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ROZPRAWA DOKTORSKA

„Ocena stężenia wybranych sfingolipidów w zmianach skórnych oraz surowicy pacjentów z łuszczycą”

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Pragnę serdecznie podziękować Pani Promotor pracy doktorskiej,

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Spis treści

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4. Analiza bibliometryczna dorobku

Mój całkowity dorobek naukowy stanowi 7 artykułów (we wszystkich jestem pierwszym autorem).
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Rodzaj publikacji	Liczba	Impact Factor	Punktacja MNiSW
Prace włączone do rozprawy doktorskiej	3	15,3	380
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1. **Mateusz Matwiejuk**, Hanna Myśliwiec, Bartłomiej Łukaszuk, Marta Lewoc, Hend Malla, Piotr Myśliwiec, Jacek Dadan, Adrian Chabowski, Iwona Flisiak: The Interplay between Bioactive Sphingolipids in the Psoriatic Skin and the Severity of the Disease. Int. J. Mol. Sci. 2023, 24, 11336. DOI: 10.3390/ijms241411336
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2. **Mateusz Matwiejuk**, Hanna Myśliwiec, Bartłomiej Łukaszuk, Marta Lewoc, Hend Malla, Piotr Myśliwiec, Jacek Dadan, Adrian Chabowski, Iwona Flisiak: Crosstalk between Serum and Skin Sphingolipids in Psoriasis. Int. J. Mol. Sci. 2023, 24, 14872. DOI: 10.3390/ijms241914872
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Praca przeglądowa włączona do rozprawy doktorskiej

1. **Mateusz Matwiejuk**, Hanna Myśliwiec, Adrian Chabowski, Iwona Flisiak. The Role of Sphingolipids in the Pathogenesis of Psoriasis. Metabolites 2022, 12, 1171. DOI: 10.3390/metabo12121171
IF – 4,1 MNiSW - 100

Pozostałe publikacje

1. **Matwiejuk M**, Myśliwiec H, Chabowski A, Flisiak I. An Overview of Growth Factors as the Potential Link between Psoriasis and Metabolic Syndrome. J Clin Med. 2023 Dec 24;13(1):109. DOI: 10.3390/jcm13010109.
   IF – 3,9 MNiSW – 140
2. **Matwiejuk M**, Mysliwiec H, Jakubowicz-Zalewska O, Chabowski A, Flisiak I. Effects of Hypolipidemic Drugs on Psoriasis. Metabolites. 2023 Mar 29;13(4):493. DOI: 10.3390/metabo13040493.
   IF – 4,1 MNiSW – 100
3. **Matwiejuk M**, Myśliwiec H, Flisiak I. Zastosowanie izokonazolu oraz izokonazolu w połączeniu z miejscowym glikokortykosteroidem w chorobach skóry. Świat Medycyny i Farmacji. 2024, 4, s. 80-84.
4. **Matwiejuk M**, Myśliwiec H, Flisiak I. Suchość i świąd skóry u pacjentów w podeszłym wieku. Choroby wieku podeszłego. 2023: 31, 12, s. 12, 15-24.

5. **Udział w konferencjach:**

A. Konferencje międzynarodowe – e-poster

The disturbances in bioactive lipids profile in the skin and serum of psoriatic patients. **Matwiejuk, M.**; Myśliwiec, H.; Łukaszuk, B.; Lewoc, M.; Malla, H.; Myśliwiec, P.; Dadan, J.; Chabowski, A.; Flisiak, I. 32nd European Academy of Dermatology and Venereology Congress. Berlin, 11-14 October 2023.

B. Konferencje krajowe – aktywne uczestnictwo

a. Ocena stężenia ceramidów oraz sfingolipidów w zmianach skórnych pacjentów z łuszczycą. **Matwiejuk, M.**; Myśliwiec, H.; Łukaszuk, B.; Lewoc, M.; Malla, H.; Myśliwiec, P.; Dadan, J.; Chabowski, A.; Flisiak, I. 32. Zjazd Polskiego Towarzystwa Dermatologicznego/100-lecie Polskiego Towarzystwa Dermatologicznego, Lublin, 31 maja-3 czerwca 2023.

b. Wpływ leczenia przeciwcukrzycowego na przebieg łuszczycy. **Matwiejuk, M**.; Myśliwiec, H.; Flisiak, I.; IX Międzynarodowa Konferencja Naukowa "Interdyscyplinarne aspekty chorób skóry i błony śluzowych", 11-12 marca 2023.

c. Wpływ leków hipolipemizujących na przebieg łuszczycy - przegląd piśmiennictwa. **Matwiejuk, M.**; Myśliwiec, H.; Flisiak, I.; Zjazd Sekcji Forum Młodych Polskiego Towarzystwa Dermatologicznego. Łódź, 20-21 października 2022.

6. Członkostwo w towarzystwach naukowych

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7. Działalność dydaktyczna

Od 2021-do chwili obecnej jestem doktorantem Szkoły Doktorskiej, Uniwersytetu Medycznego w Białymstoku. Prowadzę ćwiczenia oraz seminaria ze studentami polsko- i anglojęzycznymi na Wydziale Lekarskim z Oddziałem Stomatologii i Oddziałem Nauczania w Języku Angielskim, Uniwersytetu Medycznego w Białymstoku.

W czerwcu 2024 roku odbyłem 2-tygodniowy staż w Klinice Dermatologii i Alergologii w Uniwersytecie Medycznym w Bonn.

Rozdział 2. Wykaz stosowanych skrótów i oznaczeń stosowanych w tekście rozprawy doktorskiej

ALT – ang. *Alanine transaminase* – aminotransferaza alaninowa

ANOVA – ang. – *Analysis of Variance* - analiza wariancji

BMI – ang. *Body mass index* – wskaźnik masy ciała

CAD – *ang. Coronary Artery Diseases* – choroba niedokrwienna serca

CER – *ang. Ceramide* – ceramid

CERs – *ang. Ceramides* - ceramidy

CERT1 – *ang. Cardiac event risk test 1* – wskaźnik ryzyka sercowego 1

CRP – *ang. C-reactive protein* – białko C-reaktywne

ELOVL – *ang. Elongases of very long chain fatty acids* - elongazy bardzo długołańcuchowych kwasów tłuszczowych

ELOVL4 – *ang. Elongases of very long chain fatty acids protein 4* – elongaza 4 bardzo długołańcuchowych kwasów tłuszczowych ELOVL4

FA – *ang. Fatty acids* – kwasy tłuszczowe

HDL – *ang. High-density lipoprotein* – lipoproteina o wysokiej gęstości

HOMA-IR – *ang. Homeostatic Model Assessment for Insulin Resistance* – wskaźnik oceny homeostazy insulinooporności

HPLC – *ang. High performance liquid chromatography* – chromatografia cieczowa wysokiej wydajności

IFN-γ – *ang. Interferon gamma* – interferon gamma

KCs - *ang. Keratinocytes* - keratynocyty

LDL – *ang. Low-density lipoprotein* – lipoproteina o niskiej gęstości

MI – *ang. Myocardial infarction* – zawał mięśnia sercowego

NAFLD – *ang. Non-alcoholic fatty liver disease* - niealkoholowa stłuszczeniowa choroba wątroby

NP – *ang. Normal fatty acid and phytosphingosine basis* – baza kwasów tłuszczowych i fitosfingozyny

NS – *ang. N-acylated sphingolipid* – N-acylowany sfingolipid

PASI – *ang. Psoriasis Area and Severity Index* - wskaźnik obszaru i nasilenia łuszczycy

SC – *ang. Stratum corneum* – warstwa rogowa naskórka

SFA – *ang. Sphinganine* - sfinganina

SFA1P – *ang. Sphinganine-1-phosphate* - sfinganino-1-fosforan

SFO – *ang. Sphingosine* - sfingozyna

S1P – *ang. Sphingosine-1-phosphate* – sfingozyno-1-fosforan

TG – *ang. Triglycerides* - triglicerydy

TEWL – ang. *Transepidermal Water Loss* – przeznaskórkowa utrata wody

T2DM – *ang. Type 2 Diabetes Mellitus* – cukrzyca typu II

VLDL – *ang. Very low-density lipoprotein* - lipoproteiny o bardzo niskiej gęstości

Rozdział 3. Wstęp

3.1 Łuszczyca

Łuszczyca jest przewlekłą chorobą zapalną o podłożu immunologicznym, która jest szeroko rozpowszechniona na całym świecie [1]. Choroba ta występuje częściej u dorosłych niż u dzieci, a częstość jej występowania w tej pierwszej grupie wynosi 0,27% do 11,4% [2]. Łuszczyca może mieć różne odmiany kliniczne: plackowata, kropelkowata, krostkowa, odwrócona czy erytrodermiczna [3]. W typowych łuszczycowych zmianach skórnych można zaobserwować nieprawidłowe różnicowanie keratynocytów naskórka (parakeratoza i akantoza) oraz przenikanie komórek odpornościowych do głębszych warstw skóry [4]. W zmianach łuszczycowych stwierdzono zmniejszoną apoptozę keratynocytów [5]. Dodatkowo, keratynocyty pochodzące z blaszek łuszczycowych były bardziej odporne na apoptozę w porównaniu z keratynocytami w zdrowej skórze [6]. Łuszczyca może dotyczyć nie tylko skóry, ale także stawów oraz może współwystępować z różnymi schorzeniami ogólnoustrojowymi [7]. Ze względu na prozapalną etiologię łuszczycy, może ona współistnieć z różnymi składowymi zespołu metabolicznego, na przykład hiperlipidemią, nadciśnieniem tętniczym, otyłością i insulinoopornością. Z czasem stany te mogą prowadzić do rozwoju cukrzycy typu 2 (T2DM), choroby miażdżycowej, choroby wieńcowej lub nawet zawału mięśnia sercowego (MI) [8].

3.1.1 Zaburzenia metabolizmu lipidów w łuszczycy

U pacjentów z łuszczycą często diagnozuje się nieprawidłowe poziomy lipidów we krwi. Liczne doniesienia wskazują na podwyższone stężenie triglicerydów (TG), cholesterolu całkowitego, lipoprotein o bardzo niskiej gęstości (VLDL) i lipoprotein o niskiej gęstości (LDL) w surowicy pacjentów z łuszczycą w porównaniu z osobami zdrowymi. Natomiast stężenie lipoprotein o wysokiej gęstości (HDL) było znacznie obniżone w tej grupie chorych [9].

3.1.2 Rola sfingolipidów w łuszczycy i chorobach współistniejących

Pomimo licznych badań przeprowadzonych w ostatnich latach i znacznego rozwoju wiedzy na temat patogenezy łuszczycy, do chwili obecnej mechanizmy molekularne wpływające na występowanie chorób współistniejących nie są w pełni wyjaśnione. Sfingolipidy są jedną z głównych grup lipidów pochodzących z komórek eukariotycznych [10]. Lipidy te zawierają rdzeń sfingoidowy. Rdzeń ten jest zbudowany z cząsteczki sfingozyny, która powstaje z połączenia kwasu tłuszczowego (często kwasu palmitynowego) z aminokwasem, zazwyczaj seryną [11]. Sfingolipidy są ważnymi składnikami błon komórkowych i biorą udział w licznych procesach komórkowych, na przykład we wzroście komórki czy procesie jej programowanej śmierci [12]. Dodatkowo pełnią różnorodne funkcje przekaźnikowe, są mediatorami stanu zapalnego, biorą udział angiogenezie, odpowiedzi na stres oksydacyjny. Do rodziny sfingolipidów należą m.in.: ceramidy (CERs), sfingozyno-1-fosforan (S1P), sfingozyna (SFO), ceramido-1-fosforan, sfingomielina, galaktozyloceramid, glukozyloceramid i laktozyloceramid [10]. Najbardziej aktywnymi sfingolipidami są S1P i CERs, którym to przypisuje się różnorodne role biologiczne. CERs są w większym stopniu zaangażowane od S1P w procesy takie jak: stan zapalny, reakcja na

stres, zatrzymanie cyklu komórkowego, apoptoza i proces martwicy komórek. S1P jest cząsteczką sygnalizacyjną, która odgrywa rolę we wzroście, proliferacji, różnicowaniu i migracji komórek. S1P wiążąc się z receptorami na powierzchni komórek inicjuje proces angiogenezy [13]. Wykazano, iż poziom S1P w surowicy jest ujemnie skorelowany z rozwojem miażdżycy [10]. W obrębie skóry, S1P hamuje proliferację keratynocytów, natomiast indukuje ich migrację oraz różnicowanie [14]. Dodatkowo, obserwowano podwyższone stężenie poziomu jednego z prekursorów S1P w łuszczycowo zmienionej skórze [15]. Wyższy poziom S1P stwierdzono u pacjentów z łuszczycą o prawidłowej masie ciała w porównaniu z otyłymi pacjentami z łuszczycą. Jednocześnie, badania wskazują, że wyższy wychwyt komórkowy S1P u otyłych pacjentów, może prowadzić do zmniejszonej wrażliwości tkanek na insulinę [16]. Dodatkowo, poziom S1P w osoczu jest niestabilny w przypadku insulinooporności. Wysoki poziom glukozy zwiększa aktywność kinazy sfingozyny w komórkach śródbłonka naczyniowego *in vitro*, co przyśpiesza syntezę S1P, który również zwrotnie aktywuje komórki śródbłonka naczyniowego. Wyżej wymienione sfingolipidy (w szczególności: C24:0, C16:0, S1P) funkcjonują jako modulatory insulinooporności oraz aterogenezy związanej z przewlekłym stanem zapalnym występującym w otyłości [17]. Ostatnie badania wskazują, że receptory na które oddziałuje S1P, np. receptor sfingozyno-1-fosforanu 1, receptor sfingozyno-1-fosforanu 2 i transportera sfingolipidów 2 występują również w obrębie mięśnia sercowego i są istotne dla rozwoju embrionalnego kardiomiocytów [18].

3.1.3 Rola ceramidów w łuszczycy i chorobach współistniejących

Zmniejszony poziom CERs w surowicy został powiązany z zaburzeniami funkcjonowania bariery naskórkowej, suchością, oraz chorobami takimi jak atopowe zapalenie skóry i łuszczyca [19]. Część badań wskazuje na podwyższone poziomy CERs w osoczu (C16:0, C18:0, C20:0, C22:0 i C24:1) u pacjentów chorujących na łuszczycę. Z kolei obniżony poziom CER C12: oraz C12:0-sfingomieliny w osoczu odnotowano u pacjentów z ciężką łuszczycą w porównaniu ze zdrową grupą kontrolną. Nie zaobserwowano różnic w poziomach heksozyloceramidu lub laktozyloceramidu w osoczu osób chorych na łuszczycę w porównaniu do osób zdrowych. Poziom sfingomieliny był obniżony w skórze łuszczycowej w sposób zależny od długości łańcucha kwasów tłuszczowych, ze wzrostem C16:0, C24:1 i C24:0. Poziomy sfingomieliny C12:0 były niższe w skórze bez zmian chorobowych w porównaniu ze zmianami chorobowymi i skórą zdrową [12]. W łuszczycy, wykazano spadek ekspresji syntaz ceramidowych (CERS), elongaz (ELOVL) długołańcuchowch kwasów tłuszczowych (FA) (dłuższych niż C26), CERs [NP] i hydroksy-kwasów tłuszczowych. Udowodniono również, że stężenie syntazy ceramidowej 3 i ELOVL4 są zmniejszone w naskórku zajętym łuszczycowo i w stymulowanych interferonem gamma (IFN-γ) keratynocytach [20]. Acylceramid odgrywa istotną rolę w tworzeniu bariery naskórkowej. Opisywano obniżone poziomy niektórych rodzajów CERs, w tym zestryfikowanych omega-metabolitów hydroksyacylosfingozyny, która jest reprezentatywnym acylceramidem, przy łagodniej dysfunkcji bariery skórnej [21]. Wykazano, iż zastosowanie kremu i/lub preparatu zawierającego CERs zapewniło znaczącą poprawę kondycji skóry u pacjentów z łuszczycą. Preparaty nawilżające/naprawiające barierę ochronną i środki keratolityczne są klinicznie uznawane za cenne farmaceutyki do leczenia miejscowego łuszczycy. Stosowanie produktów zawierających CERs wykazuje korzystne działanie na poprawę funkcji bariery naskórkowej, zmniejszając przeznaskórkową utratę wody (TEWL) i

utrzymując nawilżenie warstwy rogowej naskórka (stratum corneum, SC) [22]. Wg niektórych danych [23, 24] zasadnicza zmiana budowy CERs w łuszczycy jest związana ze znacznym spadkiem odsetka CERs zawierających fitosfingozynę (3 i 6I) w porównaniu do normalnej warstwy rogowej naskórka z równoczesnym wzrostem niektórych CERs zawierających sfingozynę (2I, 2II i 5I) [23,24]. Poziom Cer [NP] i stosunek Cer [NP]/[NS] są wyższe w SC w łuszczycy w porównaniu do keratynocytów (KCs) w normalnej ludzkiej skórze [25].

Poziomy ceramidu lignocerynowego (C24:0) i ceramidu palmitooleinowego (C16:1) w surowicy są ujemnie skorelowane ze stopniem nasilenia łuszczycy wyrażonym wskaźnikiem PASI (ang. Psoriasis Area and Severity Index), u pacjentów z nadwagą. C24:0 jest kluczowym czynnikiem w utrzymaniu prawidłowej bariery naskórkowej [16]. Ceramid C24:0 hamuje stan zapalny i rozwój insulinooporności i utrzymuje prawidłową homeostazę wątroby. Ceramid nerwonowy (C24:1) dodatnio koreluje z PASI u osób z prawidłową masą ciała. C24:1 jest markerem stanu zapalnego i ma wartość prognostyczną w przewidywaniu przebiegu łuszczycy. Istnieje zależność między ilością C24:1 a białkiem C-reaktywnym (CRP) we krwi pacjentów z łuszczycą i prawidłową masą ciała. Z kolei ujemną korelację obserwowano między C24:0 a CRP u otyłych pacjentów z łuszczycą[16].

Sfingolipidy w surowicy (głównie CERs) mogą być markerami zaburzeń sercowo-naczyniowych i chorób metabolicznych. Wysokie poziomy C24 i C26i deoksy-C24 ceramidu zostały powiązane z neuropatią cukrzycową. Podwyższone poziomy CERs C18:1 i C18:0 w surowicy zostały również opisane jako istotne markery poważnych niepożądanych zdarzeń sercowo-naczyniowych wśród pozornie zdrowych osób. W szczególności poziom CER C18:1 jest podwyższony w przypadku martwicy po zabiegach angiografii wieńcowej [10]. Wysoki poziom CER C24:1 i sfingomieliny w osoczu są silnie powiązane ze śmiertelnością z przyczyn sercowo-naczyniowych [10]. Podwyższone ilości CERs C22:0 i C24:0 w osoczu mogą być czynnikiem predykcyjnym mniejszej poprawy pamięci werbalnej w odpowiedzi na

ćwiczenia u pacjentów z chorobą niedokrwienną serca (CAD) u których te umiejętności są obniżone [10]. Wykazano również, iż zwiększone poziomy CERs w sercu po epizodzie ostrego MI były związane z wyższymi wskaźnikami śmierci komórek w lewej komorze i pogorszeniem funkcji serca [26]. Należy zauważyć, że charakterystycznym wskaźnikiem dla chorób serca jest wskaźnik ryzyka sercowego 1 (CERT1), inaczej zwany testem ceramidów. Poszczególne ceramidy i odpowiadające im stosunki w osoczu są obiecującym markerem ryzyka wystąpienia CAD [27].

U pacjentów z otyłością i chorobami współistniejącymi, takimi jak cukrzyca typu 2 (T2DM), zaobserwowano podwyższony poziom CERs w surowicy w porównaniu do zdrowych osób. Po operacji bariatycznej, zaobserwowano również obniżone stężenia C14:0, C16:0, C20:0 i C24:0 w osoczu tych pacjentów [28]. W innych badaniach obniżona ilość C24:0 była powiązana ze zwiększoną wrażliwością na insulinę i redukcją masy ciała. Z kolei u otyłych młodych dorosłych zaobserwowano dodatnią korelację między γ-glutamylotranspeptydazą i C24:0. Stężenia C14:0, C16:0, C22:0 i C24:0 w surowicy były podwyższone w stanach przedcukrzycowych i cukrzycowych, a poziomy tych CERs dodatnio korelowały z wielkością wskaźnika HOMA-IR (ang. Homeostatic Model Assessment for Insulin Resistance). Podsumowując, mimo niejednoznacznych wyników badań, wiadomo, że wahania stężenia C24:0 i C14:0 mają ogromny wpływ na powstawanie zaburzeń metabolicznych, w tym u pacjentów cierpiących na łuszczycę [28]. Ceramidy C14:0 i C24:0 są również zaangażowane w patogenezę chorób wątroby. Poziom CERs (najsilniej C14:0) koreluje dodatnio ze stężeniem aminotransferazy alaninowej (ALT) we krwi. C14:0 jest też powszechnie uważany za nowy biomarker stłuszczenia wątroby, niezależny od otyłości [28].

Rozdział 4. Omówienie prac składających się na rozprawę doktorską

4.1 Publikacja I

"The Interplay between Bioactive Sphingolipids in the Psoriatic Skin and the Severity of the Disease."

4.1.1 Cel pracy

Ocena i porównanie stężenia wybranych bioaktywnych sfingolipidów w zmienionych i niezmienionych chorobowo fragmentach skóry od pacjentów z łuszczycą oraz od osób zdrowych.

