jee S-H, Hu F-C, Tseng C-H. Postprandial blood glucose is associated with generalized pruritus in patients with type 2 diabetes. Eur J Dermatol 23:688–93.

33. Seité S, Khemis A, Rougier A, Ortonne J. Importance of treatment of skin xerosis in diabetes. J Eur Acad Dermatol Venereol. 2011;25:607–9.

34. Sakai S, Kikuchi K, Satoh J, Tagami H, Inoue S. Functional properties of the stratum corneum in patients with diabetes mellitus: similarities to senile xerosis. Br J Dermatol. 2005;153:319–23.

35. Sakai S, Endo Y, Ozawa N, et al. Characteristics of the epidermis and stratum corneum of hairless mice with experimentally induced diabetes mellitus. J Invest Dermatol. 2003;120:79–85.

36. Seirafi H, Farsinejad K, Firooz A, et al. Biophysical characteristics of skin in diabetes: a controlled study. J Eur Acad Dermatol Venereol. 2009;23:146–9.

37. Hillson RM, Hockaday TD, Newton DJ, Pim B. Delayed diagnosis of non-insulin-dependent diabetes is associated with greater metabolic and clinical abnormality. Diabet Med. 1985;2:383–6.

38. Neilly JB, Martin A, Simpson N, MacCuish AC. Pruritus in diabetes mellitus: investigation of prevalence and correlation with diabetes control. Diabetes Care;9:273–5.

39. Reich A, Hrehorow E, Szepietowski J. Pruritus is an important factor negatively influencing the well-being of psoriatic patients. Acta Derm Venereol. 2010;90:257–63.

40. Reszke R, Białynicki-Birula R, Szepietowski JC. Itch in psoriasis: a new look at well-known subject. Acta Derm Venereol. 2019;99:429–34.

41. Kaaz K, Szepietowski JC, Matusiak Ł. Influence of itch and pain on sleep quality in atopic dermatitis and psoriasis. Acta Derm Venereol. 2019;99:175–80.

42. Matusiak Ł, Szczęch J, Kaaz K, Lelonek E, Szepietowski JC. Clinical characteristics of pruritus and pain in patients with hidradenitis suppurativa. Acta Derm Venereol. 2018;98:191–4.

9. ARTYKUŁ TRZECI:

ITCH IN ADULT POPULATION WITH TYPE 2 DIABETES MELLITUS:
CLINICAL PROFILE, PATHOGENESIS AND DISEASE-RELATED BURDEN IN A CROSS-SECTIONAL STUDY.

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Article

Itch in Adult Population with Type 2 Diabetes Mellitus: Clinical Profile, Pathogenesis and Disease-Related Burden in a Cross-Sectional Study

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Simple Summary: Although it is well accepted that itch might be one of the symptoms related to diabetes mellitus, very little is known about this topic from previous studies. In the current study, we aimed to investigate itch sensation in type 2 diabetes mellitus with special emphasis on the potential underlying causes. According to our study, itch was a relatively frequent symptom, present in about 36% of subjects, causing significant impairment to quality of life. Based on our findings and previous literature data, it seems that the primary cause of itch in this group of subjects is poor diabetes control with subsequent skin dryness and diabetic polyneuropathy.

Abstract: Background: Despite growing interest in itch, data regarding itch in type 2 diabetes mellitus (DM2) are still limited, and mostly based on outdated studies. This study aimed to evaluate the clinical characteristics of itch in the adult population with DM2 and explore potential underlying causes. Methods: The study group consisted of 109 adult patients with DM2. Standardized questionnaires were completed in order to assess the itch intensity [Numerical Rating Scale (three days, 24hours) (NRS)] and the Four-item Itch Questionnaire (4IIQ) and to assess the psychological impact of itch [ItchyQoL, Six-Item Stigmatization Scale (6-ISS), Hospital Anxiety and Depression Scale (HADS)]. Skin dryness was evaluated clinically and by non-invasive assessment of epidermis moisturizing. Neuropathy was assessed using the clinical Katzenwadel neuropathy scale. Results: Itch occurred in 35.8% of adult patients with DM2, with NRS_{max} three days 6.31 $\pm$ 2.16 and 8.1 $\pm$ 3.5 points in 4IIQ. Itchy patients have had significantly higher FPG levels compared with the non-itchy population ($p = 0.01$). Patients with itch had a significantly higher possibility of neuropathy compared with non-itchy subjects ($p < 0.01$). Skin xerosis was significantly more advanced in patients with itch compared to those without ($p < 0.01$). The mean ItchyQol score was assessed as 41.2 $\pm$ 13.4 points, indicating mild life quality impairment and correlated positively with itch intensity. Itchy subjects had significantly higher scores in both anxiety and depression dimensions of HADS (in each $p < 0.01$). Conclusions: We suggest that the primary cause of itch is prolonged poor diabetes control with altered glucose and insulin levels, subsequently causing skin dryness and neuropathy in long-lasting DM2.

Keywords: diabetic itch; type 2 diabetes mellitus; pruritus

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1. Introduction

Despite the growing interest in itch, data on itch in diabetes mellitus (DM) is rather limited and mostly based on outdated studies. Due to these reasons, physicians treating patients with DM may underestimate its frequency and clinical meaningfulness. DM constitutes a worldwide public health problem affecting 382 million people (8.3% of the world's population) in 2013 with a projected increase to 592 million people (10.1%) in 2035 [1]. Pathogenesis of itch in DM is not fully understood, although in DM, the underlying pathophysiology, course of disease, comorbidities, complications and treatment used all tend to predispose patients to itch development. Type 2 diabetes mellitus (DM2) comprises most cases of all DM and is largely the result of excess body weight and physical inactivity [2].

Chronic Itch (CI) is defined as an unpleasant sensation that leads to intensive scratching lasting 6 weeks or longer [3]. According to the International Forum for the Study of Itch (IFSI), we may divide the etiologic classification of chronic itch to 6 categories: (I) dermatologic, (II) systemic, (III) neurologic, (IV) psychogenic/psychosomatic, (V) mixed, and (VI) others [4]. IFSI classifies itch in diabetes as systemic itch arising on non-inflamed skin or normal-appearing skin [5]. However, researchers have recently suggested that the etiology of itch in DM is additionally involved with both dermatologic and neurologic components [6–8]. The occurrence of itch in DM ranges from 18.4 to 27.5% [9]; however, the exact prevalence is not known, as most studies used inconsistent definitions and various tools for itch evaluation and included heterogeneous diabetic populations.

This study aimed to evaluate the prevalence of itch in the adult population of patients with DM2, using standardized methods for itch assessment, as well as to provide itch characteristics and to explore potential underlying causes.

2. Materials and Methods

2.1. Patients

This prospective cross-sectional study was performed between April 2019 and March 2021 with a break due to the COVID-19 pandemic situation (April 2020–September 2020). The project was approved by the local Ethical Committee (ST.C260.18.019). We approached 250 consecutive adult patients who were either treated due to diabetes in the University Hospital in Wroclaw or were patients treated in the outpatient unit, among whom 120 agreed to participate in the study (response rate: 48%). The inclusion criteria were diagnosis of DM2 according to internationally accepted criteria [10] and an informed written participation agreement. Exclusion criteria included: mental status changes deeming the patient unable to make a detailed assessment of itch, a history of chronic itch of another origin and treatment with antipruritic drugs (including drugs for peripheral neuropathy such as gabapentin and pregabalin). Among 120 patients, 10 subjects suffered from chronic itchy dermatological disorders (atopic dermatitis and psoriasis) and one patient was newly diagnosed with notalgia paresthetica. Therefore, the final study group consisted of 109 adult patients with DM2 (Table 1).

Table 1. Characteristics of the studied population.

	Total	With Itch	Without Itch	*p*-Value *
Sex (*n*)	109	39	70	
Female	56 (51.4%)	24 (61.5%)	32 (45.7%)	NS
Male	53 (48.6%)	15 (38.5%)	38 (54.3%)	
Age (years), mean ± SD	62.4 ± 14.4	60.3 ± 13.8	63.5 ± 14.7	
Range	(21–89)	(23–83)	(21–89)	NS
Median	65	65	65	
BMI (kg/m^2), mean ± SD	29.4 ± 5.7	29.7 ± 6.1	29.2 ± 5.4	
Range	(18.7–48.4)	(18.7–48.4)	(19.1–46.0)	NS
Median	28.2	29.1	28.1	

Table 1. *Cont.*

	Total	With Itch	Without Itch	*p*-Value *
Duration of diabetes (years), mean ± SD Range Median	12.7 ± 9.5 (0–45) 12	14 ± 8.9 (0–32) 13	12 ± 12.7 (0–45) 10	NS
Level of education (*n*) Primary Secondary Higher education No data	 18 (16.5%) 49 (45%) 24 (22%) 18 (16.5%)	 7 (18%) 18 (46.1%) 9 (23.1%) 5 (12.8%)	 11 (15.7%) 31 (44.3%) 15 (21.4%) 13 (18.6%)	 NS NS NS
Stimulant use Smoking Alcohol Drugs	 48 (44%) 30 (27.5%) 3 (2.8%)	 20 (51.3%) 13 (33.3%) 2 (5.1%)	 28 (40%) 17 (24.3%) 1 (1.4%)	 NS NS NS
Packet years (years), mean ± SD Range Median	19.8 ± 19.4 (0–90) 15	18.1 ± 15.2 (0–50) 10	21 ± 21.9 (0–90) 12.5	NS
Comorbidities:				
Cardiovascular disorders	69 (35.8%)	22 (56.4%)	47 (67.1%)	NS
Thyroid and parathyroid gland disease	29 (26.6%)	12 (30.8%)	17 (58.6%)	NS
Chronic kidney disease	13 (11.9%)	6 (15.4%)	7 (10%)	NS
Malignancies in the past and neoplasms (incl. benign prostatic hyperplasia)	10 (9.2%)	5 (12.8%)	5 (7.1%)	NS
Joint diseases	5 (4.6%)	1 (2.6%)	4 (5.7%)	NS
Asthma and COPD	4 (3.7%)	1 (2.6%)	3 (4.3%)	NS
Neurological disorders	4 (3.7%)	1 (2.6%)	3 (4.3%)	NS
Infectious diseases in the past (incl. borreliosis, syphilis, meningitidis, tuberculosis)	4 (3.7%)	2 (5.1%)	2 (2.9%)	NS
Psychiatric disorders	4 (3.7%)	2 (5.1%)	2 (2.9%)	NS
Gastrointestinal disorders	3 (2.7%)	0 (0%)	3 (4.3%)	NS

SD—standard deviation, BMI—Body Mass Index, NS—not significant, COPD—chronic obstructive pulmonary disease, HADS—Hospital Anxiety and Depression Score, * Group with itch vs. group without itch.

2.2. Study Design and Applied Questionnaires

After inclusion, detailed information on demographics, comorbidities, used treatment, and physical findings was obtained. The results of routine laboratory blood tests were also noted with particular emphasis on glycated haemoglobin (HbA1c) and fasting plasma glucose (FPG). FPG shows the glycemic control state at the time of the measurements, while the HbA1c is linked to average blood glucose levels in the past 7–8 weeks preceding the measurements. If multiple laboratory tests were available, the results closest to the day of dermatological examination have been chosen.

Standardized questionnaires and scales were completed by patients in order to assess the itch intensity [Numerical Rating Scale (three days, 24hours) (NRS; 0–10 points)] and the Four-item Itch Questionnaire [11–13] (4IIQ; 3–19 points). NRS cut-off points are as follows: 1– < 3 points represent a mild itch, 3–7 points a moderate itch, ≥7–9 points a severe itch, and ≥9 points very severe itch [14]. Furthermore, the description of cutaneous sensations associated with itch, factors alleviating, and aggregating itch, itch-related burden and sleep impairment were recorded.

Skin dryness was assessed clinically and with non-invasive corneometric assessment of epidermal hydration, using a Corneometer CM825, and neurological examination of the patient was done according to the guidelines of the American Diabetes Association [15], as

previously described [12]. Based on neurological findings, all patients were assessed on the Katzenwadel neuropathy scale [16,17], where five aspects of polyneuropathy were assessed: movement functions, pain, sensorial function, motor coordination and tendon reflexes, which were assessed on a 3-point scale (range 0–2 points). The overall Katzenwadel neuropathy scale points correspond to the probability of clinically significant polyneuropathy as follows: with 0–2 points—low risk of neuropathy; 3–4 points—possible neuropathy; and 5–10 points—clinically visible neuropathy [16–18].

To assess the wide spectrum of psychological impact and itch-related burden, all itch patients were asked to complete the validated Polish language versions of an itch-specific quality of life questionnaire (ItchyQoL) and a Six-Item Stigmatization Scale (6-ISS) [17]. Regardless of experienced itching sensations, all patients were asked to fulfil the Hospital Anxiety and Depression Scale (HADS). ItchyQoL is the first questionnaire primary dedicated to itchy conditions and focuses not only on the impact of itch on daily activities but also on the characteristics of the symptoms and the experienced psychological burden level of psychological strain. It evaluates 3 dimensions of itch: symptoms, functioning and emotions [19]. ItchyQoL is also suitable for use in patients with itch without primary skin lesions. The ItchyQoL assessment consists of 22 questions, scored on a 5-point scale ranging from 1 (never) to 5 (all the time), with the sum forming the overall ItchyQol score (22–110 points). The overall ItchyQoL score corresponds to the level of itch-specific health-related quality of life (QoL) impairment as follows: 0–30 points (very mild); 31–50 points (mild); 51–80 points (moderate); and 81–110 points (severe impairment) [20]. The subscales (symptoms, functioning and emotions) are calculated as the mean scores pertaining to that particular category (range 1–5 points) [20]. For the assessment of stigmatization level (score range 0–18), 6-ISS was developed. The higher the scores, the greater the stigmatization level was observed [21]. HADS [22] is used as a self-evaluation rating scale of 14 items designed to measure anxiety and depression. It includes seven items assessing anxiety and seven for depression, each with a score of 0–3. Scores ranging from 0 to 7 are considered a normal case, from 8 to 10 a borderline case, and from 11 to 21 abnormal, and in need of further examination or requiring treatment.

2.3. Statistical Analysis

Statistical analysis of the obtained results was performed with the use of Statistica v. 12 (StatSoft, Kraków, Poland). All data was assessed for parametric or nonparametric distribution. The minimum, maximum, mean and standard deviation calculated. Quantitative variables were evaluated using the Mann–Whitney U test and Spearman's and Pearson's correlations. For qualitative data, the chi-squared test was used. Differences between more than two groups were assessed with the use of Kruskal–Wallis one-way analysis of variance on ranks. A 2-sided p value ≤ 0.05 was considered to be statistically significant

3. Results

3.1. General Demographics and Systemic Comorbidities

A total of 109 (56 females (51.4%); age range: 21–89 years; median age: 65 years) patients with DM2 were enrolled. The range of duration of diabetes was 0–44 years (mean duration: 12.8 $\pm$ 9.4; median: 12 years) (detailed characteristics of the study population is given in Table 1). Thirty-nine subjects reported itch during the course of DM2 (35.8%) while, at the time of examination (point prevalence), it was reported by 32.1% (n = 35) (Table 1). There was no significant difference between the analysed groups (itchy and non-itchy patients) concerning sex, age, body mass index (BMI), duration of the disease, level of education, smoking, drugs or alcohol intake behaviour. The most common systemic comorbidities encompassed cardiovascular disorders (63.3%), thyroid and parathyroid gland disorders (26.6%), and chronic kidney disease (11.9%), without significant differences between itch and non-itch patients. Regarding basic lab examinations, other than connected to glycemic control, there were no significant differences in glomerular filtration rate (eGFR)

or serum creatinine and urea levels in patients with itch and without itch (detailed data not shown). All patients with known thyroid disease were euthyroid.