4.1.2 Materiał i metody

Badaniem objęto 15 pacjentów (7 mężczyzn i 8 kobiet) z aktywną postacią łuszczycy plackowatej hospitalizowanych w Klinice Dermatologii i Wenerologii Uniwersytetu Medycznego w Białymstoku, w wieku (mediana) 51,0 lat (23,0 - 71,0 lat). Do grupy kontrolnej włączono 17 osób, hospitalizowanych w I Klinice Chirurgii Ogólnej i Endokrynologicznej, Uniwersytetu Medycznego w Białymstoku (11 mężczyzn i 6 kobiet) w wieku (mediana) 42,0 lat (23,0 - 84,0 lat). Nasilenie łuszczycy zostało oszacowane za pomocą wskaźnika PASI. Również przy użyciu skali PASI oceniliśmy cechy kliniczne rumień, naciek i złuszczanie w obrębie zmiany łuszczycowej wybranej do biopsji. System punktacji wahał się od 0 do 4. Wskaźnik masy ciała (BMI) obliczono na podstawie podanej przez pacjenta masy ciała i wzrostu. Żaden z pacjentów z grupy badawczej lub kontrolnej nie podlegał ograniczeniom dietetycznym, nie stosował w trakcie badania kwasów omega-3, nie przyjmował leków mogących wpływać na metabolizm lipidów. Z dokumentacji szpitalnej pacjentów, zebrano dane dotyczące chorób ogólnoustrojowych: nadciśnienia tętniczego, chorób wątroby (np. niealkoholowa stłuszczeniowa choroba wątroby (NAFLD)), chorób serca, T2DM i wyników badań laboratoryjnych. Wszelkie badania

laboratoryjne zostały zlecone przed rozpoczęciem leczenia, i obejmowały morfologię krwi obwodowej, CRP, glikemię na czczo, ALT, cholesterol całkowity, TG. Po odwirowaniu, surowicę przechowywano w temperaturze 80°C do czasu oznaczenia wybranych sfingolipidów. Wykonano biopsje o wielkości 3 mm zarówno ze skóry niezajętej chorobowo, jak i zmienionej chorobowo z tułowia pacjentów z łuszczycą po znieczuleniu miejscowym chlorkiem etylu. Próbki od zdrowych pacjentów pobrane zostały z brzegu rany podczas przeprowadzania planowanej operacji przepukliny pachwinowej w znieczuleniu ogólnym.

Sfingolipidy w tym CER, zostały oznaczone za pomocą wysokosprawnej chromatografii cieczowej (HPLC) w Zakładzie Fizjologii Uniwersytetu Medycznego w Białymstoku. Dwa metabolity sfingolipidów uwalniane z CER tj. wolna sfinganina (SFA) i SFO, zostały przekształcone w ich pochodne aldehydu o-ftalowego i analizowane przy użyciu standardowego systemu HPLC wyposażonego w detektor fluorescencji i kolumnę z odwróconą fazą C-18. Stężenie oszacowanych sfingolipidów wyrażone zostało w pikomolach na miligram tkanki.

4.1.3 Wyniki

Do badania włączono 15 pacjentów (7 mężczyzn i 8 kobiet) z aktywną łuszczycą plackowatą oraz 17 zdrowych pacjentów (11 mężczyzn i 6 kobiet) stanowiło grupę kontrolną. Średni czas trwania łuszczycy wynosił 24 lata. Mediana masy ciała wynosiła 87,0 (82,0-94,0) (kg). Średni wzrost wynosił 174,0 (162,0-176,0) (cm). Mediana BMI wynosiła 28,74 (27,72-30,35). Większość pacjentów (n= 8) miała nadwagę (53,33%), pięciu (33,33%) cierpiało na otyłość, a dwóch (13,3%) miało prawidłową masę ciała. W grupie badanej: 1 (6,67%) pacjent miał łagodną (PASI<10) postać łuszczycy, 10 (66,67%) cierpiało na umiarkowaną postać łuszczycy (PASI 10-20), a 4 (26,67%) miało ciężką postać łuszczycy (PASI>20). Stężenie SFO w zmienionej łuszczycowo skórze

pacjentów (1,72 pmol/mg) było istotnie wyższe ($p<0,05$) w porównaniu zarówno do skóry niezmienionej pacjentów z łuszczycą (0,38 pmol/mg), jak i do skóry osób zdrowych (0,27 pmol/mg). Podobnie, stężenia CERs w zmienionej chorobowo skórze (68,4 pmol/mg) było znacząco wyższe ($p < 0,05$) niż w skórze niezmienionej (16,08 pmol/mg) i skórze osób zdrowych (6,58 pmol/mg). Dodatkowo, stężenie innych parametrów określonych w tym badaniu, takich jak SFA, S1P i sfinganino-1-fosforan (SFA1P), były znacząco wyższe w skórze zmienionej łuszczycowo w porównaniu ze skórą osób zdrowych oraz wykazywały nieznaczny wzrost w skórze niezmienionej u pacjentów z łuszczycą, w stosunku do zdrowej skóry osób należących do grupy kontrolnej. Co ciekawe, w skórze klinicznie niezmienionej pacjentów z łuszczycą obserwowano wyższe stężenie CERs i SFO w stosunku do skóry osób zdrowych. Ponadto, zaobserwowano dodatnią korelację Pearsona między naciekiem skóry a SFA, a także między naciekiem a SFA1P (odpowiednio $p=0,035$ i $p=0,046$).

Zgoda Komisji Bioetycznej

Na wykonanie badań uzyskano zgodę Komisji Bioetycznej Uniwersytetu Medycznego w Białymstoku (uchwała nr APK.002.500.2021) i przeprowadzono ją zgodnie z założeniami Deklaracji Helsińskiej. Wszyscy pacjenci byli włączeni do badania po wyrażeniu świadomej pisemnej zgody.

Analiza statystyczna

Uzyskane dane zostały przeanalizowane przy użyciu pakietu statystycznego R (ver. 4.2.2). Na początku analiz dane ciągłe zostały sprawdzone pod kątem normalności (test Shapiro-Wilka) i homoscedastyczności (test Flignera-Killeena). W oparciu o powyższe testy, porównania międzygrupowe zostały wykonane przy użyciu metod parametrycznych (ANOVA z późniejszym testem t-Studenta) lub nieparametrycznych (Kruskal-Wallis). Uzyskane wartości p zostały skorygowane o wielokrotne porównania (poprawka Benjamini-Hochberg). Skorygowane wartości p mniejsze niż 0,05 uznano za istotne statystycznie.

4.2 Publikacja II

"Crosstalk between Serum and Skin Sphingolipids in Psoriasis"

4.2.1 Cel pracy

W tym badaniu podjęto próbę powiązania metabolizmu sfingolipidów w skórze pacjentów cierpiących na łuszczycę z ogólnoustrojowymi zaburzeniami metabolizmu lipidów. W tym celu porównano stężenia wybranych bioaktywnych sfingolipidów w skórze zmienionej i niezmienionej chorobowo, z ich odpowiednikami w surowicy pacjentów z łuszczycą. W ocenie uwzględniono dodatkowo związek badanych metabolitów z parametrami klinicznymi i laboratoryjnymi pacjentów z grupy badanej.

4.2.2 Materiał i metody

Badaniem objęto dwudziestu pacjentów (13 mężczyzn i 7 kobiet) z aktywną łuszczycą plackowatą, ze średnią wieku 53,2 lat i 28 zdrowych osób z grupy kontrolnej, ze średnią wieku 45,6 (8 mężczyzn i 20 kobiet). Nasilenie łuszczycy oceniono za pomocą wskaźnika PASI. BMI obliczono na podstawie podanej przez pacjentów masy ciała i wzrostu. Żaden z pacjentów z grupy badawczej, ani osób z grupy kontrolnej nie podlegał ograniczeniom dietetycznym, nie stosował w trakcie badania kwasów omega-3, nie przyjmował leków mogących zaburzać metabolizm lipidów. Z dokumentacji szpitalnej pacjentów, zebrano dane dotyczące chorób ogólnoustrojowych: nadciśnienia tętniczego, chorób wątroby (np. NAFLD), chorób serca, T2DM i wyniki badań laboratoryjnych. Badania laboratoryjne zostały wykonane przed rozpoczęciem leczenia (morfologia krwi obwodowej, CRP, glikemia na czczo,

ALT, cholesterol całkowity, TG). Wszyscy pacjenci z łuszczycą oraz osoby z grupy kontrolnej wyrazili pisemną świadomą zgodę przed włączeniem do badania. Próbki krwi obwodowej krwi obwodowej pobrano przed rozpoczęciem leczenia na czczo. Po odwirowaniu surowicę przechowywano w temperaturze -80°C do czasu oznaczenia wybranych sfingolipidów. Dodatkowo pobrano biopsje skóry o wielkości 3 mm zarówno ze skóry niezajętej chorobowo, jak i zmienionej chorobowo z tułowia pacjentów z łuszczycą po znieczuleniu miejscowym chlorkiem etylu. Biopsje 3-mm skóry od zdrowych pacjentów pobrano z brzegu rany podczas planowanej operacji przepukliny pachwinowej wykonywanej w znieczuleniu ogólnym.

Wybrane sfingolipidy (CERs, SFA, SFO, S1P, SFA1P) zostały oznaczone za pomocą HPLC w Zakładzie Fizjologii Uniwersytetu Medycznego w Białymstoku. Stężenia badanych sfingolipidów wyrażone zostały w pikomolach na miligram tkanki oraz w pikomolach na mililitr surowicy. Przeprowadzono analogiczne oznaczenia jak w poprzedniej pracy.

4.2.3 Wyniki

Średni czas trwania łuszczycy wynosił 18,33 lat, a średnia masa ciała 87,2 kg, przy średnim wzroście 171,3 cm i medianie BMI 29,9. Dziewięciu pacjentów z łuszczycą miało nadwagę (45%), 6 osób (30%) cierpiało na otyłość, a 5 (25%) pacjentów miało prawidłową masę ciała. W grupie badanej, 1 (5%) pacjent miał łagodną postać łuszczycy (PASI < 10), 13 (65%) osób miało postać umiarkowaną (PASI 10-20), a 6 (30%) cierpiało na ciężką postać łuszczycy (PASI>20). Pacjenci z grupy badanej mieli statystycznie wyższe wartości ($p<0,05$) BMI, masy ciała, TG, CRP w porównaniu z grupą kontrolną. Wykazano statystycznie wyższe ($p<0,05$) stężenie CERs, S1P, SFA1P, SFA i SFO w zmienionej chorobowo skórze w porównaniu do skóry bez zmian u osób chorych na łuszczycę, jak i w stosunku do skóry osób zdrowych. Ponadto

wykazano statystycznie istotne różnice ($p<0,05$) między zwiększonymi stężeniami CERs i SFO w skórze niezmienionej chorobowo u osób z łuszczycą w porównaniu ze skórą osób zdrowych. Stwierdzono istotnie wyższe stężenie S1P, SFA, SFO i SFA1P w surowicy pacjentów z łuszczycą w porównaniu do surowicy osób zdrowych. W porównaniu do osób zdrowych, stężenie CER było wyższe u pacjentów z łuszczycą, jednak różnica ta nie była istotna statystycznie. Dodatkowo wykazano ujemne korelacje Pearsona między stężeniem badanych związków w skórze nie zajętej chorobowo a stężeniem analogicznych metabolitów w surowicy pacjentów z łuszczycą: SFO_t vs. SFO_s ($p < 0,027$), CER_t vs. SFA_s ($p < 0,040$), CER_t vs. SFO_s ($p < 0,044$) i SFO_t vs. SFA_s ($p < 0,048$). Dodatnią korelację Pearsona obserwowano z kolei między CER_t i CER_s ($p < 0,026$), SFA_t i CER_s ($p < 0,006$), oraz SFO_t i CER_s ($p < 0,039$) (gdzie t oznacza tkankę badaną – skórę, a s- surowicę).

Zgoda Komisji Bioetycznej

Na wykonanie badań uzyskano zgodę Komisji Bioetycznej Uniwersytetu Medycznego w Białymstoku (uchwała nr APK.002.500.2021) i przeprowadzono ją zgodnie z założeniami Deklaracji Helsińskiej. Wszyscy pacjenci byli włączeni do badania po wyrażeniu świadomej pisemnej zgody.

Analiza statystyczna

Uzyskane dane zostały przeanalizowane przy użyciu pakietu statystycznego R (ver. 4.2.2). Na początku analiz dane ciągłe zostały sprawdzone pod kątem normalności (test Shapiro-Wilka) i homoscedastyczności (test Flignera-Killeena). W oparciu o powyższe testy, porównania międzygrupowe zostały wykonane przy użyciu metod parametrycznych (ANOVA z późniejszym testem t-Studenta) lub nieparametrycznych (Kruskal-Wallis). Uzyskane wartości p zostały skorygowane o wielokrotne

porównania (poprawka Benjamini-Hochberg). Skorygowane wartości p mniejsze niż 0,05 uznano za istotne statystycznie.

4.3. Publikacja III

"The Role of Sphingolipids in the Pathogenesis of Psoriasis"

Trzecia publikacja ma charakter pracy przeglądowej podsumowującej dotychczasową wiedzę na temat roli sfingolipidów w patogenezie łuszczycy. Wyniki wielu badań wskazują, że u pacjentów z łuszczycą zaburzony metabolizm sfingolipidów, może być czynnikiem łączącym patogenezę rozwoju łuszczycy z jej chorobami współistniejącymi np. zespołem metabolicznym, chorobami sercowo-naczyniowymi oraz chorobami wątroby. W celu lepszego zrozumienia znaczenia roli sfingolipidów w patogenezie łuszczycy dokładnie przeanalizowano dostępne piśmiennictwo na temat metabolizmu sfingolipidów w przebiegu tej choroby.

W skórze zajętej łuszczycowo, zaburzony jest metabolizm sfingolipidów, w tym S1P oraz CER. W łuszczycy powszechnym zjawiskiem jest zwiększona przeznaskórkowa utrata wody (TEWL) i hiperproliferacja naskórka co jest spowodowane niższym poziomem ceramidów (CERs) i podwyższonym poziomem S1P w skórze objętej łuszczycą [11].

U pacjentów z nadwagą, stężenia C24:0 i C16:1 były ujemnie skorelowane z nasileniem łuszczycy mierzonym wskaźnikiem PASI. Wzrost poziomu C24:0 przyczynia się do zmniejszenia nasilenia stanu zapalnego i rozwoju insulinooporności oraz utrzymania prawidłowej homeostazy wątroby. Ilość C24:1 dodatnio koreluje z PASI, u osób chorych na łuszczycę z prawidłową masą ciała. C24:1 jest markerem stanu zapalnego i ma wartość prognostyczną w przewidywaniu przebiegu łuszczycy. U pacjentów z otyłością i chorobami współistniejącymi, takimi jak T2DM, zaobserwowano podwyższony poziom CERs w surowicy w porównaniu do zdrowych pacjentów [28].

Podwyższony poziom CERs w surowicy pacjentów z łuszczycą może wskazywać na rozwijające się schorzenia wątroby. W chorobach wątroby ilość CERs dodatnio koreluje dodatnio bezpośrednio ze stężeniem ALT [28]. W związku z tym,

wysoki poziom C14:0 i C24:0 obserwowany u pacjentów cierpiących na łuszczycę może być związany również z chorobami wątroby.

W chorobach sercowo-naczyniowych zwiększony poziom CERs odnotowany był w tkankach mięśnia sercowego po epizodzie ostrego MI oraz związany był z wyższymi wskaźnikami śmierci komórek mięśnia sercowego w lewej komorze i pogorszeniem funkcji tego organu. Ponadto, uważa się że nadekspresja ceramidazy kwasowej, w tkance mięśnia sercowego, może zapewniać kardioprotekcję po zawale mięśnia sercowego. Natomiast podwyższony poziom S1P we krwi wskazywał na ryzyko wystąpienia bradykardii.

Reasumując, oprócz wielu publikacji potwierdzających znaczenie różnych rodzajów sfingolipidów w rozwoju i przebiegu łuszczycy, pojawiają się również liczne doniesienia, że zaburzony metabolizm tych związków może wpływać na rozwój oraz przebieg innych schorzeń ogólnoustrojowych takich jak: otyłość, T2DM, insulinooporność, choroby wątroby, czy choroby sercowo-naczyniowe. Pomimo tego, iż metabolizm sfingolipidów w różnych schorzeniach został szeroko zbadany, potrzebne są dalsze badania w celu oceny zależności współwystępowania chorób metabolicznych i zapalnych.

4.4 Wnioski.

1. Pacjenci z łuszczycą pospolitą mają odmienny profil sfingolipidowy w skórze zmienionej (wyższe stężenie CERs, S1P, SFO, SFA, SFA1P) w porównaniu do skóry niezmienionej chorobowo oraz do skóry osób zdrowych.

2. W skórze niezmienionej chorobowo u pacjentów z łuszczycą stwierdzono wyższe stężenia sfingolipidów (CERs, SFO) w porównaniu do skóry osób zdrowych. Wskazuje to, na występowanie zaburzeń i nieprawidłowości metabolizmu lipidów nawet w klinicznie pozornie niezmienionej skórze.

3. Zaobserwowane korelacje między wybranymi bioaktywnymi sfingolipidami w skórze zmienionej chorobowo a poziomem tych samych związków w surowicy pacjentów z łuszczycą, mogą wskazywać na wpływ zaburzeń metabolizmu lipidów skóry na zmiany ogólnoustrojowe.

4. Nieprawidłowy metabolizm sfingolipidów u pacjentów z łuszczycą, może wpływać na występowanie i przebieg schorzeń współistniejących z łuszczycą np. otyłości, zespołu metabolicznego, schorzeń wątroby oraz chorób sercowo-naczyniowych.

Rozdział 5. Publikacje stanowiące rozprawę doktorską

International Journal of
Molecular Sciences

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The Interplay between Bioactive Sphingolipids in the Psoriatic Skin and the Severity of the Disease

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Abstract: Psoriasis is a complex chronic immunologically mediated disease that may involve skin, nails, and joints. It is characterized by hyperproliferation, deregulated differentiation, and impaired apoptosis of keratinocytes. Sphingolipids, namely ceramide, sphingosine-1-phosphate, sphingosine, sphingomyelin, and sphinganine-1-phosphate, are signal molecules that may regulate cell growth, immune reactions, and apoptosis. Fifteen patients with psoriasis and seventeen healthy persons were enrolled in the study. Skin samples were taken from psoriatic lesions and non-lesional areas. Tissue concentration of ceramides, sphingosine-1-phosphate, sphingosine, sphingomyelin, and sphinganine-1-phosphate was measured by liquid chromatography. We assessed that all levels of ceramides, sphingosine-1-phosphate, sphingosine, sphingomyelin, and sphinganine-1-phosphate were higher in lesioned psoriatic skin than in non-affected skin. The profile of bioactive lipids in the lesional skin of patients with psoriasis differed significantly from non-involved psoriatic skin and skin in healthy subjects.

Keywords: psoriasis; ceramide; sphingosine-1-phosphate; sphinganine-1-phosphate; sphinganine; sphingosine

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1. Introduction

Psoriasis is a chronic inflammatory immune-mediated disease that is widespread around the whole world [1]. Its global prevalence is between 0.27% and 11.4% in adults and it appears more frequently in adults than in children [2]. Psoriasis may be divided into a few significant subgroups, e.g., erythrodermic, guttate, pustular, inverse, and plaque (the most common (about 90% of cases)) [3]. The most classic symptoms of plaque psoriasis are erythematous well-demarcated lesions that are generally covered by silvery scales. Those plaques may appear on large surfaces of the patient's skin and may merge together. Furthermore, typical psoriatic locations may include the extensor surfaces of the limbs, the scalp, and the lumbosacral region [4]. In typical psoriatic skin lesions, deregulated differentiation of epidermal keratinocytes (parakeratosis and acanthosis) and infiltration of immune cells into the deeper layers of the skin may be observed [5]. Interestingly, a decreased apoptosis of keratinocytes in psoriatic lesions has been noted [6]. Furthermore, keratinocytes derived from psoriatic plaques were resistant to apoptosis in comparison with keratinocytes in healthy skin [7].

Psoriasis may not only affect the skin but also joints and nails and may co-occur with various systemic conditions [8].

Mainly, due to psoriatic pro-inflammatory etiology, it may coexist with different components of metabolic syndrome, for example, hyperlipidemia, hypertension, obesity,

and insulin resistance. Over time, these conditions may lead to the development of type 2 diabetes, atherosclerotic disease, coronary artery disease, or myocardial infarction [9].

Psoriatic patients are commonly diagnosed with abnormal lipids levels. Serum amounts of triglycerides, total cholesterol, and very low-density lipoprotein (VLDL) cholesterol and low-density lipoprotein (LDL) cholesterol are raised in comparison with healthy people. However, high-density lipoprotein (HDL) cholesterol is substantially decreased in patients suffering from psoriasis [10].

Until now, the molecular mechanisms underlying psoriasis, its progression, and concomitant diseases are still unclear despite many recent studies. Sphingolipids are one of the major groups of eukaryotic lipids [11]. Sphingolipids are lipids that contain a sphingoid core. The sphingoid basis is produced with the connection of fatty acids (mainly palmitate) and amino acids (principally serine) [12]. Sphingolipids are an essential subgroup of the lipid mediator family, with both signaling and structural capabilities [13]. The abundance of sphingolipid tasks is broad and applies to the majority of the main features of cell biology, for instance, roles in cell growth, the process of cell death, the cell cycle, immune activity, nutrient uptake, cell adhesion, inflammation, metabolism, angiogenesis, responses to multiply stressors and autophagy, and reactive oxygen stress stimuli. Various types of sphingolipids have been defined, for example, ceramide (CER), sphingosine-1-phosphate (S1P), sphingosine (SFO), ceramide-1-phosphate (C1P), sphingomyelin, galactosylceramide, glucosylceramide, and lactosylceramide [11]. The most active sphingolipids are sphingosine-1-phosphate and ceramide, which are known for various signaling roles. Ceramides are more involved in inflammation, stress responses, cell cycle arrest, apoptosis, and necrosis. Nevertheless, sphingosine-1-phosphate is a signaling molecule that plays a role in cell growth, proliferation, differentiation, and migration. Moreover, the binding of sphingosine-1-phosphate to its cell surface receptors initiates angiogenesis [14]. Reduced levels of ceramide have been linked with different skin diseases involving barrier disruption and dryness, such as xerosis, atopic dermatitis, and psoriasis [15]. Elevated levels of the most analyzed ceramides ($C_{16:0}$, $C_{18:0}$, $C_{20:0}$, $C_{22:0}$, and $C_{24:1}$) have been observed in patients suffering from psoriasis (in the skin and plasma) compared with healthy controls. Furthermore, a decreased level of $C_{12:0}$-sphingomyelin has been spotted in severe psoriatic patients in comparison with healthy controls. Interestingly, the $C_{12:0}$-ceramide was the only lipid molecule that was lowered in severe psoriasis patients compared with healthy controls There were no differences observed in the levels of the hexosylceramide or lactosylceramide. Levels of sphingomyelin were impaired in psoriatic skin in a fatty-acid chain length-dependent manner, with the growth of $C_{16:0}$-, $C_{24:1}$-, and $C_{24:0}$-sphingomyelins. Levels of $C_{12:0}$-sphingomyelin were lower in non-lesional skin vs. lesional and control skin [13].

Interestingly, serum sphingolipids (mostly ceramides) may play a role as markers of atherosclerotic cardiovascular disorders and metabolic diseases. Plasma levels of C26 and C24 ceramides and deoxy-C24 ceramide have been linked with diabetic neuropathy. Moreover, elevated C18:1 and C18:0 ceramides have also been described as relevant markers of major undesirable cardiovascular effects in healthy people; especially, C18:1 ceramide is known to have a ratio of high levels of necrosis after coronary angiography procedures. C24:1 ceramide and sphingomyelin have been strongly linked with cardiovascular death rates. Elevated amounts of plasma C22:0 and C24:0 ceramides may predict a smaller enhancement in verbal memory in reply to exercise in patients with coronary artery disease where these skills are lowered. Alternatively, the serum sphingosine-1-phosphate level in atherosclerotic disease was inversely correlated, where deoxysphingolipids functioned as a biomarker in diabetes [11].

Additionally, sphingosine-1-phosphate inhibited keratinocyte proliferation and induced migration and differentiation [16]. Moreover, the level of sphingosine was heightened in psoriatic skin (one of the precursors of sphingosine-1-phosphate) [17].

In recent years, studies have mainly focused on analyzing serum lipid levels in patients with psoriasis. However, it is not yet fully understood what lipid abnormalities exist in

the skin tissue of individuals affected by this condition. The present study aims to assess the interplay between bioactive sphingolipids in the psoriatic skin and the severity of the disease.

2. Results

2.1. Study Population

A total of 15 patients (7 males and 8 females) with active plaque-type psoriasis and 17 healthy patients (11 males and 6 females) were included in the study. The median age in the control group was 42, ranging from 23 to 84 years; the median range in the psoriatic group was 51, ranging from 23 to 71 years. The average duration of psoriasis was 24 years. The median body mass was 87.0 (82.0–94.0) (kg). The mean height was 174.0 (162.0–176.0) (cm). The median BMI was 28.74 (27.72–30.35). Most of the patients ($n = 8$) were overweight (53.33%), five (33.33%) suffered from obesity, and two (13.3%) had normal weight. In the examined group, 1 (6.67%) patient had a mild (PASI < 10) form of psoriasis, 10 (66.67%) suffered from moderate psoriasis (PASI 10–20), and 4 (26.67%) had a severe (PASI > 20) form of psoriasis. Table 1 summarizes the main clinical features of the psoriatic group and the control group.

Table 1. Clinical and biochemical characteristics of the control group (CTRL) and psoriatic patients (PSO). Data are presented as median and interquartile range; a signifies different vs. PSO ($p < 0.05$); BMI—body mass index, CRP—C reactive protein, TAG—triacylglycerol, AST—aspartate transaminase, ALT—alanine transaminase.

Clinical and Laboratory Features	CTRL ($n = 17$)	PSO ($n = 15$)
Age (years)	42.0 (35.5–55.0)	51.0 (43.0–66.0)
Body mass (kg)	75.0 (67.5–78.0)	87.0 (82.0–94.0) a
Height (cm)	174.0 (166.5–176.0)	174.0 (162.0–176.0)
BMI (kg/m^2)	25.06 (23.75–27.31)	28.74 (27.72–30.35) a
CRP (mg/dL)	1.0 (1.0–1.45)	4.65 (3.06–8.11) a
Glucose (mg/dL)	93.0 (88.5–100.0)	84.0 (81.0–94.0)
TAG (mg/dL)	73.0 (67.5–82.0)	122.0 (85.0–135.0) a
AST (U/L)	22.0 (17.5–28.5)	20.0 (19.0–32.0)
ALT (U/L)	17.0 (13.0–22.0)	18.0 (15.0–27.0)
Sex (no. female/no. male)	6/11	8/7

2.2. Sphingolipid Parameters

The median concentration of sphingosine found in the psoriatic lesional skin of patients (1.72 pmol/mg) was found to be statistically and significantly higher ($p < 0.05$) than both the non-lesional skin of psoriasis patients (0.38 pmol/mg) and the skin of healthy individuals (0.27 pmol/mg). Likewise, the median ceramide concentration in the affected lesional skin (68.4 pmol/mg) was also significantly higher ($p < 0.05$) than the non-lesional skin (16.08 pmol/mg) and skin of healthy subjects (6.58 pmol/mg). Additionally, the concentration of other parameters determined in this study, such as sphinganine, sphingosine-1-phosphate, and sphinganine-1-phosphate, were found to be significantly higher in lesional skin and showed a slight non-significant increase in non-lesional skin compared with the skin of healthy individuals. Figure 1 provides a summary of the primary clinical features observed in psoriatic patients, including lesional and non-lesional skin samples, as well as the control group.

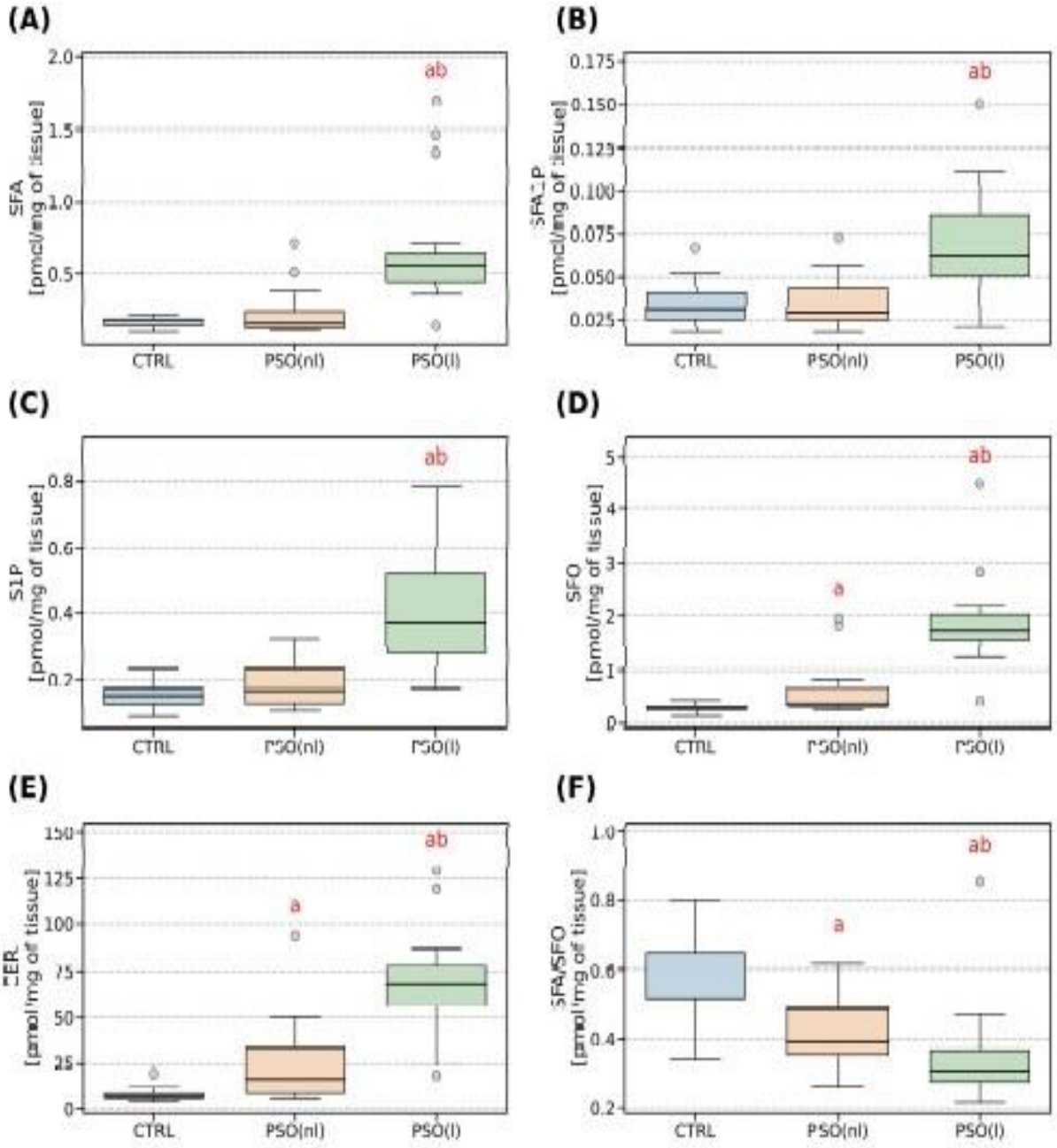

Figure 1. Comparison between sphingolipids in healthy (CTRL), psoriatic lesional (PSO (l)), and psoriatic non-lesional (PSO (nl)) skin. (**A**) Amount of sphinganine (SFA) (pmol/mg of tissue). (**B**) Amount of sphinganine-1-phosphate (SFA1P) (pmol/mg of tissue). (**C**) Amount of sphingosine-1-phosphate (S1P) (pmol/mg of tissue). (**D**) Amount of sphingosine (SFO) (pmol/mg of tissue). (**E**) Amount of ceramide (CER) (pmol/mg of tissue). (**F**) The ratio of sphinganine and sphingosine. Significance markers: a signifies different vs. CTRL ($p < 0.05$) and b signifies different vs. PSO (NL) ($p < 0.05$).

Furthermore, as illustrated in Figure 2, we observed a positive Pearson's correlation between psoriatic skin induration and sphinganine, as well as between induration and sphinganine-1-phosphate, both of which were statistically significant with p-values of less than 0.035 and 0.046, respectively. Moreover, we identified a positive Pearson's correlation in non-lesional skin of psoriatic patients between induration and sphingosine-1-phosphate and induration and sphinganine-1-phosphate.

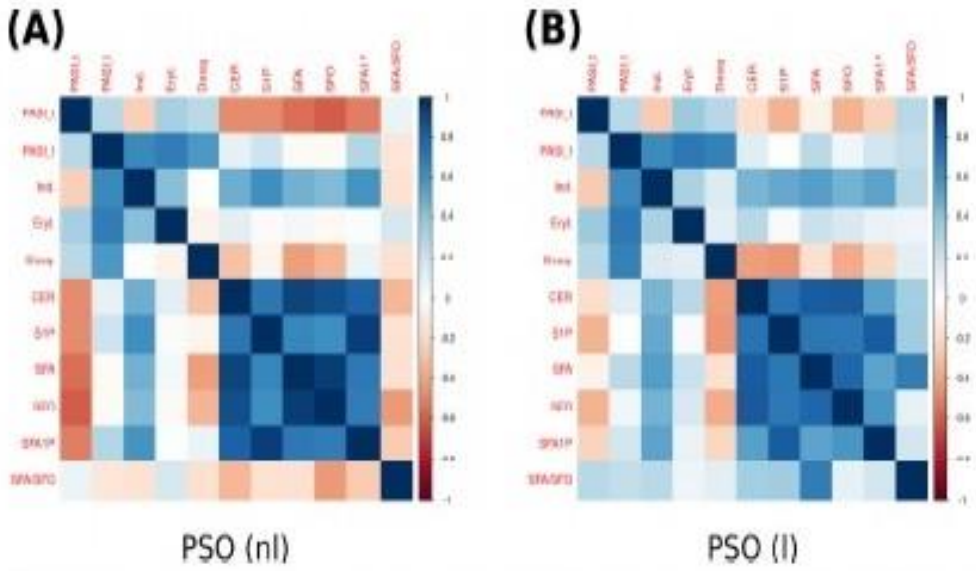

Figure 2. Correlation matrix (heatmap). Pearson correlation coefficients are depicted as shades of blue (positive correlation) or red (negative correlation). (**A**) Correlation matrix for psoriatic non-lesional (PSO (nl)) skin. (**B**) Correlation matrix for psoriatic lesional (PSO (l)) skin. CER—ceramide; Desq.—desquamation; Eryth.—erythema; Ind.—induration; PASI_l—psoriasis area severity index_lesional; PASI_t—psoriasis area severity index_total; S1P—sphingosine-1-phosphate; SFA—sphinganine; SFA1P—sphinganine-1-phosphate; SFO—sphingosine.

Additionally, we observed statistically significant positive correlations between psoriasis area and severity index_total; sphingosine, sphinganine, and sphinganine-1-phosphate; as well as between induration of skin lesions and sphinganine and induration and sphinganine-1-phosphate in lesional skin samples of psoriatic patients.

3. Discussion

We studied sphingolipid levels in psoriatic patients concerning clinical and laboratory data.

In this study, we evaluated and compared the concentrations of bioactive sphingolipids in both lesioned and non-lesioned skin samples from psoriatic patients, which, to the best of our knowledge, has not been previously explored. Our findings revealed that levels of sphingosine, sphinganine, sphingosine-1-phosphate, sphinganine-1-phosphate, and ceramide were significantly higher in the lesional psoriatic skin samples compared with the non-affected skin samples in patients with psoriasis.

Our study identified a statistically significant positive correlation between induration and both sphinganine and sphinganine-1-phosphate in non-lesioned skin samples of psoriatic patients.

Our study demonstrated an interesting finding that the SFA/SFO ratio was highest in the control group, lower in the non-lesioned skin of psoriatic patients, and the lowest in the lesioned skin of psoriatic patients.

3.1. The Role of Sphingosine-1-Phosphate

In our study, we found that sphingosine-1-phosphate levels were elevated in skin samples obtained from patients with psoriasis compared with individuals with healthy skin from patients with hernia inguinal. These findings were consistent with previous studies that also reported increased sphingosine-1-phosphate levels in the skin and serum of psoriasis patients. However, our study revealed a novel finding, indicating that the sphingosine-1-phosphate concentration was elevated specifically in skin lesions. In non-lesioned skin, sphingosine-1-phosphate levels were significantly lower than in psoriatic lesions, although still comparable to the levels found in healthy skin.

Sphingosine-1-phosphate is a signaling lipid known for its crucial role in regulating inflammation, angiogenesis, and vascular permeability [18]. In our study, we discovered a positive correlation between sphingosine-1-phosphate and induration in psoriatic skin lesions, which could be attributed to its involvement in promoting inflammation and the angiogenesis process. Interestingly, elevated plasma levels of sphingosine-1-phosphate have been observed not only in psoriasis but also in obesity when compared with healthy controls. This suggests that sphingosine-1-phosphate may have broader implications in various pathological conditions beyond psoriasis. Indeed, sphingosine-1-phosphate has been found to correlate with metabolic irregularities such as insulin resistance and adiposity. In line with this, the authors of the study identified a significant association between sphingosine-1-phosphate and features of metabolic syndrome, including body fat percentage, waist circumference, total, and LDL cholesterol levels, and fasting plasma insulin [19]. Additionally, it was observed that psoriatic patients had elevated serum concentrations of sphingosine-1-phosphate along with higher serum alanine aminotransferase (ALT) levels compared with healthy controls [20]. These findings suggest a potential link between sphingosine-1-phosphate, metabolic disturbances, and liver function in psoriatic patients. Furthermore, a statistically significant positive correlation was identified between the severity of psoriasis and the serum levels of sphingosine-1- phosphate both before and after treatment with narrow-band ultraviolet B (NBUVB) therapy ($r = 0.374$, $p = 0.003$). However, no significant correlation was found between disease duration or patient age and sphingosine-1-phosphate levels ($r = 0.393$, $p = 0.765$) [21]. This suggests that sphingosine-1-phosphate serum levels may serve as a potential marker for assessing the severity of psoriasis and monitoring the effectiveness of NBUVB treatment.

Sphingosine-1-phosphate is well-established for its ability to induce keratinocyte differentiation, exhibit anti-proliferative and pro-inflammatory effects, and inhibit epidermal cell growth in mouse models of psoriasis, as described by Vaclavkova et al. [22]. Ponesimod, on the other hand, is an orally administered selective modulator of sphingosine 1-phosphate receptor 1 (S1PR1). It functions by blocking the outflux of T cells from lymphoid organs. Based on our findings and the results reported by other researchers, targeting S1P1 to inhibit the gathering of pathogenic lymphocytes in the skin and circulation appears to be a promising therapeutic approach for the future treatment of psoriasis. This suggests that modulating the sphingosine-1-phosphate pathway could potentially offer new avenues for managing and improving psoriasis treatment outcomes. Interestingly, in the phase 2 clinical trial, by week 16, the PASI75 response to ponesimod was 46.0% (with a dose of 20 mg) and 48.1% (with a dose of 40 mg) compared with a 13.4% response for the placebo. By week 28, PASI75 was 71.4% (20 mg) and 77.4% (40 mg), respectively [22]. D'Ambrosio et al. [23] reported that ponesimod presented encouraging outcomes in phase II studies in relapsing–remitting psoriasis and multiple sclerosis. Their study suggested that lymphocyte depletion may form the basis of action for a selective S1P1 receptor modulator in chronic inflammatory and multiple autoimmune impairments for instance psoriasis. The amount of peripheral blood T cells and B blood cells decreased following the intake of 8 mg of ponesimod. CD3+ and CD 20+ counts were decreased significantly following the administration of 20–75 mg of ponesimod. This study presented that ponesimod may decrease some of the inflammatory cells, which may reduce the inflammation process in psoriasis, which is one of the backgrounds of this skin disease [23].

Another studied sphingosine-1-phosphate receptor modulator is fingolimod. De Biase et al. [24] showed a case where fingolimod led to a remission of psoriatic skin lesions in a 27-year-old patient with multiple sclerosis. Interestingly, psoriasis and multiple sclerosis are both linked with Th1 and Th17 cells. In previous studies, fingolimod has been shown to reduce the levels of sphingosine-1-phosphate, inhibit the exocytosis of lymphocytes from lymphoid tissues, and decrease the number of Th17 lymphocytes in peripheral blood, which may play a role in the treatment of multiple sclerosis and psoriasis. As a consequence, fingolimod might be a therapeutic solution if these two diseases coexist [24]. Okura et al. [25] showed that fingolimod was efficacious in improving imiquimod-induced

psoriasiform dermatitis in mice, both clinically and histologically. Moreover, the amount of IL-17A was depleted in mice skin treated with fingolimod than in mice where phosphate-buffered saline was used alone. These results may offer promising results for treating psoriasis with fingolimod, but we still need proper data on implementing this therapeutic in patients dealing with psoriasis [25].

3.2. The Characteristic of Sphingosine and Sphinganine (SFA)

In our study, we made an intriguing observation of significantly elevated concentrations of both sphinganine and sphingosine in psoriatic tissue in contrast with non-lesional and healthy skin samples. Notably, what set our findings apart was the discovery that, even in the non-affected skin of psoriatic patients, the concentration of sphingosine remained significantly higher than that observed in healthy skin. This highlighted a previously undescribed aspect of the lipid abnormalities present in psoriatic patients, underscoring the potential systemic involvement of sphingolipids in the disease.

During the de novo synthesis of ceramide, sphinganine is produced via the enzymatic conjunction of serine and palmitoyl-CoA by an enzyme called serine palmityltransferase. Sphinganine is then acylated to form ceramide. Ceramide is subsequently metabolized into glucosylceramide or sphingomyelin and can be further transformed into sphingosine and fatty acids through the action of ceramidase [17]. This enzymatic pathway plays a crucial role in the metabolism and regulation of sphingolipids in the body. Despite their relatively low stratum corneum levels (5–6% of total lipids), these sphingoid bases (SBs) (sphingosine and sphinganine) take part in the regulation of cell proliferation and differentiation, antimicrobial protection, and the upkeep of the integrity of lipid lamellae.

Previous studies investigating the composition of sphingosine and sphinganine in psoriatic skin are limited. However, our findings aligned with the observations made by Sung-Hyuk et al. [17], who reported elevated levels of sphingosine and sphinganine in psoriatic skin. Additionally, Sorokin et al. [26] reported similar results regarding sphinganine levels in psoriatic skin. These consistent findings across different studies provide further support for the involvement of sphingosine and sphinganine in the pathogenesis of psoriasis and highlight their potential significance as indicators or therapeutic targets in the disease [26].

Data regarding the sphingolipid composition of the skin in atopic dermatitis have been reported. Toncic et al. [27] found that levels of sphingosine and sphinganine were elevated in atopic dermatitis in comparison with healthy skin, although no similar differences were observed in non-lesional skin. Interestingly, our study revealed a similar elevation of sphingosine and sphinganine in psoriatic lesions, but we additionally observed an increase in sphingosine levels in non-lesional psoriatic skin. In atopic dermatitis, the ratio of sphinganine over sphingosine presented a progressive reduction from healthy skin to non-lesional and lesional atopic dermatitis skin, as reported by Toncic et al. [27]. These findings highlighted the distinct sphingolipid alterations in different skin conditions and further emphasized the complex role of sphingolipids in atopic dermatitis and psoriasis.

Indeed, Toncic et al. [27] spotted a depletion in the ratio of sphinganine over sphingosine in both lesional and non-lesional skin of individuals with atopic dermatitis. This reduction in the ratio was found to be inversely correlated with the severity of atopic dermatitis in unaffected and lesional skin. These findings suggested that alterations in the sphinganine/sphingosine ratio might play a part in the pathogenesis and severity of atopic dermatitis, highlighting the potential importance of sphingolipid metabolism in this skin condition [27].

In an interesting study by Arikawa et al. [28], it was demonstrated that altered ceramide metabolism in atopic dermatitis may be associated with increased vulnerability to colonization by Staphylococcus aureus in atopic dermatitis patients. The researchers found that levels of sphingosine were significantly decreased in both uninvolved and involved stratum corneum of atopic dermatitis patients compared with healthy individuals. Importantly, this decrease in sphingosine levels was correlated with an increased

psoriasiform dermatitis in mice, both clinically and histologically. Moreover, the amount of IL-17A was depleted in mice skin treated with fingolimod than in mice where phosphate-buffered saline was used alone. These results may offer promising results for treating psoriasis with fingolimod, but we still need proper data on implementing this therapeutic in patients dealing with psoriasis [25].

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differences in the levels of SBs and their ceramide among healthy and affected skin. In both conditions, the changes in SBs and ceramides were more prominent in the lesional skin and were associated with the severity of the disease, indicating the involvement of the immune and inflammatory responses in ceramide metabolism. Interestingly, in non-lesional skin, changes in ceramide composition were also observed, suggesting that alterations in ceramide metabolism may exist even in healthy skin. These findings highlighted the importance of studying ceramide metabolism and its clinical implications [27].

In psoriatic patients, elevated levels of ceramide were observed in the serum. However, the relationship between ceramides in the skin tissue and their influence on serum ceramide levels is not yet fully understood. It remains unclear how alterations in skin ceramide metabolism contribute to changes in serum ceramide levels in psoriasis. Ceramides have been implicated in various comorbidities, including components of metabolic syndrome. Hao et al. [32] informed that metabolic syndrome was a group of abnormalities that enhanced the chance of cardiovascular disease and diabetes. Lee et al. [33] indicated that ceramides have been associated with insulin resistance, dyslipidemia, obesity, and other metabolic abnormalities [33]. However, the specific mechanisms linking ceramides to these comorbidities and their role in psoriasis-related metabolic disturbances require further investigation.