3.2. Clinical Characteristics of Itch

At the moment of examination, itch was present in 35 subjects out of 39 who experienced CI during the course of DM (89.7%). In this group of subjects, the maximal NRS score for the itch intensity during preceding three days was 6.3 ± 2.2 points (median: 6, range 3–10 points), while during the preceding 24 h was assessed as 4.9 ± 2.5 points (median: 5, range 1–10 points), indicating a moderate itch intensity. According to NRS, not even a single patient reported a mild itch. The moderate itch was observed in 54.29% of patients, while severe itch in 28.6% of patients and very severe itch was observed in 17.14%. The mean 4 IIQ score was 8.1 ± 2.5 points (median: 8, range: 3–16).

CI was usually localized, however, mostly in more than one area (51.3%). It mainly affected lower and upper limbs (38.5% and 23.1%), the trunk (30.8%) and the scalp (23.1%). Generalized itch bothered nine patients (23.1%), while anogenital itch affected only one participant (2.6%). Out of 24 patients with itch in limbs area, eight (40%) experienced itch in the area of hands and feet. Approximately 70% of patients (69.3%) suffered from itch on a daily basis, at least a few times a week. Most frequently, subjects described itch-related sensations as burning (38.5%, n = 15) and pinching (30.8%, n = 12), followed by tingling (28.2%, n = 11), stinging and tickling (in each sensation 12.8%, n = 5). Moreover, patients who suffered from itch reported this symptom as being predominantly burdensome (38.5%, n = 15), annoying (35.9%, n = 14), or unbearable or worrisome (in each 12.8%, n = 5). Although the itch sensation appeared most frequently in the afternoon, almost all of the patients reported itch also in other times of the day or at night (Table 2). About half of itchy participants had trouble falling asleep (almost always: 20.5%, occasionally: 30.8%) and 30.8% reported awakenings because of this symptom (almost always: 18%, occasionally: 12.8%). In addition, five (12.8%) subjects used medication for insomnia due to itch. Stress and heat were the most important factors exacerbating itch while sticking to diabetic diet was described as the factor relieving itch (Figure 1).

Table 2. Occurrence of pruritus during different times of the day.

Time of the Day/Frequency	Not at All	Rarely	Often	All the Time
Morning	8 (20.5%)	24 (61.6%)	5 (12.8%)	2 (5.1%)
Afternoon	1 (2.6%)	22 (56.4%)	13 (33.3%)	3 (7.7%)
Evening	8 (20.5%)	20 (51.3%)	9 (23.1%)	2 (5.1%)
Night	9 (23.1%)	17 (43.6%)	12 (30.7%)	1 (2.6%)

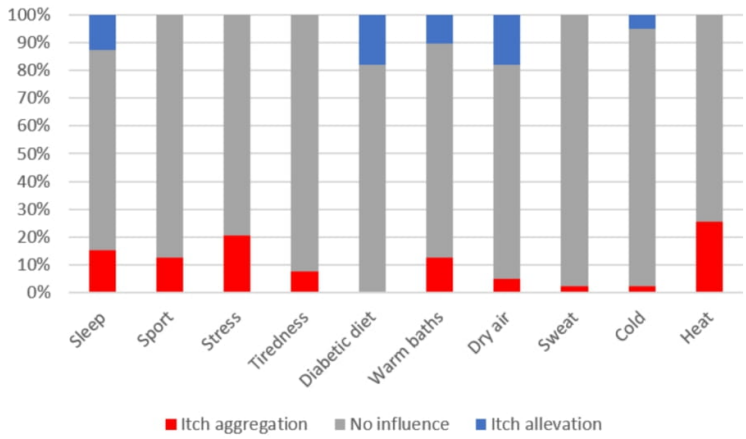

Figure 1. Factors exacerbating and relieving itch in patients with type 2 diabetes mellitus.

3.3. Factors Contributing to Itch in DM: Glycaemic Control, Polyneuropathy, Skin Xerosis, Treatment Used

Itchy patients had significantly higher FPG levels compared with the non-itchy population ($p = 0.01$) (Table 3). Although there was no significant difference regarding HBA1C in Mann–Whitney U Test in disease populations, Spearman's correlation analysis revealed a significant positive link between itch intensity measured with 4IIQ and HbA1c values (R = 0.4, $p = 0.05$) (Figure 2). Moreover, both HbA1c and FPG correlated positively with skin xerosis examined clinically (R = 0.4, $p < 0.001$, R = 0.2, $p = 0.03$, respectively), and polyneuropathy assessed in the Katzenwadel scale (R = 0.3, $p = 0.01$, R = 0.4, $p < 0.01$, respectively).

Table 3. Studied etiopathogenetic factors contributing to itch in diabetes mellitus and dependencies on selected clinical data.

	With Itch (*n* = 39)	**Without Itch (*n* = 70)**	***p*-Value**
	Glycaemic control:		
HbA1C (%), mean ± SD	8.5 ± 2	8 ± 2.3	
Range	(5.2–14)	(5–15.1)	NS
Median	8.2	7.5	
FPG (mg/dl), mean ± SD	174.6 ± 62.3	148 ± 69.2	
Range	(88–356)	(62–510)	$p = 0.01$
Median	164	124	
	Treatment of diabetes: (*n*)		
Insulin	17 (43.6%)	18 (25.7%)	$p = 0.03$
Oral treatment	20 (51.3%)	56 (80%)	$p < 0.01$
Diet only	3 (7.7%)	1 (1.4%)	NS
	Skin xerosis:		
Skin xerosis examined clinically (points), mean ± SD	1.3 ± 0.8	0.9 ± 0.9	
Range	(0–3)	(0–3)	$p < 0.01$
Median	1	1	
Epidermal hydration (AU), mean ± SD (median)			
• Forearm	27.4 ± 10.6 (28.9)	31.2 ± 12.2 (29.9)	NS
• Lower leg	32.1 ± 13.2 (33.3)	32.8 ± 12.4 (31.6)	NS
• Abdomen	20.4 ± 9.4 (18.9)	25.9 ± 16.2 (21.3)	NS
• Chest	39.4 ± 14.6 (38.2)	37.1 ± 18.5 (39.3)	NS
	Polyneuropathy:		
Other than itch sensations related to polyneuropathy (*n*):			
• Tingling	26 (66.7%)	20 (28.6%)	$p < 0.01$
• Numbness	22 (56.4%)	22 (31.4%)	$p = 0.01$
• Pain	8 (20.5%)	8 (11.4%)	NS
• Stinging	7 (17.9%)	3 (4.3%)	$p = 0.02$
• Burning	14 (35.9%)	7 (6.4%)	$p < 0.01$
• Hyperesthesia	7 (17.9%)	7 (6.4%)	NS
• Hypoesthesia	4 (10.3%)	2 (2.9%)	NS
Katzenwadel scale (points), mean ± SD	3.0 ± 1.8	1.3 ± 1.4	
Range	(0–9)	(0–5)	$p < 0.01$
Median	3	1	

HbA1C—glycated haemoglobin, FPG—fasting plasma glucose, SD—standard deviation.

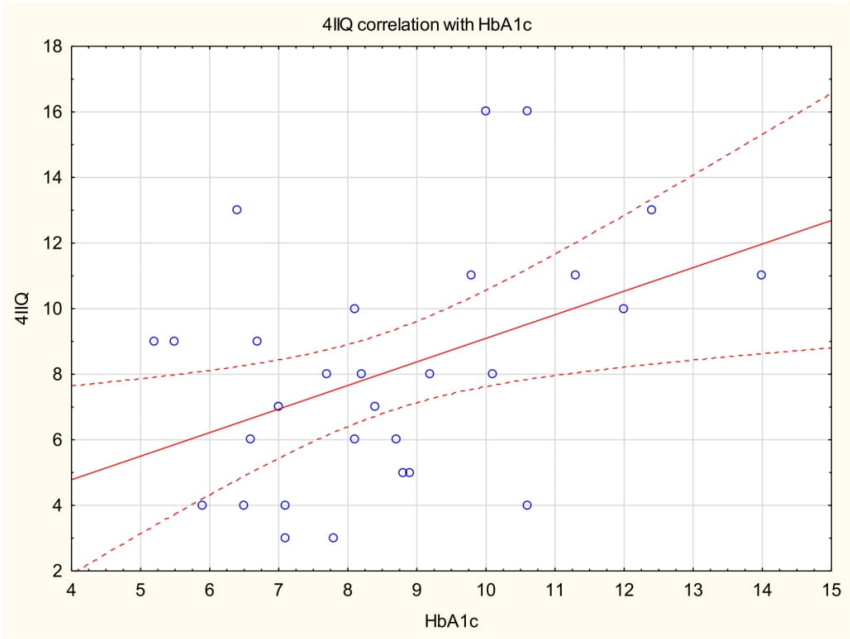

Figure 2. Spearman's correlation analysis revealed a significant positive link between itch intensity measured with a Four-Item Itch Questionnaire (4IIQ) and glycated haemoglobin (HbA1c) values (R = 0.4, $p = 0.05$).

There were significant differences regarding the treatment of DM in itchy and non-itchy subjects. All patients, who received insulin treatment, received it subcutaneously. Patients with itch were prescribed insulin treatment significantly more often, compared to non-itchy group ($p = 0.03$) and patients on oral treatment usually did not experience itch ($p < 0.01$) (Table 3). Moreover, metformin treatment was significantly more common in non-itchy subjects ($p = 0.01$). There were no significant differences regarding other groups of oral medications used (sulfonylurea derivatives [gliclazide, glimepiride], acarbose, dipeptidyl peptidase 4 inhibitors, sodium-glucose transport protein 2 inhibitors, glucagon-like peptide-1 receptor agonists) by our patients and itch (detailed data not shown).

Patients with itch usually also reported other sensations, such as tingling, numbness, stinging or burning, clinically connected to polyneuropathy ($p < 0.01$) (details shown in Table 3). The Mann–Whitney U Test revealed that itchy subjects had a significantly higher probability of neuropathy (in Katzenwadel's neuropathy scale). The possibility of clinically relevant neuropathy was diagnosed in about 50% of itchy patients (possible neuropathy in 35.6%, $n = 14$, clinically visible neuropathy in 15.4%, $n = 6$), while in the non-itchy group it was diagnosed in less than quarter (possible neuropathy in 22.9%, $n = 16$, clinically visible neuropathy in 2.9%, $n = 2$). Patients without itch had a significantly lower possibility of neuropathy compared with itchy subjects ($p < 0.01$), while clinically visible neuropathy was more frequent in the itchy group ($p = 0.01$). Patients with longer duration of the disease had higher risk of neuropathy (R = 0.4, $p < 0.01$). Patients with possible neuropathy according to Katzenwadel's neuropathy scale have felt also significantly more frequently sensations such as tingling ($p < 0.01$), numbness ($p < 0.01$) or burning ($p < 0.01$). Sensation of any of these feelings (tingling, pain, burning, numbness, stinging, hyperesthesia or hypoesthesia) was connected to higher probability of polyneuropathy ($p < 0.01$). Polyneuropathy was, however, not connected to generalized nor localized itch. The area affected with itch was not connected to the neuropathy either (detailed data not shown). Other factors (age, smoking packet year, BMI) were not linked to the possibility of polyneuropathy in our group of patients.

Skin xerosis, examined clinically, was significantly more advanced in patients with itch compared with those without ($p < 0.01$), although using corneometry, there was no difference between these groups with regard to epidermal hydration values (Table 3). However, Spearman's correlation analysis revealed a significant positive link between skin xerosis examined clinically and neuropathy assessed in Katzenwadel 's neuropathy scale (R = 0.4, $p < 0.01$) (Figure 3). What is interesting, in the corneometric assessment in the area of the thorax, is that skin hydration was lower in patients with longer duration of DM2 (R = −0.2, $p = 0.02$) and with higher probability of neuropathy (R = −0.2, $p = 0.04$). Other factors positively associated with skin dryness assessed clinically were age (R = 0.2, $p = 0.01$) and smoking packet years (R = 0.4, $p < 0.01$). Additionally, in patients with higher BMI the skin was dryer in the abdominal area in corneometrical assessment (R = −0.3, $p < 0.01$).

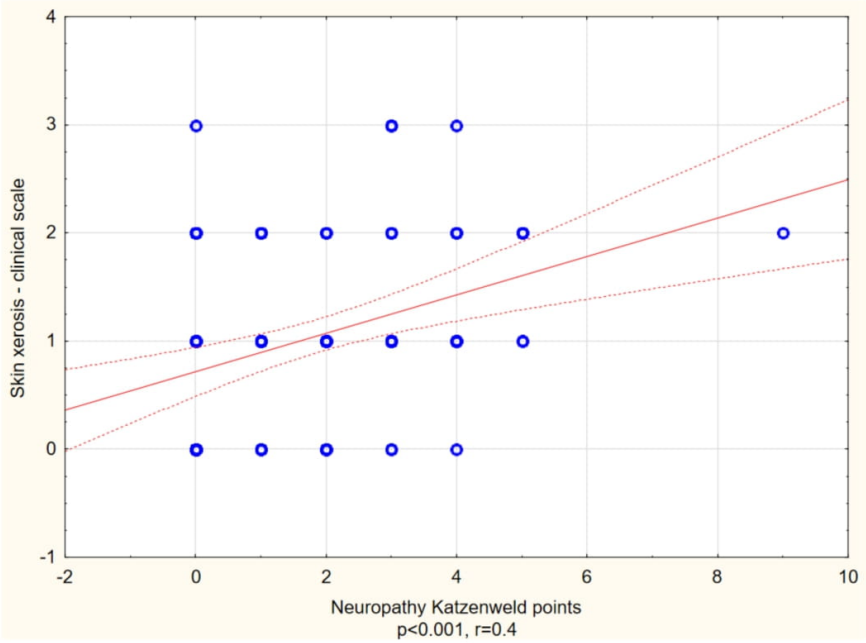

Figure 3. Spearman's correlation analysis revealed a significant positive link between skin xerosis assessed in clinical scale and neuropathy assessed with Katzenwadel neuropathy scale (R = 0.4, $p < 0.001$).

3.4. Itch and Patients Well-Being

The mean ItchyQol score was assessed as 41.2 ± 13.4 points, indicating mild itch-related QoL impairment (Table 4). Itch-related impairment of QoL ranged from very mild to moderate, with nearly a quarter (23.7%) indicating very mild, more than half (55.3%) mild and 18.4% moderate impact. One patient refused to fill out this questionnaire. A positive correlation between the intensity of itch, estimated with 4IIQ, and ItchyQol was found (R = 0.5; $p < 0.01$) (Figure 4). With reference to the results for the subscales, itch in DM2 had the highest impact on symptoms dimension, while emotion and functioning were quite equally scored (Table 5). Itch intensity measured with 4IIQ was also linked with symptoms and functioning dimensions (R = 0.5, $p < 0.01$, R = 0.5, $p = 0.01$, respectively).

Table 4. Questionnaires' scores and dependencies on selected clinical data.

	With Itch (n = 39)	Without Itch (n = 70)	p-Value
HADS-Anxiety (points), mean ± SD	7.6 ± 4.9	3.9 ± 3.9	
Range	(0–18)	(0–21)	$p < 0.01$
Median	7	3	
HADS-Depression (points), mean ± SD	5.1 ± 3	3 ± 3.3	
Range	(0–13)	(0–21)	$p < 0.01$
Median	5	3	
6-ISS, mean ± SD	1.5 ± 1.8		
Range	(0–8)	-	NA
Median	1		
ItchyQoL (raw), mean ± SD	41.2 ± 13.4		
Range	(22–71)	-	NA
Median	39		

HADS—Hospital Anxiety and Depression Scale; 6-ISS—Six-Item Stigmatization Scale; ItchyQoL— itch-specific quality of life questionnaire; NA—not applicable.