There were several limitations to our study. Firstly, we focused on the measurement of total ceramide levels without assessing the specific subtypes or compositions of ceramides. Different ceramide subtypes may have distinct roles and effects in psoriasis and their contributions to the disease process remain to be elucidated. Future studies could explore specific ceramide subtypes and their associations with psoriasis severity and clinical outcomes. Secondly, the sample size in our study was relatively small. While our findings provided important insights into sphingolipid alterations in psoriasis, larger studies involving a bigger quantity of patients are necessary to establish the significance and severity of sphingolipids in the context of psoriasis. A larger sample size would enhance the statistical power and allow for more robust conclusions. Additionally, our study focused on a specific cohort of patients; thus, the generalizability of our findings to other populations or ethnicities may be limited. Future studies should aim to include diverse patient populations to ensure the broader applicability of the results.

4. Materials and Methods

A total of 15 patients (7 males and 8 females) with active plaque-type psoriasis, at a median age of 51.0 (43.0–66.0) and 17 healthy controls (11 males and 6 females) at a median age of 42.0 (35.5–55.0) were enrolled in the study. The severity of psoriasis was estimated using psoriasis area and severity index (PASI) [34]. Body mass index (BMI) was calculated based on self-reported weight and height. None of the patients or controls were under dietary restriction. History of hypertension, liver disease (e.g., non-alcoholic fatty liver disease (NAFLD)), heart disease, diabetes mellitus, and results of the laboratory tests were collected from hospital records of the patients. Laboratory tests were measured before the treatment. All psoriatic patients gave their written informed consent before enrolment in the study. The study protocol was approved by the local university bioethical committee (no. APK.002.500.2021) according to the principles of the Helsinki Declaration. Peripheral blood samples were taken before starting the treatment after overnight fasting. After centrifugation, the serum was stored at −80 °C until it was analyzed. A size of 3 mm punch biopsies were obtained from both the non-lesional and lesional skin from the trunk of psoriatic patients following local anesthesia. Samples from healthy patients were collected from the wound edge during a planned inguinal hernia operation under general anesthesia. Furthermore, in line with the PASI score, we assessed the clinical features of erythema, induration, and desquamation within the chosen psoriatic lesion for biopsy. The scoring system ranged from 0 to 4.

4.1. Sphingolipid Analysis

The content of sphingosine, sphinganine, sphingosine-1-phosphate, and SA1P was measured simultaneously according to the method of Min et al. (2002) [35]. Briefly, tissues were homogenized in a solution composed of 25 mM HCl and 1 mM NaCl. Acidified methanol and internal standards (10 pmol of C17-sphingosine and 30 pmol of C17-sphingosine-1-phosphate; Avanti Polar Lipids (Alabaster, AL, USA)) were added and the samples were ultrasonicated in ice-cold water for 1 min. Lipids were then extracted by the addition of chloroform, 1 M NaCl and 3 N NaOH. The alkaline aqueous phase containing sphingosine-1-phosphate and SA1P was transferred to a fresh tube. The residual phosphorylated sphingoid bases in the chloroform phase were reextracted twice with methanol/1 M NaCl (1:1, *v*/*v*) solution and then all the aqueous fractions were combined. The amount of sphingosine-1-phosphate and SA1P was determined indirectly after dephosphorylation to sphingosine and sphinganine, respectively, with the use of alkaline phosphatase (bovine intestinal mucosa; Fluka (Seelze, Germany)). To improve the extraction yield of released sphingosine and sphinganine, some chloroform was carefully placed at the bottom of the reaction tubes. The chloroform fractions containing free sphingosine and sphinganine or dephosphorylated sphingoid bases were washed three times with alkaline water (pH adjusted to 10.0 with ammonium hydroxide) and then evaporated under a nitrogen stream. The dried lipid residues were redissolved in ethanol, converted to their o-phthalaldehyde derivatives, and analyzed using a high-performance liquid chromatography (HPLC) system (PROSTAR; Varian Inc. (Palo Alto, CA, USA)) equipped with a fluorescence detector and C18 reversed-phase column (OMNISPHER 5, 4.6-150 mm; Varian Inc.). The isocratic eluent composition of acetonitrile: water (9:1, *v*/*v*) (Merck, Darmstadt, Germany) and a flow rate of 1 mL min^{-1} were used.

The content of ceramide was determined by the procedure previously described by Baranowski et al. [36]. A small volume of the chloroform phase, containing lipids extracted as described above, was transferred to a fresh tube containing 31 pmol of C17-sphingosine as an internal standard. The samples were evaporated under a nitrogen stream, redissolved in 1 M KOH in 90% methanol, and heated at 90 °C for 60 min to convert ceramide into sphingosine. This digestion procedure does not convert complex sphingolipids, such as sphingomyelin, galactosylceramide, or glucosylceramide, into free sphingoid bases (Bose et al., 1998). Samples were then partitioned by the addition of chloroform and water. The upper phase was discarded and the lower phase was evaporated under nitrogen. The content of free sphingosine liberated from ceramide was then analyzed using HPLC, as described above. The calibration curve was prepared using N-palmitoylsphingosine (Avanti Polar Lipids) as a standard. The chloroform extract used for the analysis of ceramide levels also contained small amounts of free sphingoid bases. Therefore, the content of ceramide was corrected for the level of free sphingosine determined in the same sample.

4.2. Statistical Analysis

The obtained data were analyzed using R (ver. 4.2.2) statistical package. At the onset of analyses, the continuous data were checked for normality (Shapiro–Wilk test) and homoscedasticity (Fligner–Killeen test). Based on the above, the between-group comparisons were made using parametric (ANOVA with subsequent pairwise Student's *t*-tests) or non-parametric methods (Kruskall–Wallis test with subsequent pairwise Wilcoxon tests). The obtained *p*-values were adjusted for multiple comparisons (Benjamini–Hochberg correction). Corrected *p*-values lower than 0.05 were considered to be statistically significant. The results were presented in the form of box–whisker plots. The dependence between the variables of interest was determined based on Pearson's coefficients and depicted using heatmaps.

5. Conclusions

The observed differences in the profile of bioactive sphingolipids between psoriatic skin and healthy skin indicated a significant contribution of these lipids in the development

of inflammation in psoriasis. These differences, which were more pronounced in psoriatic skin, highlighted the potential influence of the studied parameters on the inflammatory processes associated with the disease.

Furthermore, the finding that sphingolipid metabolism was impaired not only in the affected skin but also in the clinically unchanged skin of psoriasis patients suggested a broader systemic involvement of lipid dysregulation in psoriasis. This implied that lipid metabolism abnormalities may extend beyond the visible psoriatic lesions and might involve the overall pathogenesis of the disease. Subsequent research is needed to fully understand the consequences of these lipid abnormalities and their potential as therapeutic targets in psoriasis management.

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References

1. Parisi, R.; Symmons, D.P.M.; Griffiths, C.E.M.; Ashcroft, D.M. Global epidemiology of psoriasis: A systemic review of incidence and prevalence. *J. Invest. Dermatol.* **2013**, *133*, 377–385. [CrossRef] [PubMed]
2. Parisi, R.; Iskander, I.Y.K.; Kontopantelis, E.; Augustin, E.; Griffiths, C.E.M.; Ashcroft, D.M. National, regional, and worldwide epidemiology of psoriasis: Systemic analysis and modeling study. *BMJ* **2020**, *369*, m1590. [CrossRef] [PubMed]
3. Zheng, M.; Jullien, D.; Eyerich, E. The prevalence and Disease Characteristics of generalized Pustular Psoriasis. *Am. J. Clin. Dermatol.* **2022**, *23* (Suppl. S1), 5–12. [CrossRef] [PubMed]
4. Rendon, A.; Schakel, K. Psoriasis Pathogenesis and Treatment. *Int. J. Mol. Sci.* **2019**, *20*, 1475. [CrossRef]
5. Lowes, M.A.; Bowcock, A.M.; Krueger, J.G. Pathogenesis and therapy of psoriasis. *Nature* **2007**, *445*, 866–873. [CrossRef]
6. Laporte, M.; Galand, P.; Fokan, D.; de Graef, C.; Heenen, M. Apoptosis in established and healing psoriasis. *Dermatology* **2000**, *200*, 314–316. [CrossRef]
7. Wrone-Smith, T.; Mitra, R.S.; Thompson, C.B.; Jasty, R.; Castle, V.P.; Nickoloff, B.J. Keratinocytes derived from psoriatic plaques are resistant to apoptosis compared with normal skin. *Am. J. Pathol.* **1997**, *151*, 1321–1329.
8. Chiricozzi, A.; Raimondo, A.; Lembo, S.; Fausti, F.; Dini, V.; Costanzo, A.; Monfrecola, G.; Balato, N.; Ayala, F.; Romanelli, M.; et al. Crosstalk between skin inflammation and adipose tissue-derived products: Pathogenic evidence linking psoriasis to increases adiposity. *Expert. Rev. Clin. Immunol.* **2016**, *12*, 1299–1308. [CrossRef]
9. Fernández-Armenteros, J.M.; Gómez-Arbonés, X.; Buti-Soler, M.; Betriu-Bars, A.; Sanmartin-Novell, V.; Ortega-Bravo, M.; Martínez-Alonso, M.; Garí, E.; Portero-Otín, M.; Santamaria-Babi, L.; et al. Psoriasis, metabolic syndrome and cardiovascular risk factors. A population-based study. *J. Eur. Acad. Dermatol. Venereol.* **2019**, *33*, 128–135. [CrossRef]
10. Nakhwa, Y.C.; Rashmi, R.; Basavaraj, K.H. Dyslipidemia in Psoriasis: A Case Controlled Study. *Int. Sch. Res. Not.* **2014**, *2014*, 729157. [CrossRef]
11. Hannun, Y.A.; Obeid, L.M. Sphingolipids and their metabolism in physiology and disease. *Nat. Rev. Mol. Cell Biol.* **2018**, *19*, 175–191. [CrossRef] [PubMed]

12. Moskot, M.; Bochenska, K.; Jakobkiewicz-Banecka, J.; Banecki, B.; Gabig-Ciminska, M. Abnormal Sphingolipid World in Inflammation Specific for Lysosomal Storage Disease and Skin Disorders. *Int. J. Mol. Sci.* **2018**, *19*, 247. [CrossRef] [PubMed]
13. Checa, A.; Xu, N.; Sar, D.G.; Haeggstrom, J.Z.; Stahle, M.; Wheelock, C.E. Circulating levels of sphingosine-1-phosphate are elevated in severe, but not mild psoriasis and are unresponsive to anti-TNF-α treatment. *Sci. Rep.* **2015**, *5*, 12017. [CrossRef]
14. Mysliwiec, H.; Baran, A.; Harasim-Symbor, E.; Choromanska, B.; Mysliwiec, P.; Justyna Milewska, A.; Chabowski, A.; Flisiak, I. Increase in circulating sphingosine-1-phosphate and decrease in ceramide levels in psoriatic patients. *Arch. Dermatol. Res.* **2017**, *309*, 79–86. [CrossRef] [PubMed]
15. Lew, B.-L.; Cho, Y.; Kim, J.; Sim, W.Y.; Kim, N.I. Ceramides and cell signaling molecules in psoriatic epidermis: Reduced levels of ceramides, PKC-alpha, and JNK. *J. Korean Med. Sci.* **2006**, *21*, 95–99. [CrossRef] [PubMed]
16. Herzinger, T.; Kleuser, B.; Schäfer-Korting, M.; Christian Korting, H. Sphingosine-1-phosphate signaling and the skin. *Am. J. Clin. Dermatol.* **2007**, *8*, 329–336. [CrossRef]
17. Sung-Hyuk, M.; Kim, J.Y.; Song, E.H.; Shin, M.K.; Cho, Y.H.; Kim, N.I. Altered Levels of Sphingosine and Sphinganine in Psoriatic Epidermis. *Ann. Dermatol.* **2013**, *25*, 321–326. [CrossRef]
18. Maceyka, M.; Harikumar, K.B.; Milstein, S.; Spiegel, S. Sphingosine-1-Phosphate signaling and its role in disease. *Trends Cell Biol.* **2012**, *22*, 50–60. [CrossRef]
19. Kowalski, G.M.; Carey, A.L.; Selathurai, A.; Kingwell, B.A.; Bruce, C.R. Plasma Sphingosine-1-Phosphate Is Elevated in Obesity. *PLoS ONE* **2013**, *8*, e72449. [CrossRef]
20. Kozłowska, D.; Harasim-Symbor, E.; Mysliwiec, H.; Milewska, A.J.; Chabowski, A.; Flisiak, I. Lipid profile disturbances may predispose psoriatic patients to liver dysfunction. *Postep. Dermatol. Alergol.* **2021**, *38*, 310–318. [CrossRef]
21. Nada, H.A.; Elshabrawy, M.M.; Ismail, N.I.; Hassan, E.T.; Jafferany, M.; Elsaie, M.L. Therapeutic implications and role of serum sphingolipids on psoriasis severity after narrow-band ultraviolet B treatment: A cross-sectional controlled study. *Dermatol. Ther.* **2020**, *33*, e13988. [CrossRef] [PubMed]
22. Vaclavkova, A.; Chimenti, S.; Arenberger, P.; Holló, P.; Sator, P.G.; Burcklen, M.; Stefani, M.; D'Ambrosio, D. Oral ponesimod in patients with chronic plaque psoriasis: A randomised, double-blind, placebo-controlled phase 2 trial. *Lancet* **2014**, *384*, 2036–2045. [CrossRef] [PubMed]
23. D'Ambrosio, D.; Steinmann, J.; Brossard, P.; Dingemanse, J. Differential effects of ponesimod, a selective S1P1 receptor modulator, on blood-circulating human T cell subpopulations. *Immunopharmacol. Immunotoxicol.* **2015**, *37*, 103–109. [CrossRef] [PubMed]
24. De Biase, S.; Lorenzut, S.; Barbarino, G.; Sanvilli, N.; D'Anna, L.; Dolso, P.; Valente, M.; Gigli, G.L. Clinical Remission of Psoriasis during Fingolimod Therapy for Multiple Sclerosis: A Case Report. XLVI National Congress in Genoa, 10–13.10.2015. Available online: http://congress.wooky.it/web/eventi/neuro2015/poster/pdf/pst211.pdf (accessed on 13 October 2015).
25. Okura, I.; Kamata, M.; Asano, Y.; Mitsui, A.; Shimizu, T.; Sato, S.; Tada, Y. Fingolimod ameliorates imiquimod-induced psoriasiform dermatitis by sequastrating interleukin-17 producing ?d cells in secondary lymph nodes. *J. Dermatol. Sci.* **2021**, *102*, 116–125. [CrossRef] [PubMed]
26. Sorokin, A.V.; Domenichiello, A.F.; Dey, A.K.; Yuan, Z.K.; Goyal, A.; Rose, S.M.; Playford, M.P.; Ramsden, C.E.; Mehta, N.N. Bioactive Lipid Mediator Profiles in Human Psoriasis Skin and Blood. *J. Invest. Dermatol.* **2018**, *138*, 1518–1528. [CrossRef]
27. Toncic, R.J.; Jakasa, I.; Hadzavdic, S.L.; Goorden, S.M.; Ghauharali-van der Vlugt, K.M.; Stet, F.S.; Balic, A.; Petkovic, M.; Pavicic, B.; Zuzul, K.; et al. Altered Levels of Sphingosine, Sphinganine, and Their Ceramides in Atopic Dermatitis Are Related to Skin Barrier Function, Disease Severity and Local Cytokine Milieu. *Int. J. Mol. Sci.* **2020**, *21*, 1958. [CrossRef]
28. Arikawa, J.; Ishibashi, M.; Kawashima, M.; Takagi, Y.; Ichikawa, Y.; Imokawa, G. Decreased levels of sphingosine, a natural antimicrobial agent, may be associated with vulnerability of the stratum corneum from patients with atopic dermatitis to colonization by Staphylococcus aureus. *J. Invest. Dermatol.* **2002**, *119*, 433–439. [CrossRef]
29. Tawada, C.; Kanoh, H.; Nakamura, M.; Mizutani, Y.; Fujisawa, T.; Banno, Y.; Seishima, M. Interferon-γ decreases ceramides with long-chain fatty acids: Possible involvement in atopic dermatitis and psoriasis. *J. Invest. Dermatol.* **2014**, *134*, 712–718. [CrossRef]
30. Alessandrini, F.; Stachowitz, S.; Ring, J.; Behrendt, H. The level of prosaposin is decreased in the skin of patients with psoriasis vulgaris. *J. Invest. Dermatol.* **2001**, *116*, 394–400. [CrossRef]
31. Cho, Y.; Lew, B.L.; Seong, K.; Kim, N.I. An Inverse Relationship Between Ceramide Synthesis and Clinical Severity in Patients with Psoriasis. *J. Korean Med. Sci.* **2004**, *19*, 859–863. [CrossRef]
32. Hao, Y.; Zhu, Y.-J.; Zou, S.; Zhou, P.; Hu, Y.-W.; Zhao, Q.-X.; Gu, L.-N.; Zhang, H.-Z.; Wang, Z.; Li, J. Metabolic Syndrome and Psoriasis: Mechanisms and Future Directions. *Front. Immunol.* **2021**, *12*, 711060. [CrossRef] [PubMed]
33. Lee, S.; Kim, S.A.; Kim, Y.; Kim, J.; Hong, G.; Hong, J.; Choi, K.; Eom, C.S.; Baik, S.; Lee, M.K.; et al. Genetic Variants Associated with Elevated Plasma Ceramides in Individuals with Metabolic Syndrome. *Genes* **2022**, *13*, 1497. [CrossRef]
34. Schmitt, J.; Wozel, G. The psoriasis area and severity index is the adequate criterion to define severity in chronic plaque-type psoriasis. *Dermatology* **2005**, *210*, 194–199. [CrossRef] [PubMed]

35. Min, J.K.; Yoo, H.S.; Lee, E.Y.; Lee, W.J.; Lee, Y.M. Simultaneous quantitative analysis of sphingoid base 1-phosphates in biological samples by o-phthalaldehyde precolumn derivatization after dephosphorylation with alkaline phosphatase. *Anal. Biochem.* **2002**, *303*, 167–175. [CrossRef] [PubMed]
36. Baranowski, M.; Zabielski, P.; Blachnio, A.; Gorski, J. Effect of exercise duration on ceramide metabolism in the rat heart. *Acta Physiol.* **2008**, *192*, 519–529. [CrossRef]

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Crosstalk between Serum and Skin Sphingolipids in Psoriasis

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Abstract: Psoriasis is a chronic, complex, immunological disorder, which may lead to many different systemic complications. Sphingolipids, including ceramide, are bioactive lipids, which take part in the regulation of immune reactions, cell growth, and apoptosis. Twenty psoriatic patients and twenty-eight control subjects were included in the study. Skin (both lesional and non-lesional) and serum samples were collected from both the control group and the psoriatic patients. The levels of sphingosine (SFO), sphingosine-1-phosphate (S1P), sphingomyelin, sphinganine (SFA), sphinganine-1-phosphate (SFA1P), and ceramide (CER) were assessed in both tissue (t) and serum (s) samples using high-performance liquid chromatography (HPLC). We identified elevated serum levels of SFO, S1P, SFA, and SFA1P in psoriatic patients when compared to healthy individuals. As far as the lesional skin and serum of psoriatic patients are concerned, we demonstrated positive associations between CER_t and CER_s, SFA_t and CER_s, and SFO_t and CER_s. Additionally, we found negative correlations in the non-lesional skin and serum of psoriatic patients, including SFO_t vs. SFO_s, CER_t vs. SFA_s, CER_t vs. SFO_s, and SFO_t vs. SFA_s. Finally, we observed a positive correlation between S1P and SFA1P in both the serum samples of psoriatic patients and the serum samples of the control group. In this study, we did not observe any correlations between psoriasis area and severity index (PASI) scores and sphingolipid levels. In conclusion, our findings indicate an interplay between skin and serum lipids in psoriatic patients, which is not observed in healthy individuals.

Keywords: psoriasis; sphingosine-1-phosphate; sphinganine; sphingosine; sphinganine-1-phosphate; ceramide

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1. Introduction

Psoriasis is a chronic, immune-mediated, non-contagious, multidisciplinary disorder that is widespread across the globe [1]. The estimated prevalence of psoriasis ranges from 0.27% to 11.4%, predominantly observed in the adult population [2]. Psoriasis has various subtypes, including inverse, plaque, erythrodermic, pustular, and guttate forms. The most prevalent subtype is plaque psoriasis, accounting for almost 90% of cases [3]. Plaque psoriasis is distinguished by well-defined, elevated, and erythematous skin lesions covered with silver scales [4]. The accelerated cell cycle of psoriatic keratinocytes and their resistance to apoptosis contributes to keratinocyte hyperproliferation, which is evident in histopathological examinations through the presence of parakeratosis and acanthosis [5].

Due to its inflammatory nature, psoriasis is not only associated with nail and joint involvement but can also coexist with a range of systemic conditions [6]. Some examples include the presence of metabolic syndrome, characterized by hypertension, hyperlipidemia, insulin resistance, and obesity. These factors, over time, can contribute to the development of conditions such as coronary artery disease, atherosclerosis, type 2 diabetes, and even

myocardial infarction [7]. Psoriatic patients commonly experience abnormal lipid levels. Specifically, their serum levels of low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, triglycerides, and total cholesterol are frequently elevated as compared to individuals without psoriasis. Concurrently, high-density lipoprotein (HDL) cholesterol tends to be diminished in individuals with psoriasis [8]. Despite the increasing number of studies investigating the potential mechanisms underlying psoriasis, the exact etiology of this disease remains unclear. Sphingolipids are one of the most important groups of human lipids [9]. Their common feature is a sphingoid core, which includes sphingosine. Precisely, the sphingoid basis is manufactured by the combination of a fatty acid (usually palmitate) and amino acid (mainly serine) [10]. Interestingly, sphingolipids constitute an exceptional subtype of lipids, capable of functioning both as structural components and signaling molecules [11]. Sphingolipids have diverse roles, including participation in cell growth, regulation of cell death, cell adhesion, modulation of immune activity, nutrient uptake, angiogenesis, inflammation, metabolism, autophagy, response to reactive oxygen species, and resistance against various stressors. Various types of sphingolipids exist, including sphingosine (SFO), sphingosine-1-phosphate (S1P), ceramides (CER), ceramide-1-phosphate (C1P), sphinganine (SFA), sphinganine-1-phosphate (SFA1P), sphingomyelin, galactosylceramide, glucosylceramide, and lactosylceramide [9]. Among the highly bioactive sphingolipids, S1P and CER stand out. These two distinct sphingolipids are associated with contrasting functions. CER primarily governs processes such as necrosis, apoptosis, stress responses, inflammation, and cell cycle arrest. In contrast, S1P primarily functions as a signaling lipid, regulating cell growth, migration, differentiation, and proliferation. Interestingly, S1P, when binding to cell surface receptors, can also initiate the process of angiogenesis [12]. A reduced concentration of CER in the skin is commonly associated with pathological skin symptoms, such as dryness and compromised skin barrier function. This phenomenon is often observed in such conditions as atopic dermatitis, psoriasis, and xerosis [13]. On the other hand, in different types of psoriasis, elevated levels of ceramides (C16:0, C18:0, C20:0, C22:0, C24:1), not only in plasma but also in the skin, were observed. Exceptionally, so far, C12:0-CER is the only sphingolipid that has been found to be decreased in non-lesional skin vs. lesional skin of psoriatic patients. The levels of hexosylceramide, or lactosylceramide, remain unchanged between psoriatic and non-psoriatic people. The degree of sphingomyelin is abnormal in psoriatic skin in a fatty acid chain length-dependent manner; specifically, the increase in C16:0, C24:1, and C24:0 sphingomyelins is marked [11].

In addition to their role in the pathogenesis of psoriasis, sphingolipids (mostly CER) can serve in human serum as indicators of metabolic disorders and atherosclerotic cardiovascular conditions. For instance, diabetic neuropathy is associated with higher plasma levels of C24 and C26 ceramides, and deoxy-C24 ceramide rates of C18:1 and C18:0 ceramides are also perceived as essential markers of cardiovascular events in healthy people. Moreover, an elevated level of C18:1 ceramide is regarded as an indicator of necrosis after coronary angiography procedures [9]. Furthermore, sphingomyelin and C24:1 are strongly connected with the cardiovascular death rate. Moreover, increased levels of C22:0 and C24:0 in plasma may indicate a slight improvement in verbal memory in response to exercise among patients with coronary artery disease, in whom these cognitive abilities are typically impaired. Furthermore, there is an inverse correlation observed between the serum levels of S1P and atherosclerotic disease. Additionally, deoxysphingolipids could potentially serve as biomarkers for the exacerbation of diabetes mellitus [9].

In recent years, researchers have predominantly focused on examining lipid levels in the serum and tissues of individuals with psoriasis. However, the precise connection between cutaneous and tissue sphingolipids in patients with psoriasis remains unclear. This present study aims to elucidate the relationship between bioactive sphingolipids in serum and psoriatic skin, in comparison to unaffected skin, in patients with psoriasis.

2. Results

2.1. Study Population

Twenty patients (13 males and 7 females) with active plaque-type psoriasis and twenty-eight subjects from the control group (8 males and 20 females) were included in the study. The mean age in the control group was 45.6 years, while in the psoriatic group, it was 53.2 years. The mean duration of psoriasis was 18.33 years, with a mean body mass of 87.2 kg, a mean height of 171.3 cm, and a median BMI of 29.9. The majority of psoriatic patients, $n = 9$, were overweight (45%), followed by $n = 6$ (30%) suffering from obesity, and $n = 5$ (25%) with a normal weight. Within the psoriatic group, 1 (5%) patient exhibited a mild form of psoriasis (PASI < 10), 13 (65%) individuals had a moderate form (PASI 10–20), and 6 (30%) suffered from severe psoriasis (PASI > 20). Table 1 presents the primary clinical characteristics of both the psoriatic and control groups. Our observations revealed statistically higher values ($p < 0.05$) of BMI, body mass, TAG, CRP, and TAG in psoriatic patients when compared to the control group. Table 2 presents concentrations of lipids measured in the psoriatic lesional skin, non-lesional psoriatic skin, skin of healthy subjects, and serum of psoriatic and healthy subjects. We observed statistically significant differences ($p < 0.05$) characterized by elevated levels of CER, S1P, SFA1P, SFA, and SFO in psoriatic lesional skin when compared to both psoriatic non-lesional skin and the skin of healthy subjects (Figure 1). Additionally, we found statistically significant variations ($p < 0.05$) featuring increased levels of CER and SFO in psoriatic non-lesional skin as compared to the skin of healthy subjects (Figure 1). Based on the serum sphingolipid concentrations, we observed a statistically significant difference ($p < 0.05$), characterized by elevated levels of S1P, SFA, and SFA1P, in the serum of psoriatic patients in contrast to the serum of healthy subjects (Figure 1). In this article, we have focused on the general amount of ceramides, without measuring the acyl chain composition.

Table 1. Clinical and biochemical characteristics of the control group (CTRL) and psoriatic patients (PSO).

Variables	CTRL	PSO
Age (years)	45.6 ± 15.14	53.2 ± 15.66
Body mass (kg)	73.8 ± 9.47	87.2 ± 15.95 a
Height (cm)	171.2 ± 7.17	171.3 ± 8.6
BMI (kg/m2)	25.18 ± 2.84	29.9 ± 6.49 a
CRP (mg/dL)	1.4 ± 0.83	8.2 ± 12.44 a
Glucose (mg/dL)	97.1 ± 16.58	89.1 ± 17.4
TAG (mg/dL)	81.9 ± 35.83	116.35 ± 40.89 a
AST (U/L)	23.3 ± 8.53	24.1 ± 12.42
ALT (U/L)	21.1 ± 16.09	22.8 ± 12.4
Sex (no. female/no. male)	20/8	7/13 a

Data are presented as the mean ± standard deviation. a—different vs. PSO ($p < 0.05$); BMI—body mass index, CRP—C reactive protein, TAG—triglycerides, AST—aspartate transaminase, ALT—alanine transaminase.

Table 2. Concentration of sphingolipids in the skin (pmol/mg of tissue, mean (standard deviation)) and serum (pmol/mL of serum, mean (standard deviation)).

Sphingolipid	CTRL_t	PSO_t (nl)	PSO_t (l)	CTRL_s	PSO_s
CER	7.82 (3.62)	24.96 (13.69) a	69.19 (28.71) ab	6920.52 (1254.24)	6882.53 (1284.32)
S1P	0.15 (0.04)	0.18 (0.07)	0.41 (0.18) ab	252.41 (100.04)	528.77 (121.23) a
SFA1P	0.03 (0.01)	0.03 (0.01)	0.07 (0.03) ab	33.59 (12.81)	62.13 (10.95) a
SFA	0.16 (0.04)	0.23 (0.17)	0.68 (0.43) ab	6.13 (2.02)	7.83 (1.87) a
SFO	0.29 (0.09)	0.6 (0.53) a	1.9 (0.84) ab	28.55 (9.49)	33.53 (6.54)
SFA/SFO	0.58 (0.12)	0.42 (0.1) a	0.35 (0.15) ab	0.24 (0.11)	0.24 (0.06)

CTRL—control subjects; PSO—psoriatic patients; suffix_t—tissue; suffix_s—serum; (nl)—non-lesional; (l)—lesional; CER—ceramide; S1P—sphingosine-1-phosphate; SFA—sphinganine; SFA1P—sphinganine-1-phosphate; SFA/SFO—sphinganine/sphingosine ratio; SFO—sphingosine; a—different vs. CTRL ($p < 0.05$); b—different vs. PSO ($p < 0.05$).

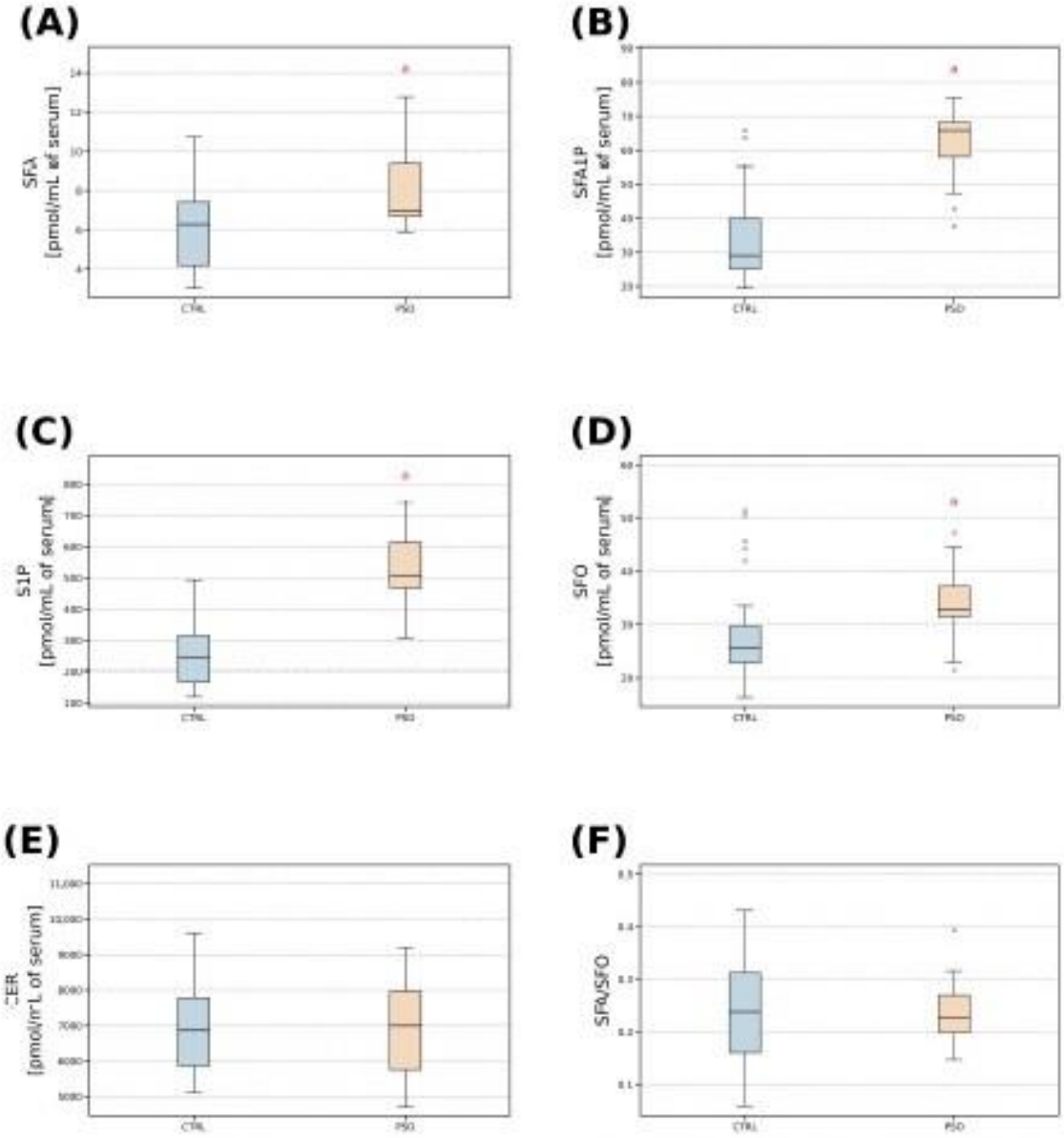

Figure 1. Comparison between sphingolipids in healthy (CTRL) and psoriatic (PSO) patients' serum. (**A**) Amount of sphinganine (SFA) (pmol/mL of serum). (**B**) Amount of sphinganine-1-phosphate (SFA1P) (pmol/mL of serum). (**C**) Amount of sphingosine-1-phosphate (S1P) (pmol/mL of serum). (**D**) Amount of sphingosine (SFO) (pmol/mL of serum). (**E**) Amount of ceramide (CER) (pmol/mL of serum). (**F**) The ratio of sphinganine and sphingosine. Significance markers: "a" signifies different vs. CTRL ($p < 0.05$).

2.2. *Sphingolipid Parameters*

It becomes evident that the concentrations of SFO, SFA, S1P, and SFA1P in the serum of patients with psoriasis were significantly elevated ($p < 0.05$) when compared to the levels of these sphingolipids in healthy individuals (Figure 1 and Table 1). While ceramide levels were found to be higher in psoriatic patients, the difference did not achieve statistical significance in comparison to healthy subjects.

We observed negative Pearson's correlations between various variables in non-lesional psoriatic skin and the serum of psoriatic patients, all of which were statistically significant. Specifically, the correlations include SFO_t vs. SFO_s ($p < 0.027$), CER_t vs. SFA_s ($p < 0.040$), CER_t vs. SFO_s ($p < 0.044$), and SFO_t vs. SFA_s ($p < 0.048$) (Figure 2A).

A positive Pearson's correlation was evident between several variables in lesional psoriatic skin and the serum of psoriatic patients. Specifically, statistically significant associ-

ations were observed between CER_t and CER_s ($p < 0.026$), SFA_t and CER_s ($p < 0.006$), and SFO_t and CER_s ($p < 0.039$) (Figure 2B).

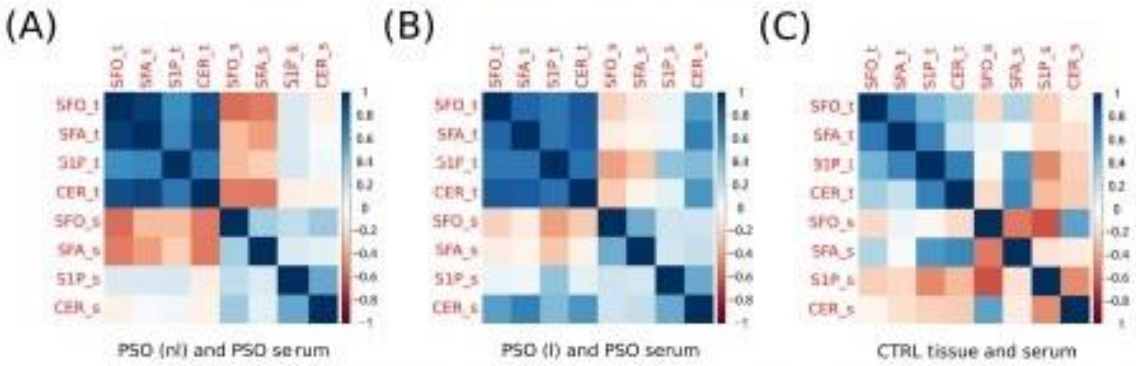

Figure 2. Correlation matrix (heatmap). Pearson correlation coefficients depicted as the shades of blue (positive correlation) or red (negative correlation). (**A**) Correlation matrix for psoriatic non-lesional (PSO (nl)) skin and serum. (**B**) Correlation matrix for psoriatic lesional (PSO (l)) skin and serum. (**C**) Correlation matrix for control (CTRL) skin and serum. CER—ceramide; S1P—sphingosine-1-phosphate; SFA—sphinganine; SFA1P—sphinganine-1-phosphate; SFO—sphingosine; suffix_s—serum; suffix_t—tissue.

There were no significant correlations between serum and skin sphingolipids in the healthy skin and serum of the control group (Figure 2C).

We identified significant positive Pearson's correlations within the serum of both psoriatic patients and the control group, specifically between S1P and SFA1P. It is noteworthy that PASI scores did not exhibit significant correlations with sphingolipids in psoriatic serum. The correlations between erythema, induration, and desquamation with PASI, as well as SFA and SFO with SFA/SFO, were readily evident due to their calculated nature (Figure 3A,B).

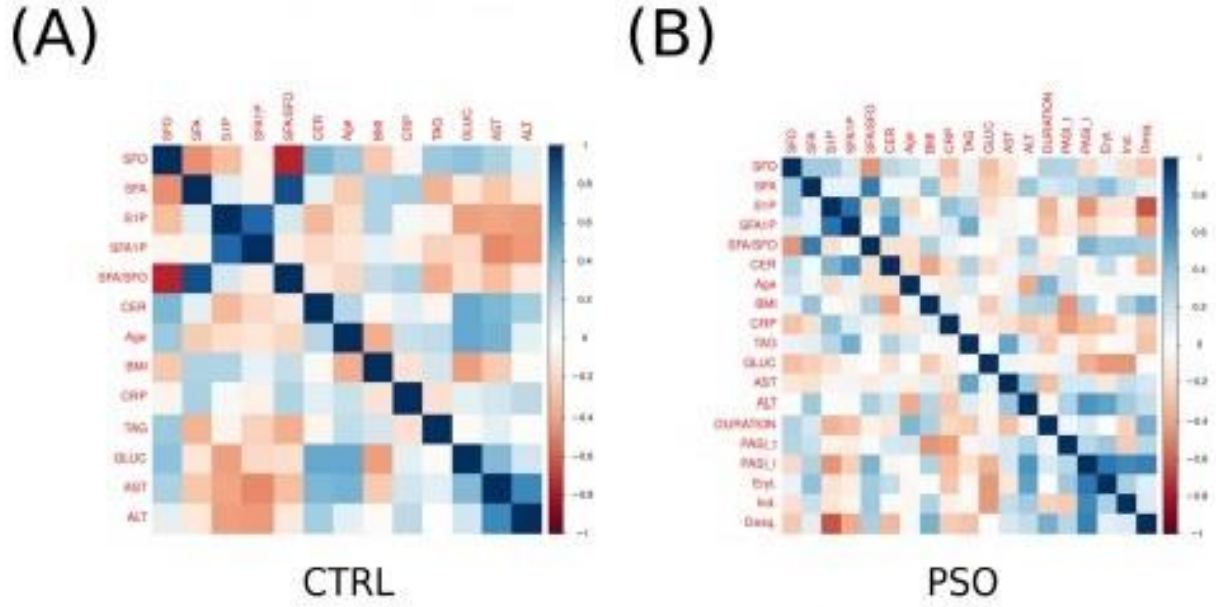

Figure 3. Correlation matrix (heatmap). Pearson correlation coefficients are depicted as shades of blue (positive correlation) or red (negative correlation). (**A**) Correlation matrix for non-psoriatic (CTRL) serum. (**B**) Correlation matrix for psoriatic (PSO) serum. ALT—alanine transaminase, AST—aspartate transaminase, BMI—body mass index, CER—ceramide, CRP—C-reactive protein, GLUC—glucose, S1P—sphingosine-1-phosphate, SFA—sphinganine, SFA1P—sphinganine-1-phosphate, SFO—sphingosine, TAG—triglycerides.

3. Discussion

In this study, we aimed to elucidate the associations between sphingolipid levels in both healthy and psoriatic patients, taking into consideration clinical and laboratory data. We conducted an assessment and comparison of the concentrations of bioactive sphingolipids in both lesional and non-lesional skin, as well as serum samples from both healthy individuals and those with psoriasis. To the best of our knowledge, this comprehensive analysis has not been previously undertaken.

Our results reveal significant elevations in the serum levels of SFO, SFA, S1P, and SFA1P among psoriatic patients compared to the control group. In addition, the levels of ceramides were higher in patients with psoriasis, although this increase did not reach statistical significance when compared to healthy individuals.

3.1. The Role of Sphingosine-1-Phosphate

In our study, we identified elevated S1P levels in serum samples collected from patients with psoriasis when compared to the serum of healthy individuals (Figure 1). Looking at the function of S1P, it is a signaling molecule that plays an essential role in regulating angiogenesis, inflammation cascade, and vascular permeability [14]. In our study, we discovered a positive correlation between S1P and SFA1P in psoriatic serum (Figure 3).

Moreover, the raised plasma levels of S1P are noted not only in psoriasis but also in patients with obesity, in comparison to normal-weight people. It may be pointed out that S1P may have an expanded influence on various pathological disorders, and not only in psoriasis. Clearly, S1P has been well documented to correlate with metabolic irregularities, such as adiposity or insulin resistance. More precisely, there is a significant link between S1P and elements of metabolic syndrome; for example, fasting plasma insulin, total and LDL cholesterol levels, body fat percentage, and waist circumference are well described [15]. Furthermore, the aforementioned study revealed that psoriatic patients exhibited elevated serum concentrations of S1P, along with increased levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), when compared to non-psoriatic patients [16]. These findings highlight a potential connection between the level of S1P, liver function, and metabolic disturbances in psoriatic patients.

S1P is well known for its ability to induce keratinocyte differentiation, exert antiproliferative and pro-inflammatory effects, and inhibit the growth of epidermal cells in mouse models of psoriasis, as demonstrated by Vaclavkova et al. [17]. Ponesimod is a selective modulator of sphingosine 1-phosphate receptor 1 (S1PR1). Its main role is blocking the process of the outflux of T cells from lymphoid organs. It is presumed that the inhibition of S1PR1 prevents the accumulation of pathogenic lymphocytes in both the skin and circulation, presenting a potentially successful approach for the treatment of psoriasis [17]. Moreover, D'Ambrosio et al. [18] reported promising results from phase II studies regarding the efficacy of ponesimod in relapsing–remitting psoriasis and also on multiple sclerosis. Their research indicates that lymphocyte reduction can establish the background for a selective S1PR1 modulator in multiple chronic and autoimmune diseases: for example, psoriasis. The quantity of peripheral blood T cells and B blood cells was reduced following the administration of 8 mg ponesimod. CD3+ and CD20+ counts were depleted significantly after the administration of 20–75 mg of ponesimod. Summing up, this paper suggests that ponesimod may lower the inflammatory cells, consequently reducing the inflammation process in psoriasis, which is of course one of the backgrounds of this skin disease [18].

3.2. Characteristics of Sphingosine and Sphinganine

In our study, we have made an intriguing observation of significantly elevated concentrations of both SFA and SFO in psoriatic serum, in comparison to healthy serum (Figure 1). We spotted a negative Pearson's correlation between SFO_t vs. SFO_s ($p < 0.027$), CER_t vs. SFA_s ($p < 0.040$), CER_t vs. SFO_s ($p < 0.044$), and SFO_t vs. SFA_s ($p < 0.048$) in non-lesional psoriatic skin and the serum of psoriatic patients, which were all statistically significant ($p < 0.05$). Moreover, we describe positive Pearson's correlations between

SFA_t vs. CER_s ($p < 0.006$) and SFO_t vs. CER_s ($p < 0.039$) in lesional psoriatic skin and the serum of psoriatic patients, which are all statistically significant. The abovementioned correlations are presented in Figure 2.

The aforementioned results, detailing lipid abnormalities present in patients with psoriasis, emphasize the potential correlation between skin and serum lipids in the context of psoriasis and may elucidate the systemic involvement of sphingolipids and their interactions in this disease.

SFA is manufactured through the enzymatic combination of serine and palmitoyl-CoA by an enzyme called serine palmityltransferase. Afterwards, SFA is acylated to the CER. Subsequently, it is metabolized into glucosylceramide or sphingomyelin and may be next transformed into SFO and fatty acids via the action of an enzyme called ceramidase [19]. This enzymatic pathway is essential in the regulation and metabolism of sphingolipids in the human body. However, the relatively modest proportion (5–6% of total lipids) of these sphingoid bases, namely SFO and SFA, within the stratum corneum, holds significant importance in cell differentiation and proliferation, the preservation of lipid lamellae integrity, and antimicrobial protection.