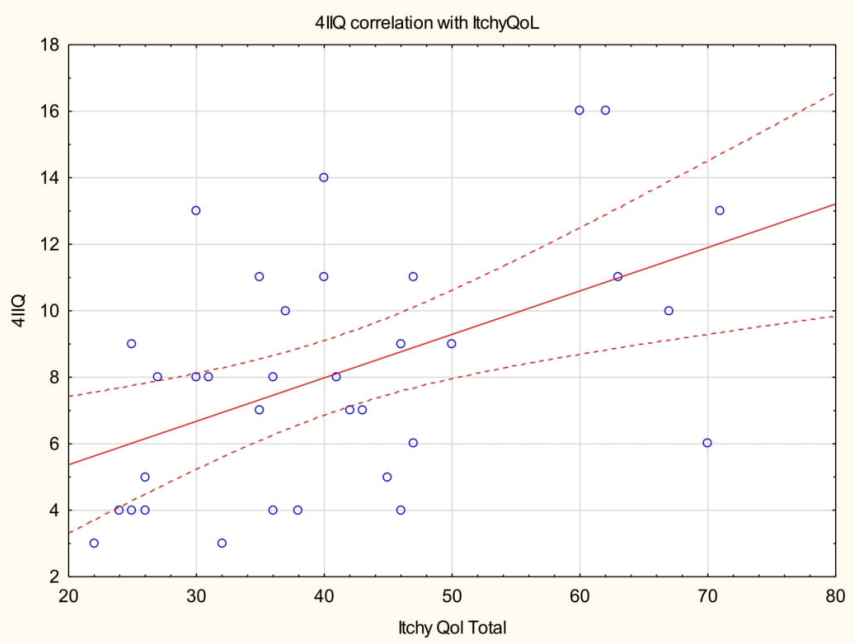

Figure 4. Spearman's correlation analysis revealed a significant positive link between itch intensity measured with Four-Item Itch Questionnaire (4IIQ) and life impairment due to itch measured with ItchyQoL (itch-specific quality of life questionnaire) (R = 0.5, $p < 0.01$).

Table 5. ItchyQoL subscale results among patients with itch in type 2 diabetes mellitus.

ItchyQol Subscale Mean Scores ± SD (Median)
Symptoms 2.1 ± 0.8 (2.1)
Functioning 1.7 ± 0.6 (1.7)
Emotions 1.8 ± 0.8 (1.6)
Combined 1.9 ± 0.6 (1.8)

ItchyQoL—itch-specific quality of life questionnaire.

All thirty-five patients with itch during the preceding three days fulfilled the 6-ISS questionnaire. The mean score was 1.5 ± 1.8 points in this cohort of our patients (Table 4). There was also no significant relationship between itch intensity and 6-ISS scores.

With reference to HADS, the prevalence of anxiety and depression among itchy patients with DM2 was estimated as 33.3% and 7.6%, respectively, while in the non-itchy group it was 5.7% (anxiety) and 1.4% (depression). Itchy subjects had significantly higher scores in both anxiety and depression dimensions of HADS (in each $p < 0.01$) (Table 4). Moreover, the itch intensity measured in NRS (24h) correlated positively with both HADS depression, as well as HADS anxiety scores (R = 0.3, $p = 0.04$, R = 0.5, $p < 0.01$, respectively) (Figures 5 and 6).

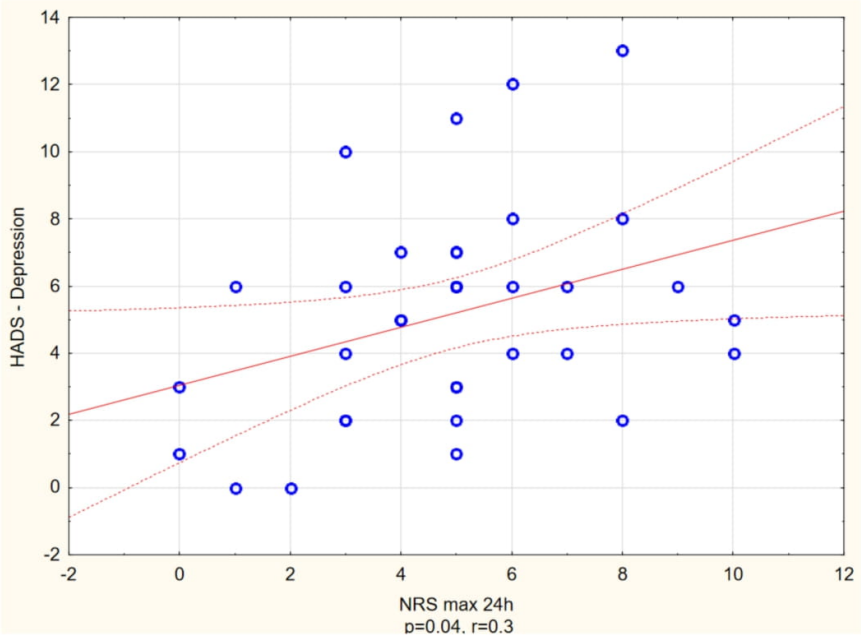

Figure 5. Spearman's correlation analysis revealed a significant positive link between maximal itch intensity measured with Numerical Rating Scale (NRS) and possibility of clinically relevant depression measured with Hospital Anxiety and Depression Scale (HADS) (R = 0.3, $p = 0.04$).

Sex, age, BMI, duration of the disease did not correlate with any of the dependencies in the utilized questionnaires.

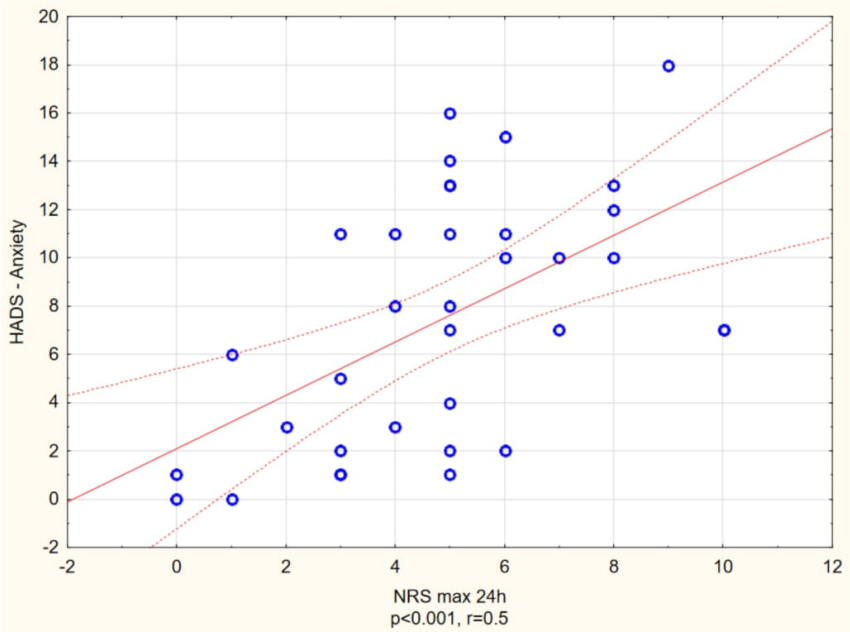

Figure 6. Spearman's correlation analysis revealed a significant positive link between maximal itch intensity measured with Numerical Rating Scale (NRS) and level of anxiety measured with Hospital Anxiety and Depression Scale (HADS) (R = 0.5, $p < 0.001$).

4. Discussion

Although the first known interest in itch in DM was in the late 1920s [23], until now, no other study or review, to our knowledge, has comprehensively investigated and characterized itch in the adult population with DM2. We found high prevalence of itch in this group of patients (35.8%), with a higher rate than reported in the majority of available studies involving patients suffering from DM (18.4–27.5%) [8,24,25]. Itch in DM2 may be both localized, affecting mainly lower extremities (38.5%), trunk (30.8%) and scalp (23.1%), as well as generalized (23.1%). According to literature, generalized itch was noted in 20–27.5% of the patients [25,26], which is in concordance with our study. Valdes-Rodriguez et al. [27] found localized itch in the scalp area in about 40% of elderly patients with DM2. Higher estimated prevalence reported in the study by Valdes-Rodriguez et al. might be connected to the fact that patients were not screened for other possible causes of itch. Moreover, anogenital itch, commonly known in the case of women as pruritus vulvae, was also a subject of studies during the years, with estimated prevalence in DM as 19–27.2% [28,29]. In our study only one subject reported anogenital pruritus (2.6%). Pruritus vulvae might be a result of vaginal infection, which is more common in poorly controlled DM. In our study we excluded patients with ongoing infections, as infections might become independent itch revelators [30]. Moreover, in our study only patients with itch lasting longer than six weeks were qualified, and that is probably why, in our patients, this prevalence was lower. Comparing to our previous study [12], which described itch in the pediatric population with type I diabetes mellitus (DM1), the prevalence of itch in the adult population was higher (22% in DM1 vs. 35.8% in DM2). The distribution of itch also differed, just as in pediatric patient itch, where it was usually localized in upper and lower extremities (68.2% and 50%, respectively). None of the affected subjects with DM1 reported generalized itch. Itch intensity in our study is in concordance with that previously reported in the pediatric population with DM1 (Table 6). In both studies, a diabetic diet was reported by patients as an itch-alleviating factor.

Table 6. Itch intensity in adult population with type 2 diabetes mellitus compared to pediatric population with type I diabetes mellitus [16].

	NRS_{max} Three Days Mean ± SD	NRS_{max} 24 h Mean ± SD	4IIQ Mean ± SD
Adult population with DM2 (current study)	6.31 ± 2.16	4.9 ± 2.5	8.1 ± 3.5 points
Pediatric population with DM1 (Stefaniak et al. 2020)	6.3 ± 3.0	5.0 ± 3.8	6.7 ± 3.5 points

NRS: Numerical Rating Scale, 4IIQ: Four-Item Itch Questionnaire, DM1: type I diabetes mellitus, DM2: type 2 diabetes mellitus.

Pathogenesis of itch in DM is not fully understood and various factors are described as contributing to the development of this symptom. Currently, the researchers believe that there are two main factors associated with the itch in diabetes—skin xerosis and diabetic polyneuropathy, indicating a dermatological or neurological origin of itch. The role of glycemic control is still being discussed. Based on our study it seems that all of these factors contribute to itch pathogenesis in the adult population with DM2. On the cellular level, insulin is an essential growth factor for cultured keratinocytes and it influences keratinocyte proliferation, migration and differentiation [31]. Additionally, according to recent studies, increased oxidative stress and nerve inflammation may also play a role in diabetic polyneuropathy [32]. One of the theories suggests that atypical changes in insulin levels in the circulating blood might be the cause of the disrupted keratinocytes. Therefore, abnormal proliferation of keratinocytes in the epidermis changes the functions of stratum corneum in patients with diabetes. Moreover, it is well known that DM induces an increase in advanced glycosylation products in the collagen of the dermis, that may be connected to skin ageing [33]. All of this may be the cause of the reduced hydration of the stratum corneum [34,35] and, subsequently, cause itch. In the current study we have shown that both HbA1c and FPG correlated positively with skin xerosis examined clinically. In our study on the pediatric population with DM1 [12], where mean duration of DM was less than six years, skin xerosis was the most important factor influencing itch presence and intensity. In the current study, patients with itch had significantly dryer skin, compared with non-itchy individuals. Newer theories suggest that itch in DM may be associated with diabetic polyneuropathy. Neuropathy or damage of the nerve fibres is a debilitating, yet surprisingly common and complex, condition. By far, DM is the most common cause of neuropathy in developed countries [36,37] with the estimated prevalence of 30%, and while up to 50% of patients will eventually develop some kind of neuropathy during the course of the disease [38]. DM may cause the damage to the peripheral nervous system in a variety of ways, but the most common presentation is a distal symmetric polyneuropathy (DSP) followed by small fiber predominant neuropathy (SFN), radiculoplexopathy and autonomic neuropathy [39]. SFN is considered an early manifestation of diabetic polyneuropathy and is known to progress to distal symmetric polyneuropathy [40]. Typical clinical manifestations of diabetic polyneuropathy (numbness, tingling, neuropathic pain, hyper and hypoesthesia and/or weakness, stocking-and-gloves distribution of symptoms, risk of ulcerations) are considered to be manifestations of DSP. SFN is a disorder of the small myelinated Aδ-fibers and unmyelinated C-fibers and it might affect small sensory fibers, autonomic fibers or both, resulting in sensory changes, autonomic dysfunction, or combined symptoms. SFN is more difficult to diagnose, as patients rarely show decreased reflexes, weakness, and impaired vibration sensations—assets which are typically screened to asses diabetic polyneuropathy. In most patients, different kinds of neuropathies come together, and are mainly a result of the long-lasting hyperglycemia, with created changes in insulin signalling as a key. The theory of itch in DM is mostly focused on itch as a result of both DSP and SFN, and is as closely related to skin xerosis, as diabetic polyneuropathy is linked to the dysfunction of sweating, which is due to impairment of the sympathetic nervous system [41]. Pereira et al. [42], in their study concerning itch in SFN, showed that in about 18% of cases, neuropathy was caused by DM. In our study, we have shown that

both HbA1c and FPG correlated positively with polyneuropathy assessed with the Katzenwadel scale. Furthermore, we have provided a clear link between skin xerosis examined clinically and polyneuropathy. What is interesting, in corneometric assessment in the area of the thorax, is that skin hydration was lower in patients with longer duration of DM2 and in subjects with higher probability of neuropathy. In our opinion, this observation may explain the pathogenesis of truncal pruritus of unknown origin (TPUO) in diabetic patients. Yamaoka et al. [8], in 2010, first documented a clear link between TPUO and DM2. As a result of a multicentre study on 391 diabetic outpatients, Yamaoka et al. [8] proved that prevalence of TPUO in diabetic subjects was significantly higher than that in age-matched nondiabetic subjects (11.3 vs. 2.9%, $p = 0.0001$). In our study, besides itching, patients usually also reported other sensations, such as tingling, numbness, stinging or burning, clinically connected to SFN and neuropathic itch [42,43]. Patients without itch had significantly lower possibility of neuropathy compared with itchy subjects, while clinically visible neuropathy was more frequent in the itchy group. Therefore, we would like to suggest itch as one of the sensations connected to diabetic polyneuropathy.

Regarding glycemic control, in our cohort, itchy patients had significantly higher FPG levels compared with the non-itchy population. Additionally, we have provided significant positive association between itch intensity measured with 4IIQ and HbA1c values. There is a paucity of literature regarding itch and parameters of glycemic control. Ko et al. [25] showed that patients with a higher postprandial glucose level had a higher probability of generalized itch. Hillson et al. [44] documented the correlation between the FPG and generalized itch in newly diagnosed and untreated patients with DM2. In patients with short-lasting DM1 [12] there was no association between itch and glycemic control, however, nearly a quarter (22.7%) considered a diabetic diet as itch-alleviating, as in this currently described study on adult population with DM2. Several antidiabetic medications (glimepiride, metformin, tolbutamide) were also associated with CI [30]. In our study, patients treated with oral medications showed lower probability of itch, compared to patients receiving insulin. Nota bene, no association was found between type of oral treatment and itch. We may only speculate but, in our opinion, this is linked to the control of the disease as well. Patients with need of insulin treatment usually cannot achieve proper disease control on oral treatment only. Based on these findings, we would like to suggest a model of itch in DM (Figure 7) with glycemic control as the main factor contributing to both skin xerosis and diabetic polyneuropathy. Based on literature and our findings, it is possible that in short-lasting DM the dermatological component plays a bigger role, while longer duration of the disease may contribute to neuropathic co-factors. Furthermore, more advanced age and comorbidities frequently associated with DM, such as metabolic syndrome and chronic kidney disease, may contribute to the dermatological component—skin dryness. Therefore, we would like to emphasize that, in our opinion, itch in diabetes should be classified as systemic itch, according to IFSI classification [4], with both dermatological and neurological components as co-factors.