Previous studies investigating the composition of SFO and SFA in psoriatic skin are limited. Regarding the changes in SFO and SFA in psoriatic serum, we are the first authors to describe these alterations. However, our scores are compatible with the findings presented by Sung-Hyuk et al. [19], who noticed an elevated amount of SFO and SFA, but only in psoriatic skin. Furthermore, Sorokin et al. [20] also show similar results regarding SFA quantity in the skin of psoriatic patients. These consistent findings across limited research provide strong evidence for the involvement of SFO and SFA in the pathogenesis of psoriasis. This underscores their potential significance as indicators or targets for therapeutic interventions in psoriasis [20].

Unfortunately, there are still no relevant data presenting the changes in SFA and SFO in serum of skin disorders other than psoriasis. Similar to psoriasis, the sphingolipid composition of the skin in atopic dermatitis (AD) has also been well studied. Toncic et al. [21] showed that the amounts of SFO and SFA soar in AD versus in healthy skin. However, no similar disturbances were described in non-lesioned atopic skin. Interestingly, our previous study revealed a similar elevation of SFO and SFA in psoriatic lesions, but we additionally observed an increase in SFO levels in non-lesioned psoriatic skin [22]. In AD, contrary to our new results, the ratio of SFA/SFO is reduced in healthy skin by comparison to non-lesioned and lesioned AD skin, which is reported by Toncic et al. [21]. Summing up, these outcomes underline the remarkable sphingolipid alterations in various skin disorders and still highlight the tangled role of sphingolipids in the pathogenesis of AD and psoriasis.

3.3. The Characteristics of Ceramides

However, in this study, we did not find any significant differences in CER concentration in psoriatic serum samples compared to healthy individuals (Figure 1). Interestingly, we observed a positive Pearson's correlation between CER_t vs. CER_s ($p < 0.026$), SFA_t vs. CER_s ($p < 0.006$), and SFO_t vs. CER_s ($p < 0.039$) in psoriatic lesional skin and the serum of psoriatic patients. Additionally, we noted a negative Pearson correlation between CER_t vs. SFA_s ($p < 0.040$) and CER_t vs. SFO_s ($p < 0.044$) in non-lesional psoriatic skin and the serum of psoriatic patients. These correlations are presented in Figure 2.

Tawada et al. [23] reported that CER quantities depend on constant sustainability between their manufacture formation and degradation. The main cause of the abnormal production of CER in psoriasis is the reduced activity of ceramide synthase [23]. Alessandrini et al. [24] presented that disturbed CER amounts can be also decreased due to a decrease in sphingomyelinase activity, which is another crucial enzyme, in addition to ceramide synthase, involved in CER synthesis. Subsequently, these ceramide levels may be reduced due to the amount of prosaposin, which is a saposin precursor and plays a major role in the process of the hydrolysis of sphingolipids [24]. According to Lew et al. [13], in psoriasis, the amount of ceramide in the epidermis is depleted together with c-Jun

N-terminal kinase and the protein kinase C alpha. Overall, the lower CER can result in the downregulation of these crucial kinases, which are known for their apoptotic cell signaling features. Consequently, this may lead to a reduction in sphingomyelinase-induced ceramides and at the same time a boost in the anti-apoptotic and proliferative characteristics of the psoriatic epidermis. [13].

In another study conducted on samples of psoriatic skin by Checa et al. [11], the authors demonstrated an elevated amount of CER in the skin of psoriatic patients compared to healthy individuals. Their outcome is consistent with that of our previous study, Matwiejuk et al. [22]. However, in contrast, Cho et al. [25] reported that the rate of CER in the lesional epidermis of psoriatic patients was more decreased than in the unlesioned epidermis [25]. The lack of significant differences in serum ceramide (CER) levels between psoriatic patients and healthy samples in our current study may be attributed to several factors. One critical consideration is the potential influence of various factors, such as differences in sample collection methods, variations in disease severity, and diverse patient characteristics, all of which could contribute to these similar outcomes. Notably, it should be highlighted that Cho et al. [25] conducted their investigation with a distinct patient cohort (10 patients), which is in contrast with our larger sample size (20 patients). This discrepancy in the number of individuals examined might provide a more comprehensive and accurate insight compared to the study of Cho et al. [25], given our broader representation of psoriasis-affected patients. Additionally, studies on greater numbers of patients still need to be performed. Even for patients suffering from AD, which was also described as disturbed amounts of ceramides, the alteration of ceramides was noted by Toncic et al. [21], who reported higher quantities of CER and glucosylceramide. Of course, these impairments are more marked in psoriatic lesions, but significantly different levels were also noted in non-lesional skin. In our previous study on psoriatic patients, Matwiejuk et al. [22] described similar observations where the CER level was higher in the lesioned skin compared to non-lesional psoriatic skin samples and healthy skin. However, in the study carried out on serum, we did not discover elevated levels of CER in healthy patients versus psoriatic patients. These similar results between the quantity of CER in the skin and serum point out that changes in CER metabolism may be similar in inflammatory skin diseases such as AD and psoriasis. Secondly, the abnormality of CER amounts may contribute to the disturbed skin barrier and cause the inflammatory processes. Still, subsequent studies are needed to discover how specific mechanisms underly CER metabolism in various skin diseases and the implications for disease pathogenesis and potential modalities.

The relationship between ceramides in the skin tissue and their influence on serum ceramide levels is not yet fully understood. In the present study, we found different significant and negative correlations between CER_t vs. SFA_s ($p < 0.040$) and CER_t vs. SFO_s ($p < 0.044$) in non-lesional psoriatic skin and the serum of psoriatic patients. Moreover, in lesional psoriatic skin and the serum of psoriatic patients, we noted a positive Pearson's correlation between SFA_t vs. CER_s ($p < 0.006$), CER_t vs. CER_s ($p < 0.026$), SFO_t vs. CER_s ($p < 0.039$). These correlations are presented in Figure 2. These findings may point out that there are various connections between different sphingolipids in psoriasis which may be the background pathomechanism of psoriasis. However, it remains unclear how alterations in skin ceramide metabolism may contribute to alterations in ceramide quantities in the serum of psoriatic patients. Moreover, CER is engaged in many comorbidities other than psoriasis and AD, including components of metabolic syndrome. Hao et al. [26] stated that a metabolic syndrome is a group of abnormalities that enhance the chance of cardiovascular disease and diabetes [26]. Lee et al. [27] showed that CER is linked with insulin resistance (IR), obesity, dyslipidemia, and other metabolic abnormalities [27]. The relationship between skin and serum ceramides is complex and intricate. While alterations in ceramide composition have been observed in both lesional and non-lesional skin of patients with various dermatological conditions, the precise cause-and-effect dynamics between skin ceramides and serum ceramides remain elusive. Further research is needed to elucidate the

potential bidirectional influence of these compartments on each other, shedding light on their intricate interconnections and implications for skin health and systemic conditions.

We must acknowledge that our study has some limitations and does not offer insights into the acyl chain composition within ceramides, nor provide data on the levels of enzymes engaged in sphingolipid biosynthesis. Addressing these limitations in future studies could contribute to a more comprehensive understanding of the sphingolipid dynamics in the context of the studied conditions. Furthermore, conducting research with a larger cohort of patients could help establish the significance and severity of sphingolipid abnormalities in the context of psoriasis. While our current findings provide valuable insights into sphingolipid disturbances and their interplay between psoriatic serum and skin, expanding the sample size would enhance the statistical power and enable us to draw more robust conclusions regarding the involvement of CER in psoriasis pathogenesis.

4. Materials and Methods

Twenty patients (13 male and 7 female) with active plaque-type psoriasis, with a mean age of 53.2, and twenty-eight healthy controls (8 male and 20 female), with a mean age of 45.6, were enrolled in the study. The severity of psoriasis was estimated using the Psoriasis Area and Severity Index (PASI) [28]. Body mass index (BMI) was calculated based on self-reported weight and height. None of the patients or controls were under dietary restriction. History of hypertension, liver disease (e.g., non-alcoholic fatty liver disease (NAFLD)), heart disease, and diabetes mellitus, and the results of the laboratory tests were collected from the hospital records of the patients. Laboratory tests were measured before treatment. All psoriatic patients gave their written informed consent before enrolment in the study. The study protocol was approved by the local university bioethical committee (no APK.002.500.2021), according to the principles of the Helsinki Declaration. Peripheral blood samples were taken before starting the treatment after overnight fasting. After centrifugation, the serum was stored at −80 °C until it was analyzed. Three mm punch biopsies were obtained from both the non-lesional and lesional skin from the trunk of psoriatic patients following local anesthesia. Samples from healthy patients were collected from the wound's edge during a planned inguinal hernia operation under general anesthesia. Furthermore, in line with the PASI score, we assessed the clinical features of erythema, induration, and desquamation within the chosen psoriatic lesion for biopsy. The scoring system ranged from 0 to 4.

4.1. Sphingolipid Analysis

The contents of sphingosine, sphinganine, sphingosine-1-phosphate (S1P), and SFA1P were measured simultaneously using the method of Min et al. (2002) [29]. Briefly, tissues were homogenized in a solution composed of 25 mM HCl and 1 mM NaCl. Acidified methanol and internal standards (10 pmol of C17-sphingosine and 30 pmol of C17-sphingosine-1-phosphate; Avanti Polar Lipids (Alabaster, AL, USA)) were added and the samples were ultrasonicated in ice-cold water for 1 min. Lipids were then extracted by the addition of chloroform, 1 M NaCl, and 3 N NaOH. The alkaline aqueous phase containing S1P and SFA1P was transferred to a fresh tube. The residual phosphorylated sphingoid bases in the chloroform phase were re-extracted twice with methanol/1 M NaCl (1:1, v/v) solution and then all the aqueous fractions were combined. The amount of S1P and SFA1P was determined indirectly after dephosphorylation to sphingosine and sphinganine, respectively, with the use of alkaline phosphatase (bovine intestinal mucosa; Fluka (Seelze, Germany)). To improve the extraction yield of released sphingosine and sphinganine, some chloroform was carefully placed at the bottom of the reaction tubes. The chloroform fractions containing free sphingosine and sphinganine or dephosphorylated sphingoid bases were washed three times with alkaline water (pH adjusted to 10.0 with ammonium hydroxide) and then evaporated under a nitrogen stream. The dried lipid residues were redissolved in ethanol, converted to their o-phthalaldehyde derivatives, and analyzed using a high-performance liquid chromatography (HPLC) system (PROSTAR; Varian Inc. (Palo Alto, CA, USA))

equipped with a fluorescence detector and C18 reversed-phase column (OMNISPHER 5, 4.6 × 150 mm; Varian Inc.). The isocratic eluent composition of acetonitrile: water (9:1, *v*/*v*) (Merck, Darmstadt, Germany) and a flow rate of 1 mL min^{-1} were used.

The content of ceramide was determined by the procedure previously described by Baranowski et al. [30]. A small volume of the chloroform phase containing lipids extracted as described above was transferred to a fresh tube containing 31 pmol of C17-sphingosine as an internal standard. The samples were evaporated under a nitrogen stream, redissolved in 1 M KOH in 90% methanol, and heated at 90 °C for 60 min to convert ceramide into sphingosine. This digestion procedure does not convert complex sphingolipids, such as sphingomyelin, galactosylceramide, or glucosylceramide, into free sphingoid bases [31]. Samples were then partitioned by the addition of chloroform and water. The upper phase was discarded and the lower phase was evaporated under nitrogen. The content of free sphingosine liberated from ceramide was then analyzed using HPLC as described above. The calibration curve was prepared using N-palmitoylsphingosine (Avanti Polar Lipids) as a standard. The chloroform extract used for the analysis of ceramide level also contained small amounts of free sphingoid bases. Therefore, the content of ceramide was corrected for the level of free sphingosine determined in the same sample.

4.2. Statistical Analysis

The obtained data were analyzed using the R (ver. 4.2.2) statistical package. At the onset of analyses, the continuous data were checked for normality (Shapiro–Wilk test) and homoscedasticity (Fligner–Killeen test). Based on the above, between-group comparisons were made using parametric (ANOVA with subsequent pairwise Student's *t*-test) or non-parametric methods (Kruskal–Wallis test with subsequent pairwise Wilcoxon test). The obtained *p*-values were adjusted for multiple comparisons (Benjamini–Hochberg correction). The corrected *p*-values lower than 0.05 were considered to be statistically significant. The results were presented in the form of box–whisker plots. The dependence between the variables of interest was determined based on Pearson's coefficients and depicted using heatmaps.

5. Conclusions

The observed differences in the sphingolipid profile and the correlations between bioactive sphingolipids in psoriatic skin and serum, as well as healthy skin and serum, demonstrate the significant contributions of these lipids to one of the many pathways involved in the pathogenesis of psoriasis. These varieties, which are more strongly highlighted in psoriatic skin and serum, underline the potential basis mentioned earlier in this article. Moreover, the engagement in the inflammatory process links this etiology of psoriasis with other diseases such as metabolic syndrome and AD.

Furthermore, the finding that sphingolipid metabolism is impaired not only in the affected skin but also in serum, at the same time, suggests a broader systemic involvement and various potential correlations between specific types of sphingolipids. These implications can lead to lipid metabolism abnormalities, which can be extended further than the visible psoriatic lesions and might play an important role in the etiology of this disease. Further studies are necessary to clarify the clinical importance of lipid abnormalities in psoriasis and their potential usefulness as therapeutic targets.

Author Contributions: Conceptualization, M.M. and H.M. (Hanna Mysliwiec); methodology, M.M., H.M. (Hanna Mysliwiec) and B.L.; software, M.M., H.M. (Hanna Mysliwiec) and B.L.; validation, B.L., H.M. (Hanna Mysliwiec), A.C. and I.F.; formal analysis, H.M. (Hanna Mysliwiec), J.D., P.M., A.C. and I.F.; investigation, M.M., M.L. and H.M. (Hend Malla); resources, M.M.; data curation, M.M., M.L. and H.M. (Hanna Mysliwiec); writing—M.M., H.M. (Hanna Mysliwiec) and B.L.; original draft preparation, M.M., H.M. (Hanna Mysliwiec) and B.L.; writing—review and editing, H.M. (Hanna Mysliwiec), B.L., P.M., J.D., A.C. and I.F.; visualization, M.M., H.M. (Hanna Mysliwiec) and H.M. (Hend Malla); supervision, H.M. (Hanna Mysliwiec), P.M., J.D., A.C. and I.F.; project administration,

M.M., H.M. (Hanna Mysliwiec), J.D., A.C. and I.F.; funding acquisition, M.M. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent was obtained from the patient(s) to publish this paper.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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

References

1. Parisi, R.; Symmons, D.P.M.; Griffiths, C.E.M.; Ashcroft, D.M. Global epidemiology of psoriasis: A systemic review of incidence and prevalence. *J. Investig. Dermatol.* **2013**, *133*, 377–385. [CrossRef] [PubMed]
2. Parisi, R.; Iskander, I.Y.K.; Kontopantelis, E.; Augustin, E.; Griffiths, C.E.M.; Ashcroft, D.M. National, regional, and worldwide epidemiology of psoriasis: Systemic analysis and modeling study. *BMJ* **2020**, *369*, m1590. [CrossRef] [PubMed]
3. Zheng, M.; Jullien, D.; Eyerich, E. The prevalence and Disease Characteristics of generalized Pustular Psoriasis. *Am. J. Clin. Dermatol.* **2022**, *23* (Suppl. S1), 5–12. [CrossRef]
4. Rendon, A.; Schakel, K. Psoriasis Pathogenesis and Treatment. *Int. J. Mol. Sci.* **2019**, *20*, 1475. [CrossRef] [PubMed]
5. Lowes, M.A.; Bowcock, A.M.; Krueger, J.G. Pathogenesis and therapy of psoriasis. *Nature* **2007**, *445*, 866–873. [CrossRef]
6. Chiricozzi, A.; Raimondo, A.; Lembo, S.; Fausti, F.; Dini, V.; Costanzo, A.; Monfrecola, G.; Balato, N.; Ayala, F.; Romanelli, M.; et al. Crosstalk between skin inflammation and adipose tissue-derived products: Pathogenic evidence linking psoriasis to increases adiposity. *Expert Rev. Clin. Immunol.* **2016**, *12*, 1299–1308. [CrossRef]
7. Fernández-Armenteros, J.M.; Gómez-Arbonés, X.; Buti-Soler, M.; Betriu-Bars, A.; Sanmartin-Novell, V.; Ortega-Bravo, M.; Martínez-Alonso, M.; Garí, E.; Portero-Otín, M.; Santamaria-Babi, L.; et al. Psoriasis, metabolic syndrome and cardiovascular risk factors. A population-based study. *J. Eur. Acad. Dermatol. Venereol.* **2019**, *33*, 128–135. [CrossRef]
8. Nakhwa, Y.C.; Rashmi, R.; Basavaraj, K.H. Dyslipidemia in Psoriasis: A Case Controlled Study. *Int. Sch. Res. Notices.* **2014**, *2014*, 729157. [CrossRef]
9. Hannun, Y.A.; Obeid, L.M. Sphingolipids and their metabolism in physiology and disease. *Nat. Rev. Mol. Cell Biol.* **2018**, *19*, 175–191. [CrossRef]
10. Moskot, M.; Bochenska, K.; Jakobkiewicz-Banecka, J.; Banecki, B.; Gabig-Ciminska, M. Abnormal Sphingolipid World in Inflammation Specific for Lysosomal Storage Disease and Skin Disorders. *Int. J. Mol. Sci.* **2018**, *19*, 247. [CrossRef]
11. Checa, A.; Xu, N.; Sar, D.G.; Haeggstrom, J.Z.; Stahle, M.; Wheelock, C.E. Circulating levels of sphingosine-1-phosphate are elevated in severe, but not mild psoriasis and are unresponsive to anti-TNF-α treatment. *Sci. Rep.* **2015**, *5*, 12017. [CrossRef] [PubMed]
12. Mysliwiec, H.; Baran, A.; Harasim-Symbor, E.; Choromanska, B.; Mysliwiec, P.; Justyna Milewska, A.; Chabowski, A.; Flisiak, I. Increase in circulating sphingosine-1-phosphate and decrease in ceramide levels in psoriatic patients. *Arch. Dermatol. Res.* **2017**, *309*, 79–86. [CrossRef] [PubMed]
13. Lew, B.-L.; Cho, Y.; Kim, J.; Sim, W.-Y.; Kim, N.-I. Ceramides and cell signaling molecules in psoriatic epidermis: Reduced levels of ceramides, PKC-alpha, and JNK. *J. Korean Med. Sci.* **2006**, *21*, 95–99. [CrossRef]
14. Maceyka, M.; Harikumar, K.B.; Milstein, S.; Spiegel, S. Sphingosine-1-Phosphate signaling and its role in disease. *Trends Cell Biol.* **2012**, *22*, 50–60. [CrossRef] [PubMed]
15. Kowalski, G.M.; Carey, A.L.; Selathurai, A.; Kingwell, B.A.; Bruce, C.R. Plasma Sphingosine-1-Phosphate Is Elevated in Obesity. *PLoS ONE* **2013**, *8*, e72449. [CrossRef] [PubMed]
16. Kozłowska, D.; Harasim-Symbor, E.; Mysliwiec, H.; Milewska, A.J.; Chabowski, A.; Flisiak, I. Lipid profile disturbances may predispose psoriatic patients to liver dysfunction. *Postepy Dermatol. Alergol.* **2021**, *38*, 310–318. [CrossRef] [PubMed]
17. Vaclavkova, A.; Chimenti, S.; Arenberger, P.; Holló, P.; Sator, P.-G.; Burcklen, M.; Stefani, M.; D'Ambrosio, D. Oral ponesimod in patients with chronic plaque psoriasis: A randomised, double-blind, placebo-controlled phase 2 trial. *Lancet* **2014**, *384*, 2036–2045. [CrossRef]
18. D'Ambrosio, D.; Steinmann, J.; Brossard, P.; Dingemanse, J. Differential effects of ponesimod, a selective S1P1 receptor modulator, on blood-circulating human T cell subpopulations. *Immunopharmacol. Immunotoxicol.* **2015**, *37*, 103–109. [CrossRef]
19. Sung-Hyuk, M.; Kim, J.-Y.; Song, E.-H.; Shin, M.-K.; Cho, Y.-H.; Kim, N.-I. Altered Levels of Sphingosine and Sphinganine in Psoriatic Epidermis. *Ann. Dermatol.* **2013**, *25*, 321–326. [CrossRef]
20. Sorokin, A.V.; Domenichiello, A.F.; Dey, A.K.; Yuan, Z.-K.; Goyal, A.; Rose, S.M.; Playford, M.P.; Ramsden, C.E.; Mehta, N.N. Bioactive Lipid Mediator Profiles in Human Psoriasis Skin and Blood. *J. Investig. Dermatol.* **2018**, *138*, 1518–1528. [CrossRef]

21. Toncic, R.J.; Jakasa, I.; Hadzavdic, S.L.; Goorden, S.M.; Ghauharali-van der Vlugt, K.M.; Stet, F.S.; Balic Petkovic, A.M.; Pavicic, B.; Zuzul, K.; Marinovic, B.; et al. Altered Levels of Sphingosine, Sphinganine, and Their Ceramides in Atopic Dermatitis Are Related to Skin Barrier Function, Disease Severity and Local Cytokine Milieu. *Int. J. Mol. Sci.* **2020**, *21*, 1958. [CrossRef] [PubMed]
22. Matwiejuk, M.; Mysliwiec, H.; Lukaszuk, B.; Lewoc, M.; Malla, H.; Mysliwiec, P.; Dadan, J.; Chabowski, A.; Flisiak, I. The Interplay between Bioactive Sphingolipids in the Psoriatic Skin and the Severity of the Disease. *Int. J. Mol. Sci.* **2023**, *24*, 11336. [CrossRef] [PubMed]
23. Tawada, C.; Kanoh, H.; Nakamura, M.; Mizutani, Y.; Fujisawa, T.; Banno, Y.; Seishima, M. Interferon-γ decreases ceramides with long-chain fatty acids: Possible involvement in atopic dermatitis and psoriasis. *J. Investig. Dermatol.* **2014**, *134*, 712–718. [CrossRef] [PubMed]
24. Alessandrini, F.; Stachowitz, S.; Ring, J.; Behrendt, H. the level of prosaposin is decreased in the skin of patients with psoriasis vulgaris. *J. Investig. Dermatol.* **2001**, *116*, 394–400. [CrossRef] [PubMed]
25. Cho, Y.; Lew, B.-L.; Seong, K.; Kim, N.-I. An Inverse Relationship Between Ceramide Synthesis and Clinical Severity in Patients with Psoriasis. *J. Korean Med. Sci.* **2004**, *19*, 859–863. [CrossRef]
26. Hao, Y.; Zhu, Y.-J.; Zou, S.; Zhou, P.; Hu, Y.-W.; Zhao, Q.-X.; Gu, L.-N.; Zhang, H.-Z.; Wang, Z.; Li, J. Metabolic Syndrome and Psoriasis: Mechanisms and Future Directions. *Front. Immunol.* **2021**, *12*, 711060. [CrossRef]
27. Lee, S.; Kim, S.-A.; Kim, Y.; Kim, J.; Hong, G.; Hong, J.; Choi, K.; Eom, C.-S.; Baik, S.; Lee, M.-K.; et al. Genetic Variants Associated with Elevated Plasma Ceramides in Individuals with Metabolic Syndrome. *Genes* **2022**, *13*, 1497. [CrossRef]
28. Schmitt, J.; Wozel, G. The psoriasis area and severity index is the adequate criterion to define severity in chronic plaque-type psoriasis. *Dermatology* **2005**, *210*, 194–199. [CrossRef]
29. Min, J.-K.; Yoo, H.-S.; Lee, E.-Y.; Lee, W.-J.; Lee, Y.-M. Simultaneous quantitative analysis of sphingoid base 1-phosphates in biological samples by o-phthalaldehyde precolumn derivatization after dephosphorylation with alkaline phosphatase. *Anal. Biochem.* **2002**, *303*, 167–175. [CrossRef]
30. Baranowski, M.; Zabielski, P.; Blachnio, A.; Gorski, J. Effect of exercise duration on ceramide metabolism in the rat heart. *Acta Physiol.* **2008**, *192*, 519–529. [CrossRef]
31. Bose, R.; Chen, P.; Loconti, A.; Grüllich, C.; Abrams, J.M.; Kolesnick, R.N. Ceramide generation by the Reaper protein is not blocked by the caspase inhibitor. *J. Biol. Chem.* **1998**, *273*, 28852–28859. [CrossRef] [PubMed]

metabolites

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Systematic Review

The Role of Sphingolipids in the Pathogenesis of Psoriasis

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Abstract: Psoriasis is a complex, chronic, immunologically mediated disease which involves skin and joints. Psoriasis is commonly connected with numerous other diseases such as liver diseases, metabolic syndrome, impaired glucose tolerance, diabetes mellitus, atherosclerosis, hypertension, and ischemic heart disease. Interestingly, comorbidities of psoriasis are an attention-grabbing issue. Additionally, it can cause impairment of quality of life and may be associated with depressive disorders. Altered levels of ceramides in psoriatic skin may lead to anti-apoptotic and pro-proliferative states, consequently leading to an over-proliferation of keratinocytes and the development of skin lesions. The pathophysiology of psoriasis and its comorbidities is not fully understood yet. Sphingolipids (including ceramides) and their disturbed metabolism may be the link between psoriasis and its comorbidities. Overall, the goal of this review was to discuss the role of sphingolipid disturbances in psoriasis and its comorbidities. We searched the PubMed database for relevant articles published before the beginning of May 2022. The systematic review included 65 eligible original articles.