In our cohort of patients, itch correlated positively with impairment of QoL as measured with ItchyQoL, both in total, as in the symptom and functioning subscores. This corresponds with other studies on both cutaneous and systemic itch and QoL assessment [45–47]. In general, it is known that CI is a highly debilitating symptom in the majority of itch patients. Moreover, itchy subjects had significantly higher scores in both anxiety and depression dimensions of HADS. As the HADS questionnaire is commonly used worldwide, it is quite easy to conduct an assessment comparing scores in various itchy disorders. For instance, the HADS results obtained in our study showed comparable deterioration to systemic itch in polycythaemia vera [48], as well as some other itchy skin disorders, including psoriasis [49], atopic dermatitis [50], urticaria [51,52], chronic prurigo [53] or acne [54], known to cause relevant disability.

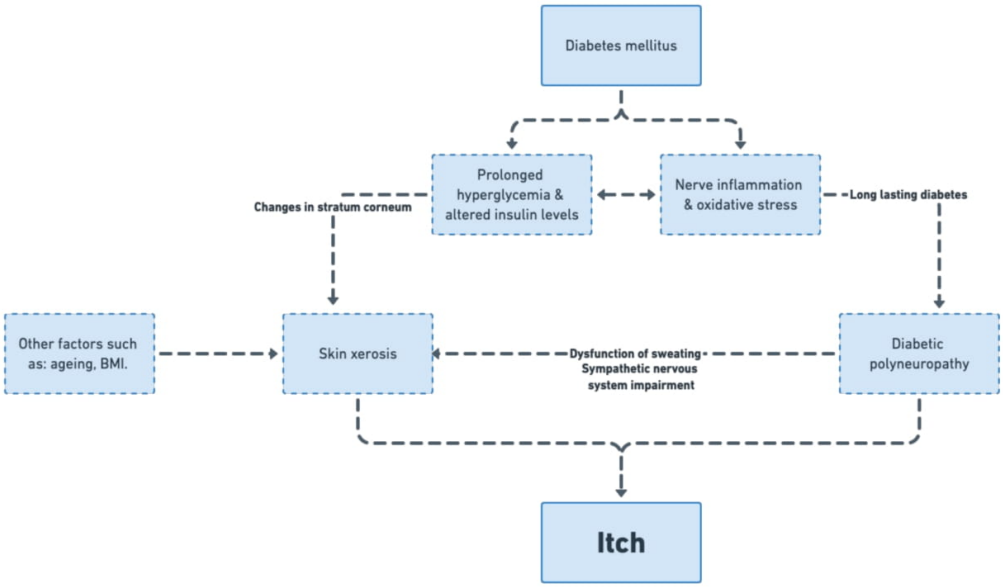

Figure 7. Proposed pathogenetic model of itch in diabetes.

This study has several limitations. Firstly, this was a single-centre study and the number of subjects with itch was relatively small, therefore, this study should be considered of an exploratory nature. In addition, the descriptive nature of the study must be considered. Secondly, insulin and sorbitol levels were not measured and there was no differentiation in the types of insulin used by the patient. Additionally, as patients with poor diabetes control and longer duration of the disease are known to have greater risk for complications, possible risk of multicollinearity have to be taken into consideration. Last, but by no means least, the period of the study was relatively long, with a break due to the COVID-19 pandemic. Despite our efforts, additional factors influencing both itch and patient well-being could affect the results.

5. Conclusions

In conclusion, itch in DM2 is a complex symptom, arising relatively frequently. Based on literature and our findings, we suggest that the primary cause of itch is prolonged poor diabetes control with altered glucose and insulin levels, subsequently causing skin dryness and small-fibre neuropathy in long-lasting DM2. Proper control of diabetes should be the main goal of treatment of itch in this group of patients, however the dermatological and neuropathic component should not be neglected. Moreover, we would like to suggest itch as one of the symptoms of diabetic polyneuropathy.

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

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References

1. Baena-Díez, J.M.; Peñafiel, J.; Subirana, I.; Ramos, R.; Elosua, R.; Marín-Ibañez, A.; Guembe, M.J.; Rigo, F.; Tormo-Díaz, M.J.; Moreno-Iribas, C.; et al. Risk of cause-specific death in individuals with diabetes: A competing risks analysis. *Diabetes Care* **2016**, *39*, 1987–1995. [CrossRef] [PubMed]
2. Sarwar, N.; Gao, P.; Kondapally Seshasai, S.R.; Gobin, R.; Kaptoge, S.; Di Angelantonio, E.; Ingelsson, E.; Lawlor, D.A.; Selvin, E.; Stampfer, M.; et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies. *Lancet* **2010**, *375*, 2215–2222. [CrossRef]
3. Ständer, S.; Streit, M.; Darsow, U.; Niemeier, V.; Vogelgsang, M.; Ständer, H.; Gieler, U.; Gollnick, H.; Metze, D.; Weisshaar, E. Diagnostic and therapeutic procedures in chronic pruritus. *J. Dtsch. Dermatol. Ges.* **2006**, *4*, 350–370. [CrossRef] [PubMed]
4. Ständer, S.; Weisshaar, E.; Mettang, T.; Szepietowski, J.; Carstens, E.; Ikoma, A.; Bergasa, N.; Gieler, U.; Misery, L.; Wallengren, J.; et al. Clinical classification of itch: A position paper of the international forum for the study of itch. *Acta Derm. Venereol.* **2007**, *87*, 291–294. [CrossRef] [PubMed]
5. Alizadeh, N.; Mirpour, S.H.; Golmohamadi, R.; Darjani, A.; Eftekhari, H.; Rafiei, R.; Gharaei Nejad, K.; Azimi, S.Z. Chronic generalized pruritus without primary skin lesions: A longitudinal prospective observational study. *Int. J. Dermatol.* **2019**, *58*, 273–278. [CrossRef] [PubMed]
6. Steinhoff, M.; Schmelz, M.; Szabó, I.L.; Oaklander, A.L. Clinical presentation, management, and pathophysiology of neuropathic itch. *Lancet Neurol.* **2018**, *17*, 709–720. [CrossRef]
7. Tseng, H.-W.; Ger, L.-P.; Liang, C.-K.; Liou, H.-H.; Lam, H.-C. High prevalence of cutaneous manifestations in the elderly with diabetes mellitus: An institution-based cross-sectional study in Taiwan. *J. Eur. Acad. Dermatol. Venereol.* **2015**, *29*, 1631–1635. [CrossRef]
8. Yamaoka, H.; Sasaki, H.; Yamasaki, H.; Ogawa, K.; Ohta, T.; Furuta, H.; Nishi, M.; Nanjo, K. Truncal pruritus of unknown origin may be a symptom of diabetic polyneuropathy. *Diabetes Care* **2010**, *33*, 150–155. [CrossRef]
9. Stefaniak, A.; Chlebicka, I.; Szepietowski, J. Itch in diabetes: A common underestimated problem. *Adv. Dermatol. Allergol.* **2019**, *36*, 177–183. [CrossRef]
10. Association, A.D. 2. Classification and diagnosis of diabetes: Standards of medical care in diabetes—2020. *Diabetes Care* **2020**, *43*, S14–S31. [CrossRef] [PubMed]
11. Reich, A.; Mędrek, K.; Szepietowski, J. Czteropunktowy kwestionariusz oceny świadu—Walidacja kwestionariusza. *Prz. Dermatol.* **2012**, *99*, 600–604.
12. Stefaniak, A.A.; Zubkiewicz-Kucharska, A.; Matusiak, Ł.; Noczyńska, A.; Szepietowski, J.C. Itch in children with type 1 diabetes: A cross-sectional study. *Dermatol. Ther.* **2020**, *10*, 745–756. [CrossRef] [PubMed]
13. Krajewski, P.K.; Olczyk, P.; Krajewska, M.; Krajewski, W.; Szepietowski, J.C. Clinical characteristics of itch in renal transplant recipients. *Front. Med.* **2021**, *7*, 615334. [CrossRef]
14. Reich, A.; Chatzigeorkidis, E.; Zeidler, C.; Osada, N.; Furue, M.; Takamori, K.; Ebata, T.; Augustin, M.; Szepietowski, J.C.; Ständer, S. 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] [PubMed]
15. Association, A.D. 11. microvascular complications and foot care: Standards of medical care in diabetes—2020. *Diabetes Care* **2020**, *43*, S135–S151. [CrossRef]
16. Katzenwadel, A.; Sachse, G.; Federlin, K. Measurement of vibration sensitivity and temperature discrimination in peripheral diabetic neuropathy. *Akt. Endokr. Stoffwechs.* **1987**, *8*, 155–160.
17. Haupt, E.; Ledermann, H.; Köpcke, W. Benfotiamine in the treatment of diabetic polyneuropathy—A three-week randomized, controlled pilot study (BEDIP study). *Int. J. Clin. Pharmacol. Ther.* **2005**, *43*, 71–77. [CrossRef]
18. Rogoziewicz, M.; Wiszniewska, M.; Wiszniewski, P.; Michalak, S.; Kozubski, W. Clinical and neurophysiological evaluation of peripheral nervous system abnormalities in patients with lymphoproliferative disorders. *Neurology* **2012**, *78*, P06.018. [CrossRef]
19. 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 1150 patients. *Acta Derm. Venereol.* **2018**, *98*, 142–143. [CrossRef] [PubMed]

20. Love, E.M.; Marrazzo, G.A.; Kini, S.; Veledar, E.; Chen, S.C. ItchyQoL bands: Pilot clinical interpretation of scores. *Acta Derm. Venereol.* **2015**, *95*, 114–115. [CrossRef]
21. Lu, Y.; Duller, P.; van der Valk, P.G.M.; Evers, A.W.M. Helplessness as predictor of perceived stigmatization in patients with psoriasis and atopic dermatitis. *Dermatol. Psychosom.* **2003**, *4*, 146–150. [CrossRef]
22. Zigmond, A.S.; Snaith, R.P. The hospital anxiety and depression scale. *Acta Psychiatr. Scand.* **1983**, *67*, 361–370. [CrossRef] [PubMed]
23. Greenwood, A.M. A study of the skin in five hundred cases of diabetes. *J. Am. Med. Assoc.* **1927**, *89*, 774–776. [CrossRef]
24. Neilly, J.B.; Martin, A.; Simpson, N.; MacCuish, A.C. Pruritus in diabetes mellitus: Investigation of prevalence and correlation with diabetes control. *Diabetes Care* **1986**, *9*, 273–275. [CrossRef]
25. Ko, M.-J.; Chiu, H.-C.; Jee, S.-H.; Hu, F.-C.; Tseng, C.-H. Postprandial blood glucose is associated with generalized pruritus in patients with type 2 diabetes. *Eur. J. Dermatol.* **2013**, *23*, 688–693. [CrossRef] [PubMed]
26. Mishra, V.N.; Mansharmani, G.G. Diabetes mellitus in geriatric females. *J. Indian Med. Assoc.* **1989**, *87*, 138–139. [PubMed]
27. Valdes-Rodriguez, R.; Mollanazar, N.; González-Muro, J.; Nattkemper, L.; Torres-Alvarez, B.; López-Esqueda, F.; Chan, Y.; Yosipovitch, G. Itch prevalence and characteristics in a Hispanic geriatric population: A comprehensive study using a standardized itch questionnaire. *Acta Derm. Venereol.* **2015**, *95*, 417–421. [CrossRef]
28. Drivsholm, T.; de Fine Olivarius, N.; Nielsen, A.B.S.; Siersma, V. Symptoms, signs and complications in newly diagnosed type 2 diabetic patients, and their relationship to glycaemia, blood pressure and weight. *Diabetologia* **2005**, *48*, 210–214. [CrossRef]
29. Wahid, Z.; Kanjee, A. Cutaneous manifestations of diabetes mellitus. *J. Pak. Med. Assoc.* **1998**, *48*, 304–305.
30. Weisshaar, E.; Szepietowski, J.C.; Dalgard, F.; Garcovich, S.; Gieler, U.; Gimenez-Arnau, A.; Lambert, J.; Leslie, T.; Mettang, T.; Misery, L.; et al. European S2k guideline on chronic pruritus. *Acta Derm. Venereol.* **2019**, *99*, 469–506. [CrossRef]
31. Wertheimer, E.; Trebicz, M.; Eldar, T.; Gartsbein, M.; Nofeh-Moses, S.; Tennenbaum, T. Differential roles of insulin receptor and insulin-like growth factor-1 receptor in differentiation of murine skin keratinocytes. *J. Investig. Dermatol.* **2000**, *115*, 24–29. [CrossRef] [PubMed]
32. Hagen, K.M.; Ousman, S.S. Aging and the immune response in diabetic peripheral neuropathy. *J. Neuroimmunol.* **2021**, *355*, 577574. [CrossRef] [PubMed]
33. Kennedy, L.; Baynes, J.W. Non-enzymatic glycosylation and the chronic complications of diabetes: An overview. *Diabetologia* **1984**, *26*, 93–98. [CrossRef] [PubMed]
34. Sakai, S.; Kikuchi, K.; Satoh, J.; Tagami, H.; Inoue, S. Functional properties of the stratum corneum in patients with diabetes mellitus: Similarities to senile xerosis. *Br. J. Dermatol.* **2005**, *153*, 319–323. [CrossRef] [PubMed]
35. Sakai, S.; Endo, Y.; Ozawa, N.; Sugawara, T.; Kusaka, A.; Sayo, T.; Inoue, S.; Tagami, H. Characteristics of the epidermis and stratum corneum of hairless mice with experimentally induced diabetes mellitus. *J. Investig. Dermatol.* **2003**, *120*, 79–85. [CrossRef]
36. Cho, N.H.; Shaw, J.E.; Karuranga, S.; Huang, Y.; da Rocha Fernandes, J.D.; Ohlrogge, A.W.; Malanda, B. IDF Diabetes atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res. Clin. Pract.* **2018**, *138*, 271–281. [CrossRef] [PubMed]
37. Johannsen, L.; Smith, T.; Havsager, A.M.; Madsen, C.; Kjeldsen, M.J.; Dalsgaard, N.J.; Gaist, D.; Schrøder, H.D.; Sindrup, S.H. Evaluation of patients with symptoms suggestive of chronic polyneuropathy. *J. Clin. Neuromuscul. Dis.* **2001**, *3*, 47–52. [CrossRef]
38. Maser, R.E.; Steenkiste, A.R.; Dorman, J.S.; Nielsen, V.K.; Bass, E.B.; Manjoo, Q.; Drash, A.L.; Becker, D.J.; Kuller, L.H.; Greene, D.A.; et al. Epidemiological correlates of diabetic neuropathy. Report from Pittsburgh epidemiology of diabetes complications study. *Diabetes* **1989**, *38*, 1456–1461. [CrossRef]
39. Callaghan, B.C.; Cheng, H.; Stables, C.L.; Smith, A.L.; Feldman, E.L. Diabetic neuropathy: Clinical manifestations and current treatments. *Lancet* **2012**, *11*, 521–534. [CrossRef]
40. Lauria, G.; Merkies, I.S.J.; Faber, C.G. Small fibre neuropathy. *Curr. Opin. Neurol.* **2012**, *25*, 542–549. [CrossRef]
41. Sun, P.-C.; Chen, C.-S.; Kuo, C.-D.; Lin, H.-D.; Chan, R.-C.; Kao, M.-J.; Wei, S.-H. Impaired microvascular flow motion in subclinical diabetic feet with sudomotor dysfunction. *Microvasc. Res.* **2012**, *83*, 243–248. [CrossRef]
42. Pereira, M.P.; Derichs, L.; Meyer Zu Hörste, G.; Agelopoulos, K.; Ständer, S. Generalized chronic itch induced by small-fibre neuropathy: Clinical profile and proposed diagnostic criteria. *J. Eur. Acad. Dermatol. Venereol.* **2020**, *34*, 1795–1802. [CrossRef]
43. Pereira, M.P.; Wiegmann, H.; Agelopoulos, K.; Ständer, S. Neuropathic itch: Routes to clinical diagnosis. *Front. Med.* **2021**, *8*, 175. [CrossRef]
44. Hillson, R.M.; Hockaday, T.D.; Newton, D.J.; Pim, B. Delayed diagnosis of non-insulin-dependent diabetes is associated with greater metabolic and clinical abnormality. *Diabet. Med.* **1985**, *2*, 383–386. [CrossRef]
45. Carr, C.W.; Veledar, E.; Chen, S.C. Factors mediating the impact of chronic pruritus on quality of life. *JAMA Dermatol.* **2014**, *150*, 613–620. [CrossRef] [PubMed]
46. Xu, T.; Shetty, A.K.; Badiger, S.; Chan, Y.H.; Yosipovitch, G. Prevalence and characteristics of pruritus and association with quality of life in people living with HIV: A cross-sectional study. *J. Pain Symptom Manag.* **2018**, *55*, e4–e7. [CrossRef] [PubMed]
47. Zeidler, C.; Steinke, S.; Riepe, C.; Bruland, P.; Soto-Rey, I.; Storck, M.; Garcovich, S.; Blome, C.; Bobko, S.; Legat, F.J.; et al. Cross-European validation of the ItchyQoL in pruritic dermatoses. *J. Eur. Acad. Dermatol. Venereol.* **2019**, *33*, 391–397. [CrossRef] [PubMed]
48. Lelonek, E.; Matusiak, Ł.; Wróbel, T.; Kwiatkowski, J.; Szepietowski, J.C. Burden of aquagenic pruritus in polycythaemia vera. *Acta Derm. Venereol.* **2018**, *98*, 185–190. [CrossRef] [PubMed]