Keywords: psoriasis; ceramide; sphingolipid; sphingosine lipid signaling; sphingosine 1-phosphate; sphingosine kinase; sphingomyelin; ceramide S1P receptor

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1. Introduction

Hannun et al. [1] highlight that the biochemical pathways leading to ceramide generation have been well studied and described in the past. Ceramides can be produced via the catabolism of sphingomyelin and glycosphingolipids, as well as via de novo biosynthesis starting from the formation of sphingoid bases and their subsequent N-acylation [1]. Kozłowska et al. [2] informed us that ceramides play a role in the pathogenesis of psoriasis vulgaris and metabolic disorders such as atherosclerosis, obesity, type 2 diabetes, and cardiovascular diseases. Palmitic ceramide may be involved in the transformation of hepatitis steatosis or obesity-derived insulin resistance [2]. Łuczaj et al. [3] found that the level of prosaposin, which is an essential cofactor in the hydrolysis of sphingolipids, is much lower in psoriatic plaques compared to non-lesional psoriatic skin [3]. Kozłowska et al. [2] revealed that psoriasis is an chronic, inflammatory, immunologically mediated disease which affects not only skin, but also knee joints, fingernails, etc. Psoriasis can systematically recurs or flare for a few weeks or months before then subsiding for a while [2].

The Figure 1 shows symptoms of psoriasis including patchy rashes, scaling, and dry and cracked skin that may bleed. Patients can also suffer from itching, burning, and soreness. There are several types of psoriasis, such as plaque, nail, guttate, inverse, pustular, and erythrodermic psoriasis. Psoriasis is characterized by abnormal differentiation in the cells of the epidermis and hyperproliferation, vasodilation, and inflammatory cell infiltration [2]. Myśliwiec et al. [4] reported that it is well known that psoriasis is linked with metabolic syndrome, obesity, insulin resistance, or cardiovascular disease. Patients with involved joints and severe psoriasis may have a higher risk of mortality [4]. Checa et al. [5] and Jeon et al. [6] described the altered levels of sphingolipids and sphingosine 1-phosphate that were observed in patients suffering from psoriasis [5,6].

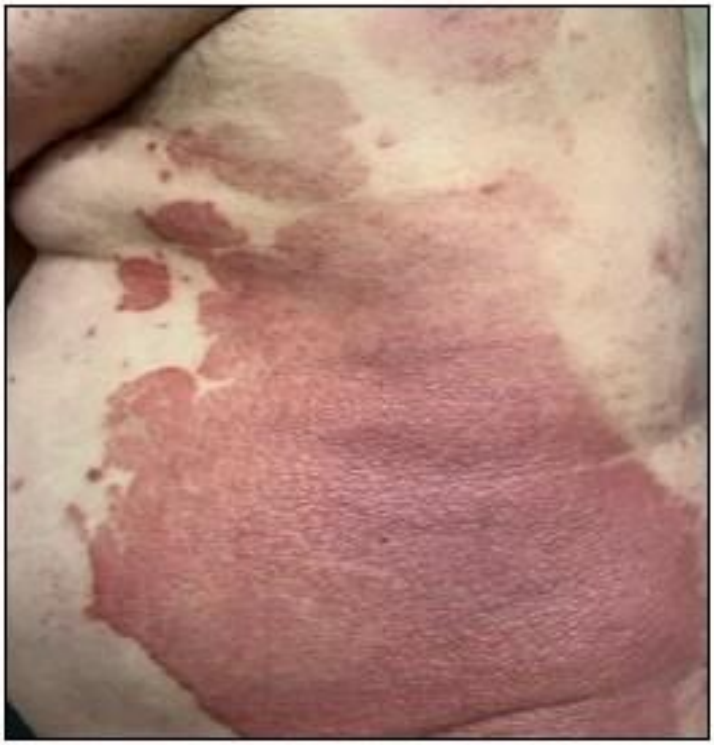

Figure 1. Clinical picture of plaque psoriasis.

2. Materials and Methods

This systematic review was written following the 2020 updated Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [7,8]. The review protocol was submitted to the Protocols database (registration number 69618). A medical literature search of PubMed (1996-present), conducted in the winter and spring of 2022, was performed using appropriate terms without date limitations. The main subject of the research was to identify the role of sphingolipid metabolism in the pathogenesis of psoriasis and its comorbidities: cardiovascular diseases, liver disease, and metabolic disorders. Medical subject headline terms included: "sphingolipid's metabolism in psoriasis", "sphingolipid's metabolism in heart disease", "lipids in the pathogenesis of psoriasis", "lipidomics psoriasis", "lipid signaling in psoriasis", "lipid mediator in psoriasis", "psoriasis and œramides", "psoriasis and S1P", "psoriasis and sphingosine-1-phosphate", and "psoriasis and sphingomyelin". Non-English publications, duplicated publications, and articles with low clinical significance were excluded from the analysis. Original animal and human studies were included in the systematic review. The results of search strings were merged together and duplicates were removed. Afterwards, the titles and abstracts of the remaining studies were screened in order to identify relevant articles that addressed the review subject. Afterwards, the titles and abstracts of the remaining studies were independently screened by two reviewers (M.M. and H.M.) in order to identify relevant articles that addressed the review subject. Disagreements between reviewers were resolved by the opinion of a third reviewer (A.C.). Finally, the selected eligible articles were fully reviewed.

3. Results and Discussion

The search resulted in the retrieval of 2864 records, of which 204 were screened for relevance and 65 ultimately included in qualitative synthesis, according to Figure 2.

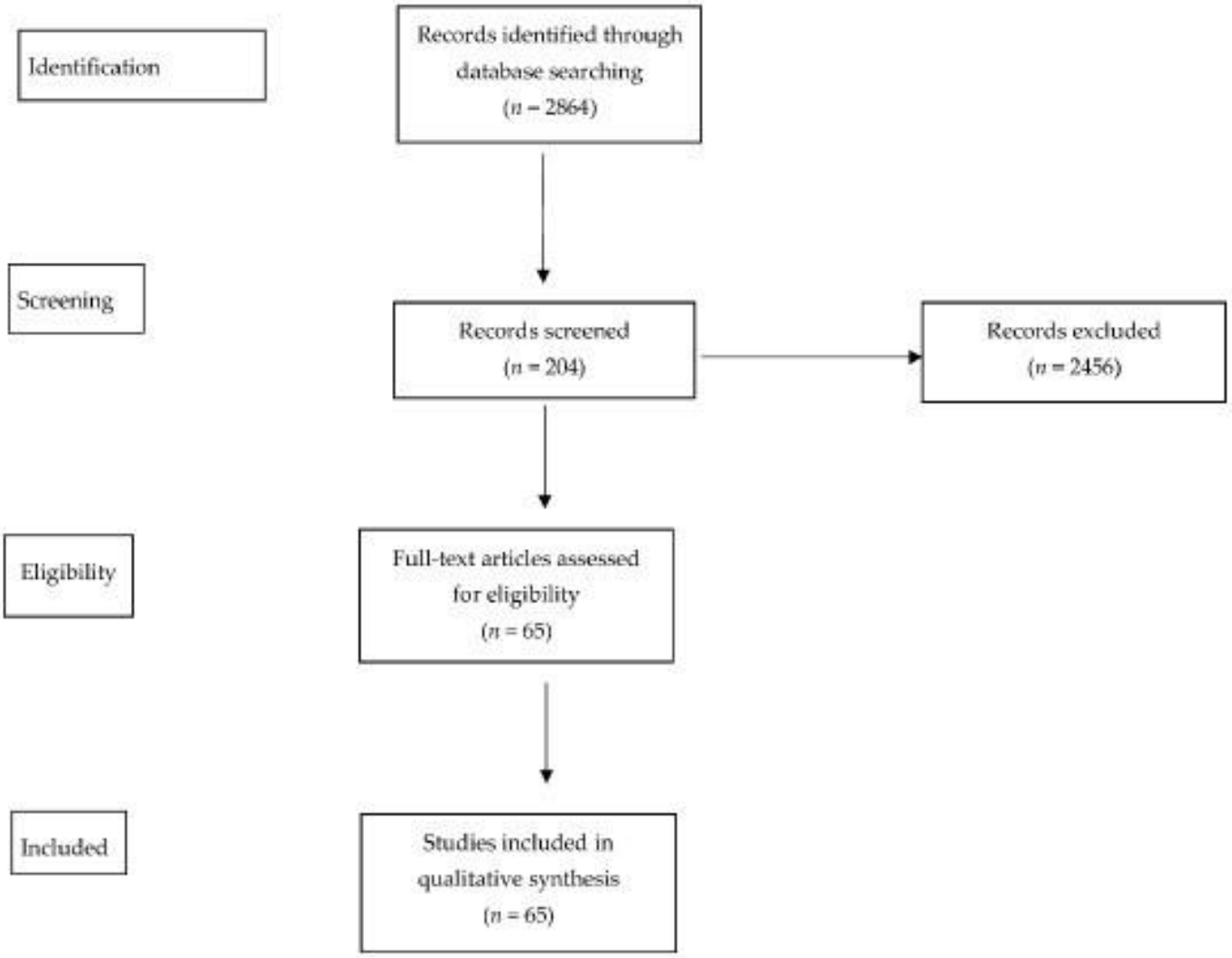

Figure 2. The search process.

3.1. Ceramides—An Overview

Lew et al. [9] highlighted from other studies that ceramides have apoptotic and antiproliferative effects. In psoriasis, the level of ceramides in the epidermis is decreased along with protein kinase C alpha (PKC-α) and c-Jun N-terminal kinase (JNK). PKC-α and JNK are apoptotic cell-signaling molecules that are induced by ceramides. According to the above authors, the loss of ceramides results in downregulation of PKC-α and JNK, which decreases sphingomyelinase-induced ceramide generation and boosts the proliferative and anti-apoptotic features of psoriatic epidermises [9]. Yokose et al. [10] reported that it has been demonstrated that the level of on-hydroxy fatty acid/phytosphingosine base ceramide Cer [NP] and the Cer [NP]/[NS] ratio are higher in the stratum corneum (SC) compared to keratinocytes (KCs) in normal human skin; Cer [NP] is the most abundant ceramide subclass in the SC, while non-hydroxy fatty acid/sphingosine base ceramide (Cer [NS]) is the most abundant Cer subclass in KCs [10]. Lee et al. [11] additionally reported that the genes involved in sphingolipid metabolism had been proven previously (e.g., ceramide glucosyltransferase (UGCG, also known as glucosylceramide synthase), acid beta-glucosidase (GBA), and acid sphingomyelinase (SMPD1)); UGCG transfers glucose to ceramide to form glucosylceramide, GBA plays a role in hydrolyzing glucosylceramide, and SMPD1 transfers sphingomyelin to ceramide. Moreover, during keratinocyte differentiation, glucosylceramide is synthesized by the UGCG enzyme, and glucosylceramide is stored in intracellular lamellar granules and then released into the intercellular space where it is

hydrolyzed by GBA to ceramide, the major lipid component of the epidermal barrier [11]. Alessandrini et al. [12] reported on decreased levels of glucosylceramide-b-glucosidase (GlcCer'ase) that were observed in the skin of patents with psoriasis vulgaris compared to normal controls. In addition, lesional psoriatic skin showed an increased level of GlcCer'ase compared to non-lesional skin in all cases, both at the RNA and at the protein level [12].

3.2. Sphingosine 1-Phosphate (S1P) Involvement in Psoriasis Pathogenesis

Jeon et al. [6] found that S1P is a bioactive substance that regulates cell growth and differentiation. S1P is an essential regulator of the differentiation and proliferation of human keratinocytes [6]. Moskot et al. [13] suggested that S1P is responsible for angiogenesis, IL-17 uprising, Th17 cell development, and T cell migration [13]. Kozłowska et al. [2] noted that S1P is an insulin resistance and obesity marker. The concentration of S1P in plasma is correlated with metabolic syndrome in obesity. Patients suffering from psoriasis have higher levels of S1P than healthy people. It has been demonstrated that the amount of S1P in psoriatic patients differs depending on the patient's weight [2]. Sorokin et al. [14] discovered that decreased S1P levels may be linked with the keratinocyte hyperproliferation observed in psoriasis. Oxidized low-density lipoprotein (LDL) has been shown to be stored in psoriatic lesional skin, along with increased levels of low-density lipoprotein receptor-related protein 1 (Lrp1) and the apoB protein. The increased lipolysis and β-oxidation noted in patients suffering from psoriasis might be explained by higher skin tissue demand in bioactive lipid mediators that are involved in revealing inflammation processes [14]. Ji et al. [15] found that sphingosine-1-phosphate receptor 1 (S1PR1) modulators could mitigate psoriatic symptoms in animal models. A selective S1P1 receptor agonist (Syl930), which selectively modulates S1PR1, weakened the thickening of back skin in a sodium lauryl sulphate-induced mouse model of psoriasis and induced other strong antiproliferative and anti-inflammatory effects, such as the alleviation of acanthosis and parakeratosis and the thickening of the epidermis, in a propranolol-induced guinea pig psoriasis model when administered orally [15]. Hong et al. [16] showed the influence of a novel SphK1 activator, K6PC-5, on Ca^{2+} signaling in human keratinocytes, as well as on epidermal proliferation and differentiation in both murine skin and cultured cells. The activation of SphK1 by K6PC-5 was revealed while new substances derived from bioactive and short-chain pseudoceramides were being developed to promote keratinocyte differentiation; K6PC-5 represents a compound with novel activities not anticipated from its simple short-chain pseudoceramide structure. Interestingly, these results reveal that K6PC-5 and S1P have an antiproliferative effect on the epidermis of murine skin [16]. Schuster et al. [17] suggested that attenuated chemokine (C-C motif) ligand 2 (CCL2) production translates to a lowered influx of Mφs (macrophages) into inflamed tissue. Mφs and monocytes take part in auto-immune diseases such as psoriatic arthritis or MS (multiple sclerosis). Elevated CCL2 production in resident Mφs after activation of S1pr4 (sphingosine-1-phosphate receptor 4) suggests that S1pr4 acts as an enhancer of the initial inflammatory response, which fits the observation that S1P levels are often elevated in inflammatory diseases [17]. Setyawan et al. [18] proved that treatment with sphingosine 1-phosphate (S1P) receptor modulators seemed to be associated with decreased rates of thromboembolic events (TEs) and had a protective effect on TEs; however, significant proof was only found for ischemic stroke (IS) [18]. Rujimongkon et al. [19] demonstrated that sericin reduced sphingosine-1-phosphate lyase (SPL) expression in psoriatic skin. This result suggests that the expression of SPL in response to sericin-treated psoriatic skin decreased immune response and keratinocyte proliferation. SPL plays an enzymatic role and is active in immune responses and autoimmune diseases. SPL deficiency impaired neutrophil trafficking into inflammatory tissues. Decreasing SPL expression reduces cell proliferation and induces keratinocyte differentiation. This proof suggests that SPL is mainly active in the immune response process and functions in the regulation of cell development [19]. Okura et al. [20] found that fingolimod is similar in chemical structure to S1P and behaves as an antagonist of subtypes of S1P receptors, for instance S1P receptors 1, 3, 4, and 5, after phosphorylation by

sphingosine kinase in vivo. It has been shown that application of fingolimod ameliorated imiquimod (IMQ)-induced psoriatic dermatitis histologically and clinically. After 6 days, the mRNA expression level of IL-17A was decreased in the skin of fingolimod-treated mice. Flow cytometric analyses revealed that fingolimod reduced the percentage and the number of IL-17 producing T cells infiltrating into the skin, whereas it increased them in inguinal lymph node-induced psoriasis by hindering IL-17A-producing T cells from emigrating from the inguinal lymph nodes to the skin [20]. Interestingly, Shin et al. [21] proved that HWG-35D functions as a highly selective sphingosine kinase 2 (SK2) inhibitor and blocks ex vivo Th17-development. Viable use at concentrations as low as 100 nM suggests that the development and optimization of SK2 inhibitors with drug-like properties for treatment of psoriasis is warranted. However, erythema was not eradicated with half dosages of HWG-35D, though thickness and scaling were significantly reduced. In that study, SK2 inhibition using HWG-35D reduced suppressor of cytokine signaling (SOCS1) levels during Th17 polarization. SOCS1 is critical in regulating Th17 differentiation by maintaining signal transducer and activator of transcription 3 (STAT3) and small mothers against decapentaplegic (Smad) transcriptional activities. Th17 differentiation is markedly reduced in SOCS1-deficient naïve $CD4^+$ T cells or in suppressor of cytokine signaling 3 (SOCS3) overexpressed T cells [21]. Bocheńska et al. [22] demonstrated in their study that elevated SPHK1 gene activity in psoriatic lesioned skin can generate excessive synthesis of sphingosine phosphate 1, which results in the production of tumor necrosis factor alpha (TNF-α). Consequently, it may activate the nuclear factor kappa light chain enhancer of activated B cells (NF-κB) pathway or secretion of interleukin 8 (IL-8) [22].