49. Tee, S.I.; Lim, Z.V.; Theng, C.T.; Chan, K.L.; Giam, Y.C. A prospective cross-sectional study of anxiety and depression in patients with psoriasis in Singapore. *J. Eur. Acad. Dermatol. Venereol.* **2016**, *30*, 1159–1164. [CrossRef]
50. Tan, W.F.; Voo, S.Y.M.; Sulaiman, N.; Robinson, S. Psychosocial burden of patients with atopic dermatitis at two tertiary referral centres in malaysia. *Med. J. Malays.* **2021**, *76*, 643–652.
51. Choi, G.S.; Nam, Y.H.; Park, C.S.; Kim, M.Y.; Jo, E.J.; Park, H.K.; Kim, H.K. Anxiety, depression, and stress in Korean patients with chronic urticaria. *Korean J. Intern. Med.* **2020**, *35*, 1507–1516. [CrossRef] [PubMed]
52. Tat, T.S. Higher levels of depression and anxiety in patients with chronic urticaria. *Med. Sci. Monit.* **2019**, *25*, 115–120. [CrossRef] [PubMed]
53. Zeidler, C.; Pereira, M.P.; Dugas, M.; Augustin, M.; Storck, M.; Weyer-Elberich, V.; Schneider, G.; Ständer, S. The burn in chronic prurigo: Patients with chronic prurigo suffer more than patients with chronic pruritus on non-lesional skin: A comparative, retrospective, explorative statistical analysis of 4484 patients in a real-world cohort. *J. Eur. Acad. Dermatol. Venereol.* **2021**, *35*, 738–743. [CrossRef] [PubMed]
54. Altunay, İ.K.; Özkur, E.; Dalgard, F.J.; Gieler, U.; Tomas-Aragones, L.; Lien, L.; Poot, F.; Jemec, G.B.E.; Misery, L.; Szabo, C.; et al. Psychosocial aspects of adult acne: Data from 13 European countries. *Acta Derm. Venereol.* **2020**, *100*, adv00051. [CrossRef] [PubMed]

11. ARTYKUŁ CZWARTY:

SMALL-FIBRE NEUROPATHY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND ITS RELATIONSHIP WITH DIABETIC ITCH: PRELIMINARY RESULTS.

SHORT COMMUNICATION

Small-fibre Neuropathy in Patients with Type 2 Diabetes Mellitus and its Relationship with Diabetic Itch: Preliminary Results

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Diabetes mellitus (DM) is the main cause of small-fibre neuropathy (SFN) in developed countries (1, 2). Notably, one of the possible manifestations of SFN is itch (3–9). The aim of this study was to assess SFN as a potential cause of itch in DM, as well as other factors that may contribute to itch in DM, such as glycaemic control and skin xerosis (10, 11).

MATERIALS AND METHODS

This prospective study evaluated itch among 23 patients with diabetes mellitus type 2 (DM2). Itch intensity was assessed with the Numerical Rating Scale (NRS) and the 4-Item Itch Questionnaire (4IIQ). Skin dryness was evaluated clinically and by non-invasive assessment of epidermis moisturizing. Neuropathy was assessed using clinical Katzenwadel neuropathy scale and SFN was assessed with intraepidermal nerve fibre density (IENFD). Patients' characteristics, study design and methods are shown in Appendix S1.

RESULTS

Twelve patients experienced itch during the study period, with the mean itch intensity assessed on a numerical rating scale (NRS_{max}) over a period of 3 days rated as 8 ± 2 points (range 5–10 points, median 8 points), indicating severe itch. Mean itch NRS_{max} in the previous 24 h was 6.4 ± 2.5 points (range 1–10 points, median 6 points), while the mean result of the 4 Item Itch Questionnaire (4IIQ) was 6 ± 2.6 points (range 3–13 points, median 5.5 points). Itch was usually localized, affecting mainly the lower extremities (58.3%, $n=7$). Two subjects reported generalized itch (16.7%). Regarding neuropathy, there was a visible trend, although this was not statistically significant, for more pronounced neuropathy assessed clinically in patients with itch ($p=0.091$). In addition, a positive trend between itch intensity assessed with the 4IIQ and neuropathy assessment on the Katzenwadel scale was revealed (R=0.5, $p=0.08$) (Table SI). The possibility of clinically relevant neuropathy was diagnosed in approximately 66.7% of itchy patients (possible neuropathy in 41.7%, $n=4$, clinically overt neuropathy in 25%, $n=3$), while in the non-itchy group it was diagnosed in approximately one-quarter (possible neuropathy in 27.3%, $n=3$, no patients had clinically overt neuropathy) (**Table I**). More than 80% of patients with itch (83.3%, $n=10$) reported other sensations (tingling, numbness, pain, stinging, burning, hyperaesthesia, hypoaesthesia) clinically connected to polyneuropathy, while it was only approximately 50% in the non-itchy group (54.5%, $n=6$), with significant differences in experienced tingling or numbness ($p=0.022$ and $p=0.043$, respectively). The possibility of clinically relevant polyneuropathy (total score) correlated positively with the HbA1c values ($p=0.02$); however, there were no significant differences regarding glycaemic control (fasting plasma glucose and glycated haemoglobin) between itchy and non-itchy subjects (Table SII). Moreover, our analysis revealed that the total score on the Katzenwadel scale correlated negatively with skin dryness assessed with corneometry in the forearm and abdominal area (R=–0.5, $p=0.032$ and R=–0.5, $p=0.022$, respectively), as well as there being a tendency to drier skin on the lower legs (R=–0.4, $p=0.093$) and skin dryness assessed clinically (r=0.4, $p=0.074$) (Table SIII). Furthermore, itchy subjects had significantly drier skin measured with corneometry in the abdominal area ($p=0.016$), as well as on the lower leg; however, this only had marginal significance ($p=0.056$). Skin dryness assessed with corneometry in the area of the forearm correlated negatively with disease duration (R=–0.5, $p=0.022$).

Table I. Studied aetiopathogenetic factors contributing to itch in diabetes mellitus and dependencies on itch: neuropathy

	With itch ($n=12$)	Without itch ($n=11$)	p-value*
Katzenwadel scale (points), mean ± SD	3.2 ± 1.7	1.2 ± 1.1	0.091[b]
Median (range)	4 (0–5)	1 (0–3)	
IENFD (fibers/mm) mean ± SD	2.7 ± 1.6	3.7 ± 2.0	NS[b]
Median (range)	2.8 (0–5.2)	3.4 (1.2–6.4)	
Other symptoms linked to diabetic polyneuropathy, *n* (%)			
Numbness	8 (66.7)	2 (18.2)	0.022[c]
Tingling	9 (75)	3 (27.3)	0.036[c]
Pain	3 (25)	2 (18.2)	NS[c]
Stinging	2 (16.7)	1 (9.1)	NS[c]
Burning	5 (41.7)	2 (18.2)	NS[a]
Hyperaesthesia	4 (33.3)	1 (9.1)	NS[c]
Hypoaesthesia	1 (8.3)	0 (0)	NS[c]

[a]χ^2 test, [b]Mann–Whitney *U* test, [c]Fisher's exact test.
SD: standard deviation; NS: not significant; IENFD: intraepidermal nerve fibre density. *Group with itch vs group without itch.

All patients included in the study, had a decreased intraepidermal nerve fibre density (IENFD) (3.2 ± 1.8; median 3.0, range 0–6.2 fibers/mm, $n=23$) in comparison with normative values for the distal leg at the innervation site of the sural nerve (12). The mean value of IENFD for the itchy group was lower than for the non-itchy subjects (2.7 ± 1.6; median 2.8, range 0–5.2 fibers/mm and 3.7 ± 2.0;

median 3.4, range 0–6.4 fibers/mm, respectively); however, this difference did not reach statistical significance. In the whole group studied no subject score was inside the normal range (12).

The IENFD did not correlate with itch intensity assessed by NRS and 4IIQ (detailed data not shown), nor with age, disease duration or glycaemic control.

Females had a higher IENFD (4.0 ± 1.8 [0–4.6] fibers/mm) compared with males (2.9 ± 1.6 [2.0–6.4] fibers/mm; $p = 0.016$), while there was a visible trend to drier skin assessed with corneometry (chest area) in patients with lower IENFD (R = 0.4, $p = 0.088$). Patients with lower IENFD have a higher possibility of neuropathy on Katzenwadel neuropathy scale (R = –0.4, $p = 0.053$).

Patients with severely reduced IENFD (<30% of the normative cut-off value (12)) did not differ according to itching sensations experienced, age, duration of disease, glycaemic control, skin dryness or clinical possibility of neuropathy. A total of 11 patients (47.8%; 6 out of the itchy group and 5 out of non-itchy group) had severely reduced IENFD (Fig. S1). Although not significant, the current study indicates that severely reduced IENFD occurred more frequently in males ($p = 0.058$), patients who reported alcohol usage ($p = 0.068$) and those experiencing stinging sensations ($p = 0.093$).

DISCUSSION

To the best of our knowledge, this is the first study to assess IENFD as a factor contributing to itch in patients with DM. The aim of this study was to determine potential pathogenetic factors in this entity.

In 2005 Brenaut et al. (7) showed that itch might be a symptom of SFN, present in approximately 68% of affected subjects. Recently, in 2020, Pereira et al. (5) proposed diagnostic criteria for chronic generalized itch arising from SFN, and they constitute 3 obligatory criteria: (*i*) presence of chronic itch (CI); (*ii*) symptom begins on normal-appearing skin; and (*iii*) reduced IENFD as per normative values. In addition, several facultative criteria, such as alleviation of itch characteristics (burning, tingling and sensation, such as needle pricks, itch occurring in attacks, moderate to severe itch intensity, daily and long-lasting occurrence) with cold/ice or emollient application and aggregation with warmth and calmness have been proposed. SFN-related itch is a subtype of neuropathic itch with peripheral nerve damage (3, 6). CI arising from neuropathic conditions typically begins on normal-appearing skin, or if scratching behaviour has ensued, patients may also present with chronic scratch lesions. In the study group all itchy patients fulfilled the above-mentioned criteria, CI on non-lesioned skin lasting longer than 6 weeks was diagnosed, and all patients had reduced IENFD compared with normative values (12). The mean itch intensity in the current study group was assessed as 8 ± 2 points, indicating severe itch. Clinically, the vast majority of patients reported pruralgia, with only 2 patients (16.7%) reporting itch exclusively. In addition, patients in the itchy group significantly more frequently experienced tingling or numbness sensations, compared with the non-itchy population (Table I).

Similarly, as in other studies (5, 8), in the current study cohort of patients itch intensity was not correlated with the IENFD values. In our previous study (13) we proposed a pathogenetic model in which prolonged poorly controlled DM resulting in diabetic polyneuropathy contributes to skin dryness and, subsequently, causes itch. Also, in this study subjects with drier skin had lower IENFD, while itchy subjects had significantly drier skin.

All of the aforementioned observations require a cautious approach in the clinical decision-making process, as the groups of patients were relatively small; however, other studies assessing SFN were completed with a similar number of biopsies. In addition, the morphology of the nerve fibres was not assessed. Nevertheless, our experience demonstrates that patients with CI in DM will benefit from a holistic and interdisciplinary approach, taking all possible factors: neuropathy, skin xerosis, but, mainly, glycaemic control, into consideration.

In conclusion, although there was no difference in IENFD between itchy and non-itchy subjects, SFN should be considered as a possible origin of itch in patients with DM, as this may affect further management of itch in diabetes.

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REFERENCES

1. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF diabetes atlas: global estimates of diabetes prevalence for 2017 and projections for 2045.

Diabetes Res Clin Pract 2018; 138: 271–281.
2. Johannsen L, Smith T, Havsager AM, Madsen C, Kjeldsen MJ, Dalsgaard NJ, et al. Evaluation of patients with symptoms suggestive of chronic polyneuropathy. J Clin Neuromuscul Dis 2001; 3: 47–52.
3. Pereira MP, Wiegmann H, Agelopoulos K, Ständer S. Neuropathic itch: routes to clinical diagnosis. Front Med 2021; 8: 641746.
4. Ständer S, Streit M, Darsow U, Niemeier V, Vogelgsang M, Ständer H, et al. Diagnostisches und therapeutisches Vorgehen beichronischem Pruritus. J Dtsch Dermatol Ges 2006; 4: 350–370.
5. Ständer S, Weisshaar E, Mettang T, Szepietowski J, Carstens E, Ikoma A, et al. Clinical classification of itch: a position paper of the International Forum for the Study of Itch. Acta Derm Venereol 2007; 87: 291–294.
6. Pereira MP, Derichs L, Meyer Zu Hörste G, Agelopoulos K, Ständer S. Generalized chronic itch induced by small-fibre neuropathy: clinical profile and proposed diagnostic criteria. J Eur Acad Dermatol Venereol 2020; 34: 1795–1802.
7. Brenaut E, Marcorelles P, Genestet S, Ménard D, Misery L. Pruritus: an underrecognized symptom of small-fibre neuropathies. J Am Acad Dermatol 2015; 72: 328–332.
8. Bonsang B, Brenaut E, Talagas M, Uguen A, Bonsang-Kitzis H, Misery L, et al. Small-fibre neuropathy and pruritus: histological patterns of nerve fibres in skin biopsies. Br J Dermatol 2020: 182: 504–506.
9. Akabane AL, Smith GP. Cutaneous manifestations of small fibre polyneuropathy. J Eur Acad Dermatology Venereol 2022; 36: 100–107.
10. Stefaniak A, Chlebicka I, Szepietowski J. Itch in diabetes: a common underestimated problem. Adv Dermatol Allergol 2019; 36: 177–183.
11. Stefaniak AA, Zubkiewicz-Kucharska A, Matusiak Ł, Noczyńska A, Szepietowski JC. Itch in children with type 1 diabetes: a cross-sectional study. Dermatol Ther 2020; 10: 745–756.
12. Provitera V, Gibbons CH, Wendelschafer-Crabb G, Donadio V, Vitale DF, Stancanelli A, et al. A multi-center, multinational age- and gender-adjusted normative dataset for immunofluorescent intraepidermal nerve fibre density at the distal leg. Eur J Neurol 2016; 23: 333–338.
13. Stefaniak AA, Krajewski PK, Bednarska-Chabowska D, Bolanowski M, Mazur G, Szepietowski JC, et al. Itch in adult population with type 2 diabetes mellitus: clinical profile, pathogenesis and disease-related burden in a cross-sectional study. Biology 2021; 10: 1332.

Appendix S1

MATERIALS AND METHODS

Patients

This study was performed in October 2020 and March 2021. The project was approved by the local ethics committee in Wroclaw (Poland) (ST.C260.18.019). A total of 60 consecutive adult patients who were treated for diabetes mellitus type 2 (DM2) in the University Hospital in Wroclaw or patients treated in the outpatient unit were invited to join the study. Of these, 23 agreed to participate (response rate 38.3%). Therefore, a total of 23 (12 males (52.2%); age range 46–78 years, median age 68 years) adult patients with DM2 were enrolled. The range of duration of diabetes was 1–26 years (mean duration 13.7 ± 6.7 years; median 12 years) (detailed characteristics of the study population are given in **STable I**). Women tended to experience itch more frequently ($p = 0.058$). There was no difference in age, duration of diabetes or stimulant use between the studied groups. All patients in itchy group presented with itch on non-lesional skin (International Forum for the Study of Itch group II), without chronic scratch lesions. A distal leg 4-mm punch biopsy was obtained from all patients for the intraepidermal nerve fibre density (IENFD) assessment.

Study design and applied methods

After inclusion, detailed information on demographics, glycated haemoglobin (HbA1c) and fasting plasma glucose (FPG) were obtained. The main clinical parameter, i.e. the presence of chronic itch (CI) was documented, including the affected anatomical locations. A numerical rating scale (NRS; 0: no itch; 10 points: worst imaginable itch) was used to assess maximal values of itch intensity, both in the last 3 days and last 24 h. NRS cut-off points were as follows: 1–2 points represented mild itch, 3–6 points moderate itch, 7–8 points severe itch, and ≥ 9 points very severe itch (S1). In addition, the 4-item Itch Questionnaire (4IIQ), previously used by our group in many studies on different types of itch (S2, S3), was used to assess CI more objectively. 4IIQ evaluated the extent of pruritus (1–3 points), severity (1–5 points), frequency (1–5 points), as well as sleep disturbances due to itching (0–6 points) within 7 days before examination: scoring ranged from 3 points (mild pruritus) to 19 points (maximal pruritus).

Skin dryness was assessed clinically using a graduation 4-point scale (range 0–3 points; 0 points – no symptoms of dry skin; 1: ashiness, but no discernible flakes; 2: small to medium flakes; 3: large flakes and prominent "cracked glass pattern") (S4, S5). Subsequently, results of non-invasive corneometric assessment of epidermal hydration, using a Corneometer CM825 (Courage+Khazaka Electronic GmbH, Köln Germany) were recorded.

STable I. Characteristics of the study population

	Total ($n = 23$)	With itch ($n = 12$)	Without itch ($n = 11$)	p-value*
Sex, *n* (%)				
Female	11 (47.8)	8 (66.7)	3 (27.3)	0.058[a]
Male	12 (52.2)	4 (33.3)	8 (72.7)	
Age, years, mean ± SD	65.2 ± 7.9	64.8 ± 8.3	65.7 ± 7.9	
Median (range)	68 (46–78)	67.5 (46–72)	68 (52–78)	NS[b]
Duration of diabetes, years, mean ± SD	13.7 ± 6.7	12.7 ± 7.3	14.8 ± 6.2	
Median (range)	12 (1–26)	12 (1–25)	13 (5–26)	NS[b]
Stimulant use, *n* (%)				
Alcohol	6 (26.1)	3 (25)	3 (27.3)	NS[c]
Smoking	10 (43.5)	6 (50)	4 (36.4)	NS[c]

[a]χ^2 test, [b]Mann–Whitney *U* test, [c]Fisher's exact test.
SD: standard deviation; NS: not significant. *Group with itch vs group without itch.

Neurological examination of the patients was performed according to the guidelines of the American Diabetes Association (S6). Each patient was questioned as to the presence or absence of pruralgia (tingling, numbness, pain, stinging, burning), symptoms associated with diabetic polyneuropathy, such as hyperaesthesia, hypoaesthesia and weakness in the feet; the presence or absence of similar upper-limb symptoms; and the presence or absence of unsteadiness on ambulation. Five sensory testings were evaluated: pain sensation with a pinprick, temperature sensation with the Tip-therm (Thermo Feel®) device, light touch sensation using the Semmes-Weinstein monofilament test with standardized 10 g monofilament, vibratory sensation with a 128-Hz standard tuning fork and the position sensation. Based on these findings, all patients were assessed with the Katzenwadel neuropathy scale (S7, S8), where 5 aspects of polyneuropathy were assessed: movement functions, pain, sensorial function, motor coordination and tendon reflexes, on a 3-point scale (range 0–2 points). The overall Katzenwadel neuropathy scale points correspond to the probability of clinically significant polyneuropathy, with 0–2 points representing low risk of neuropathy; 3–4 points representing possible neuropathy, and 5–10 points representing clinically overt neuropathy (S7–S9).

In order to assess IENFD biopsies were immediately fixed in 4% paraformaldehyde for 2 h, and then kept in 5% sucrose overnight, buffered in 10% and 20% sucrose and after 6 h stored in liquid nitrogen. Three 40-µm cryosections were sectioned from each biopsy, thawed on microscope slides (Dako Cytomation GmbH, Hamburg, Germany) and processed for immunofluorescence staining. In brief, sections were incubated overnight with the primary antibody, a polyclonal antibody against the neurone-specific hydrolase protein gene product (PGP) 9.5 (rabbit 1:200; Zytomed, Berlin, Germany) at room temperature. The sections were stained with the secondary antibody antirabbit-fluorescein isothiocyanate (FITC) (1:200; swine antirabbit immunoglobulin FITC; Dako, Glostrup, Denmark) for 2 h. Fluorescent samples were read using a Zeiss Axioplan fluorescence microscope (Zeiss, Oberkochen, Germany) by 1 trained and blinded investigator. It was scanned for sub- and intraepidermal nerves through 2 planes: horizontally along the epidermal-dermal border and vertically by focusing through the thickness of the section in order to detect each nerve branch and its course, as suggested by guidelines (S10, S11).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (Armonk, NY, USA). Data are shown as number of cases (percentage of cases) and medians. Correlation analyses were performed with Spearman's rho. The Mann–Whitney *U* test and the Kruskal–Wallis test were used for comparisons of continuous variables between groups as appropriate, while the χ^2 test and the Fisher's exact test were performed for group comparisons of categorical variables. The level of statistical significance was set at $p < 0.05$, while when the p-values where ≥ 0.05 and < 0.1 it was noted as a trend.

REFERENCES

S1. Reich A, Chatzigeorkidis E, Zeidler C, Osada N, Furue M, Takamori K, et al. Tailoring the cut-off values of the visual analogue scale and numeric rating scale in itch assessment. Acta Derm Venereol; 2017: 97: 759–760.
S2. Reich A, Medrek K, Szepietowski J. Tailoring the cut-off values of the visual analogue scale and numeric rating scale in itch assessment. Przegl Dermatol 2012; 99: 600–604.
S3. Krajewski PK, Olczyk P, Krajewska M, Krajewski W, Szepietowski JC. Clinical characteristics of itch in renal transplant recipients. Front Med 2021; 7: 615334.
S4. Eberlein-Ko B, Nig È, Scha È Fer T, Huss-Marp J, Darsow U,

Mo M, et al. Skin surface pH, stratum corneum hydration, trans-epidermal water loss and skin roughness related to atopic eczema and skin dryness in a population of primary school children. Acta Derm Venereol 2000; 80: 188–191

S5. Cook TH, Craft TJ. Topographics of dry skin, non-dry skin, and cosmetically treated dry skin as quantifed by skin profilometry. J Soc Cosmet Chem 1985; 36: 143–152.

S6. American Diabetes Association. 11. Microvascular complications and foot care: standards of medical care in diabetes. 2020; 43: S135–S151.

S7. Katzenwadel A, Sachse G, Federlin K. Messung von Vibrationsempfinden und Temperaturdiskrimination bei der peripheren diabetischen Neuropathie. Akt Endokrin Stoffw 1987; 8: 155–160.

S8. Rogoziewicz M. Clinical and neurophysiological evaluation of peripheral nervous system abnormalities in patients with lymphoproliferative disorders. Neurology 2012: 78: P06.01.

S9. Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic polyneuropathy – a three-week randomized, controlled pilot study (BEDIP study). Int J Clin Pharmacol Ther 2005; 43: 71–77.

S10. Lauria G, Hsieh ST, Johansson O, Kennedy WR, Leger JM, Mellgren SI, et al. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. Eur J Neurol 2010; 17: 903–912.

S11. Hays AP. Utility of skin biopsy to evaluate peripheral neuropathy. Curr Neurol Neurosci Rep 2010; 10: 101–107.

Supplementary material to article by A. A. Stefaniak et al. "Small-fibre Neuropathy in Patients with Type 2 Diabetes Mellitus and its Relationship with Diabetic Itch: Preliminary Results"

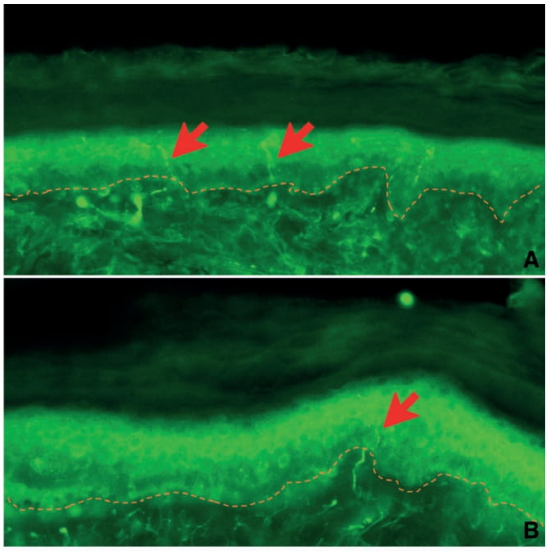

Fig. S1. Assessment of intraepidermal nerve fibre density (IENFD). Exemplary microscopic photographs of diabetic skin. (A) Reduced epidermal nerve fibre density (6.1 fibers/mm). (B) Severely reduced IENFD (<30% of normative cut-off value) (1.7 fibers/mm). The basement membrane is highlighted by a *dashed red line*. *Red arrows*: nerve fibres crossing the dermo-epidermal junction.

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Supplementary material to article by A. A. Stefaniak et al. "Small-fibre Neuropathy in Patients with Type 2 Diabetes Mellitus and its Relationship with Diabetic Itch: Preliminary Results"

Table SI. Statistically significant correlations or trends (performed with Spearman's rho)

Correlation	R	*p*-value
Skin dryness assessed with the corneometry in the area of the chest and IENFD	0.4	0.053
Skin dryness assessed with the corneometry in the area of the forearm and duration of the disease	−0.5	0.022
Katzenwadel neuropathy scale and IENFD	−0.4	0.053
Katzenwadel neuropathy scale and corneometry forearm	−0.5	0.032
Katzenwadel neuropathy scale and corneometry abdomen	−0.5	0.022
Katzenwadel neuropathy scale and corneometry lower leg	−0.4	0.093
Katzenwadel neuropathy scale and skin dryness assessed clinically	0.4	0.074
Katzenwadel neuropathy scale and 4IIQ	0.5	0.08

IENFD: intraepidermal nerve fibres density (fibers/mm); 4IIQ: 4 Item Itch Questionnaire.

Table SII. Studied aetiopathogenetic factors contributing to itch in diabetes mellitus and dependencies on itch: glycaemic control

	With itch ($n = 12$)	Without itch ($n = 11$)	*p*-value*
HbA1C (%), mean±SD	8.4±1.9	7.4±1.9	
Median (range)	8.2 (5.5–12.0)	7.0 (5.0–11.3)	NS
FPG (mg/dl), mean±SD	173.5±63.7	144±42.7	NS
Median (range)	163 (90–318)	127.5 (98–230)	

SD: standard deviation; NS: not significant; HbA1C: glycated haemoglobin; FPG: fasting plasma glucose.
*Group with itch vs group without itch measured with Mann–Whitney *U* test.

Table SIII. Studied aetiopathogenetic factors contributing to itch in diabetes mellitus and dependencies on itch: skin dryness

	With itch ($n = 12$)	Without itch ($n = 11$)	*p*-value*
Epidermal hydration (AU), mean±SD (median)			
Forearm	24.1±12.7 (21.3)	34.1±19.0 (31.4)	NS[b]
Lower leg	27.1±17.1 (24.5)	38.0±12.9 (37.6)	0.056[b]
Abdomen	17.0±13.4 (15.9)	28.5±11.1 (30.6)	0.016[b]
Chest	34.8±15.6 (33.8)	45.3±23.6 (48.2)	NS[b]
Skin xerosis examined clinically (points), mean±SD (median)	1.4±0.8 (2)	1.0±0.6 (1)	NS[a]

[a]χ^2 test, [b]Mann–Whitney *U* test.
SD: standard deviation; NS: not significant. *Group with itch vs group without itch.

12. STRESZCZENIE W JĘZYKU POLSKIM

Rozprawa doktorska powstała w oparciu o monotematyczny cykl czterech 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. Artykuły zostały opublikowane w recenzowanych czasopisach o łącznym współczynniku wpływu 14,617 oraz 370 punktów ministerialnych.

Pierwszą pracą spośród cyklu jest przegląd systematyczny piśmiennictwa dotyczącego świądu w cukrzycy. W pracy przedstawiono aktualny stan wiedzy na temat świądu w cukrzycy zarówno typu 1 jak i 2. Przeglądu dokonano według wytycznych protokołu PRISMA.

Kolejne dwie prace wchodzące w skład cyklu prezentują wyniki badań dotyczących klinicznej charakterystyki świądu, potencjalnych czynników patogenetycznych oraz wpływu świądu na jakość życia pacjentów z cukrzycą: w populacji dziecięcej z cukrzycą typu 1 (100 pacjentów włączonych do badania) oraz w populacji dorosłych z cukrzycą typu 2 (104 pacjentów włączonych do badania). Badania przeprowadzono w latach 2019-2021 z przerwą wywołaną stanem pandemii COVID-19. Od pacjentów włączonych do badania zostały zebrane dane demograficzne, historia choroby, dane dotyczące chorób towarzyszących oraz sposobu leczenia. Oznaczone zostały również parametry wyrównania cukrzycy - stężenie hemoglobiny glikowanej HBa1C oraz stężenie glukozy na czczo.

Główny badany parametr – świąd – został oceniony z użyciem skali numerycznej (ang. Numerical Rating Scale, NRS) oraz czteropunktowym kwestionariuszem oceny świądu (ang. 4-Item Itch Questionnaire, 4IIQ). Pacjenci zostali poproszeni o ocenę natężenia najgorszego świądu w ciągu ostatnich trzech dni i 24 godzin. Jakościowa ocena świądu została dokonana za pomocą kwestionariusza opisowej oceny świądu.

W celu oceny potencjalnych przyczyn świądu u pacjentów przeprowadzone zostało badanie neurologiczne. Skóra została oceniona klinicznie przez badacza pod kątem suchości z wykorzystaniem ogólnie przyjętej czterostopniowej skali. Ponadto u każdego badanego został dokonana bezinwazyjna ocena stopnia nawilżenia naskórka z wykorzystaniem korneometru CM825 (Courage & Khazaka, Koeln, Germany®).

Do oceny jakości życia, stygmatyzacji oraz objawów depresyjnych i lękowych pacjentów związanych ze świądem wykorzystano zwalidowane skale w polskich wersjach językowych. W populacji dziecięcej użyto skali dziecięcego dermatologicznego wskaźnika jakości życia – (ang. children Dermatology Life Quality Index, cDLQI), a u pacjentów

dorosłych skali jakości życia związana ze świądem ItchyQol, 6-stopniowa skali stygmatyzacji (ang. 6-item stigmatization scale, 6-ISS) oraz Szpitalnej Skali Lęku i Depresji (ang. Hospital Anxiety and Depression Scale, HADS).
W kolejnym etapie badania u wybranych pacjentów dorosłych (12 osób ze świądem i 11 bez świądu w przebiegu cukrzycy) została pobrana w znieczuleniu miejscowym 4 mm biopsja sztancowa skóry z podudzia w celu immunohistochemicznej oceny gęstości włókien nerwowych (ang. intraepidermal nerve fibre density, IENFD). PGP 9,5 został wykorzystany jako marker unerwienia skórnego. Wyniki tego badania zostały opublikowane w czwartej pracy.

Świąd występował u 22% dzieci z cukrzycą typu 1 ze średnim maksymalnym nasileniem 5,9 ± 3,0 punktów w $NRSmax_{3dni}$ i 6,7 ± 3,5 punktów w 4IIQ (mediana 5,5 punktu) oraz u 35,8% dorosłych pacjentów z cukrzycą typu 2, z $NRSmax_{3dni}$ 6,3 ± 2,2 oraz 8,1 ± 3,5 punktów w 4IIQ. W populacji dziecięcej u większości pacjentów świąd był zlokalizowany oraz ograniczony do kilku obszarów ciała; najczęściej dotyczyło on kończyn górnych (68,2%), następnie kończyn dolnych (50%) i tułowia (31,8%). U pacjentów dorosłych świąd również najczęściej dotyczył kończyn dolnych i górnych (38,5% i 23,1%). Klinicznie zbadana suchość skóry była znacznie bardziej zaawansowana u dzieci ze świądem w porównaniu z dziećmi bez świądu ($p < 0,01$). W populacji dorosłych z cukrzycą typu 2 pacjenci ze świądem mieli istotnie wyższe stężenie glukozy na czczo w porównaniu z populacją bez świądu ($p = 0,01$). Pacjenci ze świądem mieli także istotnie wyższe prawdopodobieństwo neuropatii w porównaniu z osobami bez świądu ($p < 0,01$). Suchość skóry była istotnie bardziej zaawansowana u pacjentów ze świądem w porównaniu z osobami bez świądu ($p < 0,01$). Wszyscy pacjenci, niezależnie od odczuwanego świądu, mieli obniżoną IENFD w stosunku do wartości normatywnych (grupa ze świądem: 2,7 włókna/mm, grupa nie świądowa: 3,7 włókna/mm). Osoby z bardziej suchą skórą miały tendencję do niższej IENFD ($R=0,32$, $p=0,088$), podczas gdy pacjenci z grupy świądowej mieli skórę istotnie bardziej suchą ($p=0,02$). Zarówno w populacji dziecięcej jak i u dorosłych nasilenie świądu wiązało się z pogorszeniem jakości życia.
Podsumowując, świąd jest częstym objawem w cukrzycy, w sposób znamienny wpływającym na psychospołeczne funkcjonowanie chorych. Wyniki własne wskazują, że pierwotną przyczyną świądu w cukrzycy jest permanentna niewystarczająca kontrola cukrzycy ze zmienionym poziomem glukozy i insuliny, powodująca następnie suchość skóry i neuropatię, szczególnie w długotrwającej cukrzycy.

13. STRESZCZENIE W JĘZYKU ANGIELSKIM

The doctoral dissertation is based on a monothematic series of four articles published in international scientific journals indexed in PubMed and included in the list of Journal Citation Reports and in the list of scientific journals of the Ministry. The articles were published in peer-reviewed journals with a total impact factor of 14.617 and 370 ministerial points.

The first paper in the series is a systematic review of the literature on itch in diabetes. The paper presents the current state of knowledge on itch in both: type 1 and 2 diabetes. The review was performed according to PRISMA guidelines.

The next two papers in the series present the results of a study on the clinical characteristics of itch, potential pathogenetic factors and the impact of itch on the quality of life of patients with diabetes: in a pediatric population with type 1 diabetes (100 patients included in the study) and in an adult population with type 2 diabetes (104 patients included in the study). The study was conducted between 2019 and 2021 with an interruption caused by the COVID-19 pandemic state. 100 consecutive patients aged 7-18 years with type I diabetes and 104 consecutive adult patients with type II diabetes were included in the study. Inclusion criteria: diabetes confirmed according to worldwide guidelines. Exclusion criteria: chronic dermatoses, liver disease, and mental status unable to consciously complete the questionnaires. Demographic data, medical history, data on concomitant diseases and treatment were collected from patients included in the study. Glycated haemoglobin HBa1C and fasting glucose parameters were also determined.

The main parameter investigated - itch - was assessed using Numerical Rating Scale (NRS) and 4-Item Itch Questionnaire (4IIQ). Patients were asked to assess the intensity of itch over the past three days and 24 hours. Qualitative assessment of itch was performed using a descriptive itch assessment questionnaire.

To assess potential causes of itch, patients were examined neurologically. The ankle and knee joint reflex, vibration sensation with a 128-Hz ENT reed, temperature sensation with a Tip-Therm device (Thermo Feel®), touch sensation with a monofilament, and pain sensation were evaluated with a neurological hammer. A toe-to-nose and heel-to-knee test was evaluated to assess coordination of movement, and the patient's gait was assessed. The skin was clinically assessed by the investigator for dryness using a generally accepted four-point scale. In addition, each subject underwent non-invasive assessment of epidermal hydration using a CM825 corneometer (Courage & Khazaka, Koeln, Germany®).

Validated scales in Polish language versions will be used for assessment of quality of life, stigmatization and depressive and anxiety symptoms of patients connected with itch. In pediatric population the Children Dermatology Life Quality Index (cDLQI) scale was used, in adult patients itchyQol, 6-item stigmatization scale (6-ISS) and Hospital Anxiety and Depression Scale (HADS) were used.

In the next stage of the study, in selected adult patients (12 with itch and 11 without diabetic itch), a 4 mm skin punch biopsy was taken under local anaesthesia from the lower leg for immunohistochemical assessment of intraepidermal nerve fibre density (IENFD). PGP 9.5 was used as a marker of cutaneous innervation. The results of this study were published in the fourth paper.

Itch was present in 22% of children with type 1 diabetes with a mean maximum severity of 5.9 ± 3.0 points on the NRS and 6.7 ± 3.5 points on the 4IIQ (median 5.5 points) and in 35.8% of adult patients with type II diabetes, with NRSmax3days of 6.3 ± 2.2 and 8.1 ± 3.5 points on the 4IIQ. In the pediatric population the itch was localized and limited to several body regions; the most frequent was the upper limbs (68,2%), followed by the lower limbs (50%) and the trunk (31.8%). In adult patients, itch also most frequently affected the lower and upper limbs (38.5% and 23.1%). Clinically examined skin dryness was significantly more advanced in children with itch compared to children without itch ($p < 0.01$). In the adult population with type II diabetes, patients with itch had significantly higher fasting glucose levels compared to the population without itch ($p = 0.01$). Patients with itch also had a significantly higher likelihood of neuropathy compared to those without itch ($p < 0.01$). Dry skin was significantly more advanced in patients with itch compared to those without itch ($p < 0.01$). All patients, regardless of perceived itch, had lower IENFD compared to normative values (itchy group: 2.7 fibers/mm, non-itchy group: 3.7 fibers/mm). Those with drier skin tended to have lower IENFD ($R=0.32$, $p=0.088$), while patients in the itch group had significantly drier skin ($p=0.02$). In both pediatric and adult populations, increased itch was associated with decreased quality of life.

In conclusion, itch is a common symptom in diabetes, significantly affecting the psychosocial functioning of patients. Our results indicate that the primary cause of itch in diabetes is permanent inadequate diabetic control with altered glucose and insulin levels, subsequently causing dry skin and neuropathy, especially in long-term diabetes.

14. OPINIA KOMISJI BIOETYCZNEJ

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

OPINIA KOMISJI BIOETYCZNEJ Nr KB – 440 /2020

Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu, powołana zarządzeniem Rektora Uniwersytetu Medycznego we Wrocławiu nr 133/XV R/2017 z dnia 21 grudnia 2017 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 28 z 1997 r. poz. 152 z późniejszymi zmianami) w składzie:

prof. dr hab. Jacek Daroszewski (choroby wewnętrzne, endokrynologia, diabetologia)
prof. dr hab. Krzysztof Grabowski (chirurgia)
dr Henryk Kaczkowski (chirurgia szczękowa, chirurgia stomatologiczna)
mgr Irena Knabel-Krzyszowska (farmacja)
prof. dr hab. Jerzy Liebhart (choroby wewnętrzne, alergologia)
ks. dr hab. Piotr Mrzygłód, prof. nadzw. (duchowny)
mgr prawa Luiza Müller (prawo)
dr hab. Sławomir Sidorowicz (psychiatria)
prof. dr hab. Leszek Szenborn, (pediatria, choroby zakaźne)
Danuta Tarkowska (pielęgniarstwo)
prof. dr hab. Anna Wiela-Hojeńska (farmakologia kliniczna)
dr hab. Andrzej Wojnar, prof. nadzw. (histopatologia, dermatologia) przedstawiciel Dolnośląskiej Izby Lekarskiej)
dr hab. Jacek Zieliński (filozofia)

pod przewodnictwem
prof. dr hab. Jana Kornafela (ginekologia i położnictwo, onkologia)

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

„Aspekty kliniczne świądu w cukrzycy"

zgłoszonym przez **lek. Aleksandrę Stefaniak** uczestnika studiów doktoranckich w Katedrze i Klinice Dermatologii, Wenerologii i Alergologii Uniwersytetu Medycznego im. Piastów Śląskich we Wrocławiu oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła **wyrazić zgodę** na przeprowadzenie badania w Klinice Dermatologii, Wenerologii i Alergologii; w Klinice Endokrynologii i Diabetologii Wieku Rozwojowego a także Klinice Chorób Wewnętrznych, Zawodowych Nadciśnienia Tętniczego i Onkologii Kliniczne oraz Klinice Endokrynologii, Diabetologii i Leczenia Izotopami Uniwersyteckiego Szpitala Klinicznego im. Jana Mikulicza Radeckiego we Wrocławiu pod nadzorem prof. dr hab. Jacka Szepietowskiego p**od warunkiem zachowania anonimowości uzyskanych danych**.

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

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

Opinia powyższa dotyczy projektu badawczego będącego podstawą rozprawy doktorskiej.

Wrocław, dnia 14 września 2020 r.

Uniwersytet Medyczny we Wrocławiu
KOMISJA BIOETYCZNA
przewodniczący
prof. dr hab. Jan Kornafel

15. CURRICULUM VITAE

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Kierunek Lekarski, Wydział Lekarski z Oddziałem Lekarsko-Dentystycznym w Zabrzu
Masaryk University (Brno, Czechy) 10.2016 – 12.2017
ERASMUS + Exchange Scholarship

Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu 10.2021 –06/2022
Niekomercyjne badania kliniczne, studia podyplomowe

Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu 10.2018 – obecnie
Studia doktoranckie, Klinika Dermatologii, Wenerologii i Alergologii

Doświadczenie:

- **Zawodowe:**

01/11/2019 – obecnie Wrocław, Polska

Lekarz młodszy asystent (w trakcie specjalizacji) • *Klinika Dermatologii, Wenerologii i Alergologii, Uniwersytecki Szpital Kliniczny im. Mikulicza Radeckiego we Wrocławiu*

01/10/2018 – 29/10/2019 Wrocław, Polska
Lekarz (stażysta) • *Uniwersytecki Szpital Kliniczny im. Mikulicza Radeckiego we Wrocławiu*

Staże międzynarodowe:

- 03/2021 - Münster University Hospital (12 miesięcy) Münster, Niemcy
- 08/2017 – St. Anne's University Hospital (1 miesiąc) Brno, Czechy
- 07/2017 – Hunsrück Klinik | Stiftung Kreuznacher Diakonie (1 miesiąc) Hunsrück, Niemcy
- 07/2016 – Centro Hospitalar São João (1 miesiąc) Porto, Portugalia

- **Naukowe:**

1/10/2019 – 30/06/2022 Wrocław, Polska
Badacz • Projekt "Świąd w cukrzycy", Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu • finansowany w ramach projektów Wybitnych Doktorantów z Rady Inicjatywy Doskonałości

2/10/2020 – 31/12/2021
Uczestnik Mentoring & Networking Circle • Society for Investigative Dermatology, mentorzy: Prof. Alice P. Pentland, M.D (Univeristy of Rochester, USA) Maria L. Wei, MD, PhD (Univeristy of California San Francisco, USA)

01/07/2019 – 31/12/2021 Warszawa, Polska
Rada naukowa • Projekt "Liczba nowotworów skóry wzrasta – zbadaj się!" realizowany w ramach Programu Operacyjnego Wiedza Edukacja Rozwój 2014 – 2020 współfinansowanego ze środków Europejskiego Funduszu Społecznego

Publikacje:

- **26 pełnotekstowych artykułów opublikowanych w międzynarodowych czasopismach indeksowanych w bazie PubMed, z czego 9 jako pierwszy autor**
- **Całkowity współczynnik wpływu (*Impact Factor*) opublikowanych prac = 97,602**
- **Indeks Hirscha = 4**

Granty & Nagrody:

- Wyróżnienie w doktoranckim programie stypendialnym im. Ludwika Hirszfelda Wrocławskiego Centrum Akademickiego (2021)
- Laureatka stypendium im. Otto Braun-Falco w Competence Center for Chronic Pruritus w University Hospital of Münster Department of Dermatology (Münster) – 2021 (Cel: Prace nad wpływem neuropatii z małych włókien na świąd w przebiegu cukrzycy)
- Laureatka stypendium Niemieckiej Centrali Wymiany Akademickiej DAAD 2021/2022 – University Hospital of Münster Department of Dermatology (Münster)
- Eli Lilly Scholarship European Academy of Dermatology and Venereology 2021
- Wybrana do reprezentacji Polski podczas Euroderm Excellence Forum 2021 w Rzymie
- Finalistka konkursu "Popularyzator Nauki" organizowanego przez serwis Nauka w Polsce w ramach Ministerstwa Nauki i Szkolnictwa Wyższego (2020)
- Laureatka konkursu „Młode talenty 2019" – nagroda Dolnośląskiego Klubu Kapitału dla wybitnych talentów (2019)
- Grant naukowy "Itch in diabetes" pod kierownictwem prof. Jacka Szepietowskiego finansowany w ramach projektów Wybitnych Doktorantów z Rady Inicjatywy Doskonałości, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu, Polska (o wartości 50 000 PLN)
- Grant edukacyjny "Dolnośląscy Liderzy Medycyny" finansowany z Rady Inicjatywy Doskonałości, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu, Polska (o wartości 25 000 PLN)
- Wielokrotne stypendia rektora dla najlepszych studentów i doktorantów

Członkostwo w towarzystwach naukowych:

Polskie Towarzystwo Dermatologiczne • International Society of Dermatology • European Academy of Dermatology and Venerology • European Hidradenitis Suppurativa Foundation • Women's Dermatological Society • European Society for Dermatology and Psychiatry

16. DOROBEK NAUKOWY

(z wyłączeniem prac stanowiących cykl publikacji do Rozprawy Doktorskiej)

Publikacje w międzynarodowych czasopismach:

1. **Stefaniak AA,** Szepietowski JC, Baran W. Unilateral papular granuloma annulare in a type I diabetic child: a case report and literature review. *Adv.Dermatol.Allergol* 2022; 102:art.adv00675
   IF: 1,837, Punkty Ministerialne: 40
2. **Stefaniak AA**, Pereira MP, Zeidler C, Ständer S. Pruritus in pregnancy., *Am.J.Clin.Dermatol.* 2022; 23(2):231-246
   IF: 7,403 Punkty Ministerialne: 100
3. **Stefaniak AA,** Knecht K, Matusiak Ł, Szepietowski JC. Sudden onset of unilateral facial paralysis with ear pruritus: a quiz. *Acta Derm.-Venereol*. 2022; 102:art.adv00675
   IF: 4,437 Punkty Ministerialne: 100
4. Chlebicka I, **Stefaniak AA**, Matusiak Ł, Szepietowski JC. Basal cell carcinoma: what new can be learned about the most common human cancer? A cross-sectional prospective study of 180 cases in a single center. *Adv.Dermatol.Allergol*. 2021; 38(6):1086-1091
   IF: 1,837, Punkty Ministerialne: 40
5. Jastrząb B, **Stefaniak AA,** Hryncewicz-Gwóźdź A, Nockowski P, Szepietowski JC. Pityriasis Lichenoides et Varioliformis Acuta Triggered by Human Papillomavirus Vaccine: A Case Report and Literature Review. *Acta Derm.-Venereol.* 2021;101(7):art.adv00507
   IF: 4,437 Punkty Ministerialne: 100
6. Chlebicka I, **Stefaniak AA**, Matusiak Ł, Szepietowski JC. Burden of itch in patients with basal cell carcinoma. *Acta Derm.-Venereol.* 2021;101(7):art.adv00507
   IF: 4,437 Punkty Ministerialne: 100
7. **Stefaniak AA**, Krajewski PK, Białynicki-Birula R, Nowicka D, Szepietowski JC Is Face and Mask Touching a Real Struggle During COVID-19 Pandemic? A prospective study among medical students. *Front.Med.* 2021;8:art.663873
   IF: 5.091, Ministerialne: 20
8. Jaworecka K, Kwiatkowska D, Marek L, Tamer F, **Stefaniak AA,** Szczegielniak M, Chojnacka-Purpurowicz J, Matławska M, Gulekon A, Szepietowski JC, Narbutt J,

Owczarczyk-Saczonek A, Reich A. Characteristics of Pruritus in Various Clinical Variants of Psoriasis: Results of the Multinational, Multicenter, Cross-Sectional Study. *Life.* 2021; 11(7):623
IF: 3,871, Ministerialne: 70

9. Chlebicka I, Jastrząb B, **Stefaniak AA,** Szepietowski J. Basal cell carcinoma secondary to trauma: A 3-year experience of the single center. *Adv Clin Exp Med.* 2021; 30(1):83–86
IF: 1,727, Punkty Ministerialne: 40
10. Chlebicka I, **Stefaniak AA**, Bieniek A, Matusiak L, Woźniak Z, Szepietowski JC. Basal cell carcinoma within rhinophyma: coincidence or relationship? *Adv.Dermatol.Allergol.* 2021; 38(5): 855-857
IF: 1,837, Punkty Ministerialne: 40
11. **Stefaniak AA,** Wójcik E, Matusiak Ł, Szepietowski JC. Axitinib-induced scrotal ulcers: a novel cutaneous adverse event *J.Eur.Acad.Dermatol.Venereol.*, 2021; 35 (1): e77-e78
IF: 6,166, Punkty Ministerialne: 140
12. Chlebicka I, **Stefaniak AA**, Matusiak Ł, Szepietowski JC. Is Basal Cell Carcinoma an Itchy Tumor? Clinical Characteristics of Itch in Basal Cell Carcinoma. *J. Clin. Med.* 2020; 9:2386
IF: 4,241, Punkty Ministerialne: 40
13. Chlebicka I, **Stefaniak AA**, Matusiak Ł, Szepietowski JC. Scalp Lesions Referred For Surgical Procedures: Single-center 5-year Experience in Southwestern Poland. *In Vivo* 2020; 34(5):2733-2738
IF: 2,155, Punkty Ministerialne: 40
14. Wójcik E, **Stefaniak AA,** Szepietowski JC. sQuiz your knowledge! Itchy, polymorphic skin lesions in patient with clear cell renal carcinoma. *Eur.J.Dermatol.* 2020; 30(6):769-770
IF: 3,496, Punkty Ministerialne: 70
15. Chlebicka I, Jastrzab B, **Stefaniak AA**, Hryncewicz-Gwozdz A, Szepietowski JC. Giant superficial basal cell carcinoma diagnosed and treated as psoriasis: report of two cases and a literature review. *Acta Derm.-Venereol* 2020; 100(6): art.adv00194
IF: 4,437 Punkty Ministerialne: 100

16. Krajewski PK, Chlebicka I, **Stefaniak AA**, Szepietowski JC. Coexistance of Favre-Racouchot disease, cutis romboidalis nuchae and skin neoplasms. *Adv.Dermatol.Allergol* 2020; 37:1
    IF: 1,837 Punkty Ministerialne: 70
17. **Stefaniak AA**, Białynicki-Birula R, Krajewski P, Matusiak Ł, Goldust M, Szepietowski JC. Itch in the era of COVID-19 pandemic: an unfolding scenario. *Dermatol. Ther.* 2020; 33(5):art.e13477
    IF: 2,851 Punkty Ministerialne: 70
18. Chlebicka I, **Stefaniak AA**, Bieniek A, Szepietowski JC. Basal cell carcinoma arising in port wine stains: coincidence or correlation? *Adv. Dermatol.Allergol.* 2020; 37(2):272-273
    IF: 1,837 Punkty Ministerialne: 70
19. Chlebicka I, Rygał A, **Stefaniak AA**, Szepietowski JC. Basal cell carcinoma—Primary closure of moderate defect of mid forehead. *Dermatol.Ther.* 2020; 33(3):art.e13322
    IF: 2,851 Ministerialne: 70
20. **Stefaniak AA**, Chlebicka I, Krajewski P, Woźniak Z, Szepietowski JC. Do Not Judge a Book by its Cover: Masquerading as Keratoacanthoma. *Acta Derm.-Venereol.* 2019; 100:adv00074
    IF: 4,437 Punkty Ministerialne: 100
21. Chlebicka I, **Stefaniak AA**, Woźniak Z, Szepietowski JC Uncountable Skin Lesions in a Mentally Disabled Patient. October *Acta Derm.-Venereol.* 2019; 100(1): art.adv00004
    IF: 4,016 Punkty Ministerialne: 100
22. Chlebicka I, **Stefaniak AA**, Woźniak Z, Szepietowski JC Non-healing erythematous, ulcerated lesion on the hand. *Acta Derm.-Venereol.* 2019; 9:839-840
    IF: 4,016 Punkty Ministerialne: 100
23. Włodarek K, **Stefaniak AA**, Matusiak Ł, Szepietowski JC. Could Residents Adequately Assess the Severity of Hidradenitis Suppurativa? Interrater and Intrarater Reliability Assessment of Major Scoring Systems. *Dermatology* 2019; **5**:1-7
    IF: 5,366 Punkty Ministerialne: 100

Autorstwo rozdziałów w podręcznikach:

1. Chlebicka I, **Stefaniak A**, Szepietowski J. Powikłania dermatologiczne u dziecka otyłego. W: Otyłość wieku rozwojowego. Warszawa 2020, PZWL Wydawnictwo Lekarskie, s.169-178, 978-83-200-6028-7.

3 Doniesienia zjazdowe

1. **Stefaniak A**, Chlebicka I, Woźniak Z, Szepietowski JC. Czerniak guzkowy klinicznie amelanotyczny imitujący rogowiaka kolczystokomórkowego. *Forum Dermatol.* 2019 T.5 nr 4 s.155, Zjazd Sekcji Forum Młodych Polskiego Towarzystwa Dermatologicznego, Łódź, Polska, 24-25.10.2020

3. **Stefaniak A**. Czy gra edukacyjna może być porywająca? Case study projektu. *Książka abstraktów*, s.9, II Ogólnopolska Konferencja Naukowa Epidemie wielkie i małe. Kontekst farmaceutyczny, medyczny i kulturowy. Wroclaw, Poland, 9.05.2019

4. **Stefaniak A**, Chlebicka I, Wójcicka K, Szepietowski JC. Niepełnosprawność intelektualna w zespole znamionowych nabłoniaków podstawnokomórkowych. *Przegl.Dermatol.* 2019 Vol.106 no.4 s.450. WawDerm 2019 - Warszawskie Dni Dermatologiczne. Warszawa, Polska, 3-5.10.2019

5. **Stefaniak A**. Gruźlica skóry - opis przypadku. Interdyscyplinarność przyszłością nauki. *Księga abstraktów*, s.39. W: Interdyscyplinarność przyszłością nauki. Zieleniec, 10-12 listopada 2018

6. Włodarek K, **Stefaniak A**, Reich A, Matusiak Ł, Szepietowski JC. Assessment of reliability of six commonly used scoring systems for hidradenitis suppurativa in a group of dermatology residents. *Exp.Dermatol*. 2019 Vol.28 suppl.2 s.19-20 poz.032 OS06-05, 8th European Hidradenitis Suppurativa Foundation (EHSF) Conference. Wrocław, Poland, 6-8 February 2019

7. Chlebicka I, **Stefaniak A**, Gojny Ł, Szepietowski JC. Depression screening in patients with basal cell carcinoma. *Acta Derm.-Venereol.* 2019 Vol.99 no.8 s.749 poz.P7, 18th Congress of the European Society for Dermatology and Psychiatry. Giessen, Germany, 20-22 June 2019

8. **Stefaniak A**. Is diabetes type 1 an itchy disease? Clinical characteristics of itch in children with diabetes type 1. *Przegl.Dermatol.* 2020 nr 1 spec. s.e10, VII Ogólnopolska i Międzynarodowa Konferencja Naukowa „Interdyscyplinarne aspekty chorób skóry i błon śluzowych" Warszawa, 5-6 marca 2021 roku

9. **Stefaniak A**, Chlebicka I, Matusiak Ł, Szepietowski JC. Itch-related psychosocial burden of basal cell carcinoma. *Brit.J.Dermatol*. 2021 Vol.185 no.3 s.e103-e104 poz.P28, 19th Congress - European Society for Dermatology and Psychiatry (ESDaP) & 2nd Brain Skin Colloquium Conference. 11th - 12th June 2021

10. Pawłowski M, Fila-Witecka K, Łuc M, Senczyszyn A, Rymaszewska J, Pawłowska E, Kamińska D, Poznański P, Krajewska M, **Stefaniak A**, Szepietowski J, Pokryszko-Dragan A,

Budrewicz S, Pawłowski T, Rymaszewska J. Perceived stress level among patients with chronic illness during Covid pandemia. *Eur.Psychiatr.* 2021 Vol.64 suppl.1 s.S286-S287 poz.EPP0389, 29th European Congress of Psychiatry - EPA Virtual 2021., 10-13 April, 2021.

17. OŚWIADCZENIA WSPÓŁAUTORÓW

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Wydział Lekarski
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e-mail: dermwen@umw.edu.pl http://www.derm.umed.wroc.pl

Wrocław, 2022-05-19

OŚWIADCZENIE

Oświadczam, że w pracy:

Aleksandra Stefaniak, Iwona Chlebicka, Jacek C Szepietowski. *Itch in diabetes: a common underestimated problem*. Adv. Dermatol. Allergol. 2021 Vol.38 no.2 s.177-183

mój udział polegał na nadzorze naukowym oraz akceptacji finalnej wersji manuskryptu.

Iwona Chlebicka

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Wydział Lekarski
Katedra i Klinika Dermatologii, Wenerologii i Alergologii
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Ul. Chałubińskiego 1, 50-368 Wrocław
Tel. +4871/327-09-41 Fax. +4871/327-09-42
e-mail: dermwen@umw.edu.pl http://www.derm.umed.wroc.pl

Wrocław, 2022-05-19

OŚWIADCZENIE

Oświadczam, że w pracy:

Aleksandra Stefaniak, Iwona Chlebicka, Jacek C Szepietowski. *Itch in diabetes: a common underestimated problem*. Adv. Dermatol. Allergol. 2021 Vol.38 no.2 s.177-183

mój udział polegał na współtworzeniu koncepcji badań, nadzorze naukowym, pomocy w tworzeniu manuskryptu oraz akceptacji jego finalnej wersji.

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Wydział Lekarski
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p.o. kierownik: dr n. med. Agnieszka Zubkiewicz-Kucharska

Wrocław, 2022-05-19

OŚWIADCZENIE

Oświadczam, że w pracy:

Aleksandra A Stefaniak, Agnieszka Zubkiewicz-Kucharska, Łukasz Matusiak, Anna Noczyńska, Jacek C Szepietowski. *Itch in children with type 1 diabetes: a cross-sectional study.* Dermatol.Ther.(Heidelberg) 2020 Vol.10 no.4 s.745-756

mój udział polegał na pomocy w rekrutacji pacjentów do badania, nadzorze naukowym oraz akceptacji finalnej wersji manuskryptu.

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Noczyńska Anna

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19.05.2022

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kierownik: prof. dr hab. Marek BOLANOWSKI

Wrocław, dnia 20.05.2022 r.

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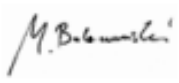
Z wyrazami należnego szacunku,



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Münster, 20.05.2022

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To whom it may concern.

I declare that at work:

Aleksandra A Stefaniak, Konstantin Agelopoulos, Dorota Bednarska-Chabowska, Grzegorz Mazur, Sonja Ständer, Jacek C Szepietowski Small-fibre Neuropathy in Patients with Type 2 Diabetes Mellitus and its Relationship with Diabetic Itch: Preliminary Results Acta Derm Venereol 2022; 102: adv00719. DOI: 10.2340/actadv.v102.933

My contribution consisted of statistical analysis, scientific supervision and approval of the final version of the manuscript.

Kind regards,

Konstantin Agelopoulos

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