3.3. Phospholipids in the Pathogenesis of Psoriasis

Shao et al. [23] showed that the fusion of TNF-α and IL-17A is a strong booster of phospholipase A2 Group IIF (PLA2G2F), phospholipase A2 group IVD (PLA2G4D), and phospholipase A2 group IVE (PLA2G4E) expression. Lipidomic analyses showed that phospholipase A2 (PLA2) impacts the mobilization of a phospholipid–eicosanoid pool, which is altered in psoriatic lesions and functions to boost immune responses in keratinocytes. Moreover, overexpression of PLA2G2F (one of the sPLA2s) in a transgenic mouse model led to the progress of chronic epidermal hyperplasia and hyperkeratosis, similar to what has been observed in the pathology of psoriasis. PLA2G4D, which is a cPLA2, is raised in psoriatic mast cells and facilitates CD1a expression, which can be identified by lipid-specific CD1a-reactive T cells that result in the production of IL-22 and IL-17A. Therefore, lipid metabolism and PLA2 enzymes have a pathogenic role in psoriasis. In psoriasis and pityriasis rubra pilaris (PRP) skin, the three PLA2s are mainly visualized in the epidermis, with small effect on other cell types. Of the three upregulated PLA2s where this was explored, PLA2G2F was identified in skin homeostasis and is expressed in the suprabasal epidermis, where it is upregulated during calcium-induced differentiation or stimulation with IL-22. It is involved in hyperproliferative epithelial diseases such as psoriasis and skin cancers. PLA2G4D, a cPLA2, was demonstrated to be expressed in psoriatic mast cells, prompt the release of exosomes, and contribute to the generation of neolipid skin antigens present in CD1a-reactive T cells, which contributes to the output of IL-22 and IL-17A. In addition, resolvin D1, a docosahexaenoic acid (DHA)-derived anti-inflammatory eicosanoid, is lowered in psoriatic skin and downregulated by PLA2s, which ensures a protective role in psoriasis-like dermatitis [23]. Li et al. [24] demonstrated that, in different studies, the levels of leukotriene D4 and leukotriene E3 in serum were significantly higher in psoriasis patients than in healthy controls. The general content of chenodeoxycholic acid in psoriasis vulgaris was reduced compared to healthy controls. It is assumed that the scarcity of bile acid might be involved in the pathogenesis of psoriasis [24]. Farwanah et al. [25] note that the ceramide amount in the uninvolved skin of atopic dermatitis (AD) and psoriasis patients is reduced when compared to healthy skin, with the reduction being more emphasized in psoriasis patients [25]. Moon et al. [26] demonstrated that sphingosine and sphinganine amounts are significantly elevated in psoriatic epidermis compared to non-lesional epidermis and

that boosted expression of ceramides is positively linked with the clinical severity of psoriasis [26]. Interestingly, Łuczaj et al. [27] demonstrated that the levels of several species of different groups of phospholipids, including phosphatidylcholines (PC), phosphatidylinositols (PI), phosphatidylserines (PS), and ether-linked phosphoethanolamine (PEo), are decreased in the keratinocytes of patients suffering from psoriasis. The decrease in PC content may be due to the increased activity of lecithin-cholesterol acyltransferase (LCAT), which carries fatty acids from PC to cholesterol. Different possible mechanisms leading to a reduction in PC levels may be connected with the movement of acyl chains from PC to SM that is catalyzed by PC-SM transacylase, which is an enzyme also occurring in keratinocytes. The process of phospholipid transformation catalyzed by cyclooxygenase and lipoxygenase results in the generation of D-series prostaglandins and J-series prostaglandins. These mediators, through various metabolic pathways, boost apoptosis of keratinocytes. Moreover, reactive oxygen species (ROS)-dependent lipid peroxidation end creates, namely 4-hydroxy-2-onenal (4-HNE) and 4-hydroy hexenal (4-HHE), which improve apoptosis through their commitment in the receptor pathway of apoptosis. Increased ROS production and reduced antioxidant capacity results in higher lipid peroxidation. Consequently, this increase may explain the reduction in PS and PI levels noted in keratinocytes of patients with psoriasis. In that study it was also suggested that the scarcity of PI species could be the result of their increased phosphorylation to phosphoinositides by phosphatidylinositol kinases with elevated activity in the psoriatic epidermis. Furthermore, that analysis shows that ultraviolet B (UVB) irradiation causes upregulation of PC species, PC plasmalogens (PCp), and PEo species, all of which are downregulated in non-irradiated psoriatic keratinocytes. One possible explanation for this may be a significant rise in lipid peroxidation in the keratinocytes of patients suffering from psoriasis, which was recently reported. Treatment of keratinocytes from psoriatic patients with cannabidiols (CBD) leads to successive significant reductions in the levels of PC, PS, and most PEo species in the continuation of the pro-apoptotic changes observed in these cells during the development of psoriasis. These changes are compliant with the increased oxidative stress and inflammation process in psoriatic keratinocytes treated with CBD. Regardless of the general tendency towards a reduction in phospholipid levels, the content of PEo molecular species, namely PEo (36:1) and PEo (40:4), is considerably elevated in psoriatic keratinocytes treated with CBD. This finding indicates that treatment with CBD partially prevents the upregulation of PC, PCp, and PEo, as seen in keratinocytes of healthy individuals exposed to UVB radiation. However, treatment of UVB-irradiated psoriatic keratinocytes with CBD results in a significant decline in the level of SM. In contrast, the increase in SM observed in psoriatic keratinocytes not exposed to UVB radiation may suggest the potential role of CBD in increasing epidermal water loss. This lack of water can lead to cell death, which is characteristic for psoriatic keratinocytes. Therefore, it is suggested that the discovered response of keratinocytes in psoriasis patients to CBD treatment is more helpful when performed in the absence of UVB phototherapy. Nevertheless, results of the latest studies on psoriatic patients have proven that topical treatment with an ointment enriched in CBD greatly improves skin parameters, symptoms, and the PASI. Psoriatic keratinocytes represent an increase (in negative zeta potential) compared to control keratinocytes, probably due to changes in the composition of the membrane of phospholipids. Negative zeta potential indicates translocation of PS to the outer layer of the membrane. CBD treatment significantly reduced the negative zeta potential. This result was only noted in keratinocytes from patients with psoriasis. With UVB irradiation, the negative zeta potential skyrocketed remarkably in comparison to the control keratinocytes. Control keratinocytes treated with CBD after UVB irradiation were characterized by substantially reduced negative zeta potential (by up to 27%) compared to irradiated keratinocytes. Irradiation with UVB caused a decline in the negative zeta potential of psoriatic keratinocytes (by 25%) compared to the psoriatic group. In contrast, treatment with CBD after UVB irradiation did not result in a statistically significant alteration in negative zeta potential, which contrasts with psoriatic keratinocytes treated with CBD after UVB exposure [27]. Zeng et al. [28] found that lysoglycerophospholipids

(for example as lysophosphatidic acid (LPA) and lysophosphatidylcholine (LPC)) and glycerophospholipid metabolism (including phosphatidic acid (PA), phosphatidylcholine (PC), and phosphatidylinositol (PI)) were substantially heightened in plasma from patients with psoriasis. LPC and LPA are the most prominent lysoglycerophospholipids and are considered to be inflammatory lipids, which take part in several immune-mediated diseases such as atherosclerosis and the autoimmune disease systemic lupus erythematosus (SLE). In that study, the authors found that LPC was significantly heightened in psoriasis plasma and that the opposite was seen for PC [28]. Kim et al. [29] provided evidence that lysophosphatidic acid receptor 5 (LPAR5) takes part in NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation in macrophages of psoriatic lesions and in keratinocyte activation to output inflammatory cytokines, which results in psoriasis pathogenesis. During tests on the effects of ki16425, an LPAR1/3 antagonist, on IMQ-induced psoriasis-like mice, ki16425 was shown to mitigate IMQ-induced psoriasis-like symptoms, mostly by inhibiting keratinocyte hyperproliferation. The authors also found that ki16425 significantly inhibited mRNA expression of inflammatory cytokines such as TNF-α, IL-6, IL-17, and IL-36γ in skin lesions, as well as PASI levels. IL-36γ, an IL-1 family cytokine, is secreted from keratinocytes stimulated by TNF-α and IL-17 in the psoriatic epidermis to enable T helper subset polarization and promote self-amplifying loops. LPA boosted Rho-associated protein kinase 2 (ROCK2) and PI3K/AKT signaling pathway-mediated cell cycle transformation and proliferation in keratinocytes. Ki16425 or LPAR1 knockdown inhibited these processes and stopped cell proliferation, hence leading to lower IMQ-induced psoriasis-like symptoms [29]. Pang et al. [30] found that, in a Chinese community, the fasting serum values for total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein A-I (ApoA-I) in a patient group with vulgaris psoriasis were all significantly reduced compared to those in healthy controls. The levels of fasting serum triglycerides (TG) and apolipoprotein B100 ($ApoB_{100}$) did not show any significant discrepancies between the patient group and healthy controls. In that study, 86 patients with psoriasis were divided into three groups based on PASI score: mild (PASI < 12, $n = 11$), moderate (PASI $\geq$ 12 and <30, $n = 54$), and severe (PASI $\geq$ 30, $n = 21$) groups. In the first group, the levels of ApoA-I and HDL-C were decreased compared to the healthy control group. In the moderate and the severe group, the values for TC, LDL-C, HDL-C, and ApoA-I were all lower than the healthy control group. The levels of TG and $ApoB_{100}$ remained unchanged with disease status when compared to the healthy control group. Interestingly, comparing the different groups of psoriasis patients, the levels of HDL-C and ApoA-I varied substantially. Specifically, the values for HDL-C and ApoA-I were remarkably lower in the severe group compared to the moderate group [30]. Ferretti et al. [31] noted higher levels of lipoprotein(a) (Lp(a)) in the serum of patients with psoriasis compared to control group. Elevated levels of lipid hydroperoxides and lower paraoxonase 1 (PON1) activity were observed in the serum of patients in contrast to healthy subjects, confirming that psoriasis is associated with oxidative stress. The imbalance between oxidative stress and antioxidant enzymes and the elevation of Lp(a) serum levels were related to the extent and severity of psoriasis. Finally, outcomes demonstrated that Lp(a) levels were positively correlated with markers of lipid peroxidation and negatively related to PON1 activity, implying that subjects with higher levels of Lp(a) are more exposed to oxidative damage [31]. Tyrrell et al. [32] revealed that zic family member 1 (ZIC1) was marked with a probable main regulator of many genes that are present in the oxidized ceramide pathway. This is made of several enzymes that directly oxygenate ceramides *ALOX12B*, *ALOXE3*, and *SDR9C7*, as well as downstream genes such as *TGM1*, which encodes the transglutaminase that couples hydrolyzed omega hydroxyl ceramide to involucrin (*IVL*) and other corneocyte lipid envelope (CLE) proteins. Some genes are upregulated in psoriasis, for instance, antimicrobial proteins, *SERPINs*, and *S100s*. Another zinc finger protein, ZNF450, manages to act as a keratinocyte proliferation regulator, and mutations in ZNF450 were implicated in the development of psoriasis [32]. Yamamoto et al. [33] demonstrated that, in psoriasis and skin cancer, the

secreted phospholipase ($sPLA_2$-IIF) is upregulated in the thickened epidermis and prompts epidermal hyperplasia through production of the unique lysophospholipid plasmalogen lysophosphatidylethanolamine (P-LPE). Some alterations in *Pla2g2e*$^{-/-}$ skin under normal conditions were enhanced to examine the impact of *Pla2g2e* scarcity on these skin disorders. However, neither imiquimod (IMQ)-induced psoriasis nor dinitrofluorobenzene (DNFB)-induced contact dermatitis were agitated in *Pla2g2e*$^{-/-}$ mice in comparison with *Pla2g2e*$^{+/+}$ mice. This was in contrast to *Pla2g2f*$^{-/-}$ mice, where ear swelling was significantly ameliorated in both models. Moreover, although the level of P-LPE, a main metabolite produced by $sPLA_2$-IIF, was selectively reduced in IMQ-treated *Pla2g2f*$^{-/-}$ skin relative to WT mice, as noted previously, the levels of P-LPE and other lipid metabolites were similar to the psoriatic skins of *Pla2g2e*$^{-/-}$ and WT mice. Unlike $sPLA_2$-IIF that promotes epidermal hyperplasia, $sPLA_2$-IIE plays a minimal role in these skin disorders, further emphasizing the functional segregation of these two $sPLA_2$s in the skin. Furthermore, *Pla2g2f*$^{-/-}$ mice display attenuated psoriasis with a concomitant reduction in the lysophospholipid P-LPE, whereas skin edema and lipid profiles in these disease models are barely affected in *Pla2g2e*$^{-/-}$ mice. These differences can be clarified, at least in part, by explicit localizations of these two $sPLA_2$s in skin niches as well as by their distinct substrate specificities, which could have different impacts on epidermal homeostasis and diseases. This belief also contrasts with the worsening of psoriasis and contact dermatitis with lifted Th1/Th17 immune responses in mice missing $sPLA_2$-IID, a "resolving $sPLA_2$" that is expressed in dendritic cells and which regulates the functions of immune cells rather than keratinocytes by producing ω3 polyunsaturated fatty acids (PUFA)-derived pro-resolving lipid mediators. In contrast to $sPLA_2$-IIF, which selectively gathers P-LPE in psoriatic skin, $sPLA_2$-IIE appears to mobilize different unsaturated fatty acids and lysophosphatidylethanolamines (LPEs) in normal skin. Consistent with these in vivo data, $sPLA_2$-IIE unleashes these fatty acids and LPEs in an in vitro enzyme label using a skin-extracted phospholipid mixture as a substrate. Given its spatiotemporal localization, it is tempting to speculate that $sPLA_2$-IIE conveys unsaturated fatty acids and LPEs in hair follicles during anagen. It has been reported that several PUFA metabolites (e.g., prostaglandins) or LPA variably affect hair growth, quality, and cycling. However, the skin levels of PUFA metabolites and LPA are not profoundly impacted by *Pla2g2e* deficiency, indicating that $sPLA_2$-IIE-derived PUFAs are largely uncoupled from downstream lipid mediators [33]. Gaire et al. [34] reported that suppressing LPA_5 activity with a pharmacological antagonist alleviated imiquimod (IMQ-induced) psoriasis-like symptoms. It also attenuated macrophage infiltration into psoriasis lesions. Activation of LPA_5 signaling was found to upregulate macrophage NLRP3 expression in psoriasis lesions. Interestingly, in vitro studies revealed that LPA could activate NLRP3 inflammasome in lipopolysaccharide (LPS)-primed macrophages through LPA_5 [34]. Syed et al. [35] described that, in psoriatic skin, a positive combination of sphingosine kinases (SPHKs) and NLRP3 inflammasome components was noted, with some of these representing targets of NF-κB signaling. Other NF-κB target genes featured in mosaic images, both in healthy and psoriatic skin, pointing out that regulation of NLRP3 inflammasome components might involve other signaling pathways than NF-κB alone [35]. Ogawa et al. [36] found decreased expression of the differentiation-specific proteins keratin 1, involucrin, and loricrin in epidermal fatty acid-binding protein (E-FABP)/keratinocytes relative to E-FABP/keratinocytes. E-FABP expression was elevated in response to increased lipid traffic, which is related to abnormal keratinocyte proliferation and differentiation in psoriasis. It was proven that E-FABP enhances keratinocyte differentiation by boosting the transcriptional activity of peroxisome proliferator-activated receptors (PPARs) by transporting fatty acids directly to PPARs. Altered fatty acid metabolism and abnormal keratinocyte differencing in psoriatic skin may be related to this drastic upregulation of E-FABP expression in psoriasis. Many saturated fatty acids are less abundant in E-FABP/keratinocytes, which is consistent with a previous report showing that E-FABP preferentially binds to saturated fatty acids in vitro. This is a remarkable correlation between E-FABP and fatty acids and the increased expression of E-FABP in psoriasis, and the pathogenesis of psoriasis

may be influenced by E-FABP activity through the impaired metabolism of fatty acids and their derivatives [36]. Shou et al. [37] noted the pathogenic role of ferroptosis in sensitizing Th22/Th17-type cytokines, thereby providing candidate markers of psoriasis aggravation. Ferroptosis is a non-apoptotic form of programmed cell death, which is associated with the exertion of damage-associated molecular patterns (DAMPs) and alarmins. The paradigm of ferroptosis comprises lipid peroxidation accumulation and iron overload. It was suggested that the induction of ferroptosis, especially lipid peroxidation of psoriatic keratinocytes, leads to inflammatory responses, which could be rescued by ferroptosis inhibitor Fer-1. Notably, inhibition of ferroptosis with ferrostatin-1 (Fer-1) is beneficial for the treatment of psoriasis. Psoriasis is connected with irregularities in lipid metabolism, free radical generation, and lymphokine production. The levels of nitric oxide, ROS, malondialdehyde (MDA), and epidermal iron in psoriasis patients were increased, while at the same time the levels of superoxide dismutase, glutathione peroxidase activity, glutathione peroxidase 4 (GPX4) expression, and total antioxidant capacity were decreased. These levels correlated with the severity of the disease. Interestingly, in that study, a significant elevation in Acyl-CoA Synthetase Long Chain Family Member 4 (ACSL4) and 4-HNE-modified protein levels was observed, as well as a reduction in GPX4 in psoriatic lesions, which are crucial regulators in the process of ferroptosis [37].

3.4. Sphingolipids in the Pathogenesis of Psoriasis

Moskot et al. [13] stated that an epidermal barrier in psoriasis is known for amended sphingolipid levels. In the composition of ceramides in psoriasis, very long chain (VLC) ceramides and non-hydroxy fatty acid/sphingosine base ceramide CER[NS] are increased, and ultra-long chain (ULC) ceramides are decreased. In psoriasis, a common phenomenon is trans epidermal water loss (TEWL) and lower retention capacity, which is due to lower levels of phytosphingosine-carrying ceramides, for instance on-hydroxy fatty acid/phytosphingosine base ceramide Cer[NP], alpha-hydroxy fatty acid/phytosphingosine base ceramide Cer[AP], and acylceramides (acylCer). Decreased acylCer reflects hyperproliferation in psoriasis and the permeability barrier, and the reduced amount of ceramides may generally be reflected by boosted ceramide degradation [13]. Holleran et al. [38] revealed that, in psoriasis, a decrease in ceramide synthases (CERS), elongases (ELOVLs), very long FAs (longer than C26), ceramides NP, and on-hydroxy fatty acid/6-hydroxy-sphingosine base NH was observed, although it is worth noting that ceramides NS with shorter FAs (shorter than C24) are increased. Those changes all correlated with the abnormal function of the epidermis. It is also proven that ceramide synthase 3 (CERS3) and ELOVL4 are decreased in interferon gamma (IFN-γ) stimulated keratinocytes. Nevertheless, IFN-γ is increased in psoriatic skin and may be related to epidermal dysfunction. These changes may lead to inflammation, epidermal hyperplasia, and, finally, to the exacerbation of psoriasis. Looking at the inflammatory process in psoriatic skin, it is worth mentioning that levels of IL-6 and IL-8 are increased, both of which are typical psoriasis-associated proinflammatory cytokines. This rise is caused by psoriasis-like HPKs (Human Primary Keratinocytes), and even the psoriasis marker DEFB4A was also observed to have increased. That definitely shows that keratinocytes from psoriatic lesions are very similar in their function to psoriasis-like HPKs. In psoriatic non-lesional skin, decreased mRNA expression of glucosylceramide-β-glucosidase is observed compared to healthy skin. Interestingly, the mRNA level of this enzyme was higher in psoriatic plaques than in non-lesional skin. Psoriatic lesions (both active-type and chronic-type plaques) were characterized by a reduction in prosaposin in comparison to psoriatic non-lesional skin and healthy skin. Prosaposin, an essential forerunner of saposin and a nonenzymatic cofactor, is required in the process of sphingolipid hydrolysis by, for example, β-glucocerebrosidase. The enzymatic transformation of glucosylceramides to ceramides may be disturbed by reduced levels of prosaposin and saposin in psoriatic skin [38]. According to Wang et al. [39], PsA (psoriasis arthritis) patients had significantly higher levels of ApoB, TC, and LDL and a higher ApoB/ApoA1 ratio than psoriasis without

arthritis (PsO) patients [39]. Myśliwiec et al. [40] observed lower concentrations of fatty acids in psoriatic patients and in the PsA group. It was noted that ample amounts of interferon-γ were present in psoriatic skin lesions. This decreases the mRNA expression of elongases of long-chain fatty acids (FA), which is involved in FA metabolism and chain elongation. This could have led to the observed FA profile in that analysis. Higher percentages of saturated fatty acids (SFA) and subdivided into monounsaturated fatty acids (MUFA) and a lower percentage of polyunsaturated FA (PUFA) in both psoriatic groups compared to the healthy controls were also observed. It is widely known that SFA have proinflammatory effects. In contrast, MUFA are believed to have an anti-inflammatory function. Eicosanoids, which are derived from n-6 PUFA arachidonic acid (prostaglandins and leukotrienes), can worsen inflammatory processes, and oxylipins generated from n-3 PUFA (resolvins, maresins, protectins) characterize anti-inflammatory features. The noticed rise in SFA percentage in the PsA group may show a potential connection between PsA and the increased risk of metabolic comorbidity, as SFA are generally linked to higher cardiometabolic risk. The significant distinction in FA profile between psoriasis and PsA in that study was the higher SFA/UFA ratio in the PsA group. It was proven that SFA/UFA ratio is higher in obese psoriatic patients and in individuals with hypertension. Moreover, SFA/UFA ratio correlated positively with disease duration. The authors suggested that the higher SFA/UFA ratio in psoriatic arthritis may indicate a cardiometabolic risk profile in psoriasis and in psoriatic arthritis [40]. Souto-Carneiro et al. [41] found that lipid β-methylenes, lipid α-methylenes, and lipid polyunsaturated allylic methylenes express substantially differently in PsA and seronegative rheumatoid arthritis (negRA) patients, with all methylenes higher in PsA patients. Lipid β-methylenes and lipid α-methylenes can mostly be associated with changes in the levels of lipids in the serum. Since they reflect the lipid β-methylenes and α-methylenes common to most medium and long-chain fatty acids, the lipid polyunsaturated allylic methylenes reflect polyunsaturated allylic methylenes because of the presence of PUFAs, which are known to play a central role in the homeostasis of the immune system. PUFAs have been associated with both proinflammatory (ω6-PUFAs) and anti-inflammatory (ω3-PUFAs) capabilities [41]. Gao et al. [42] reported that, in the early stages of psoriasis, PLA2G4B expression rose due to stress response, which caused abnormal lipid metabolism. The release of free fatty acids and lysophospholipids can be presented to CD1b through activation of myeloid dendritic cells. This causes naïve CD8þ T cells and Th17 to produce inflammatory factors such as IL-17 and IL-36. The increase in the local concentration of inflammatory factors is involved in lipid metabolism and immunological dysregulation response, further aggravating inflammation of the skin lesion site and leading to excessive proliferation of keratinocytes. After using an siRNA emulsifier (siRNA505 PLA2G4B liposome emulsifier and betamethasone), the fluorescence intensity of PLA2G4B decreased significantly, which means that the emulsifier can penetrate the skin surface to play a key role in that process [42]. Tawada et al. [43] demonstrated that IFN-γ downregulates elongation of very long chain fatty acids protein 1 (ELOVL1) and CERS3, which in turn lowers the levels of CERs with long-chain fatty acids in human skin. Additionally, the authors showed that the proportion of CER[NH] with a total carbon number between 40 and 43 (C40–C43 CER[NH]) was elevated, whereas that of C47–C50 CER[NH] was decreased in AD and psoriasis patients compared to healthy controls. The proportion of C44–C46 CER[NH] was decreased only in psoriasis patients. Similar changes in CER[ADS]/[NP] and CER[AP] levels were observed in psoriasis but not in AD; the proportion of C38–C43 CER[ADS]/[NP] and C38–C42 CER[AP] was increased, whereas that of C49–C52 CER[ADS]/[NP] and C45–C48 CER[AP] was decreased. A significant difference in the proportion of C44–C48 CER[ADS]/[NP] was also observed between psoriasis patients and controls. No obvious difference was observed in the proportion profiles of CER[AH]/[NS] and CER[NDS]/[AS] among psoriasis, AD, and control groups [43]. Additionally, Utsunomiya et al. [44] showed that acylceramide (acylCer) and its derivative protein-bound ceramide have an essential role in skin permeability barrier formation. Modestly reduced levels of some ceramide species, including esterified omega-

hydroxyacyl-sphingosine (EOS) which is a representative acylceramide, were consistent with mild skin barrier dysfunction in dermokine (DMKN)-αβγ-/- mice. Additionally, the lipid droplets detected in the stratum corneum may be reflecting the defective secretion of lamellar body content. Furthermore, levels of protein-bound 16 ceramide were also modestly decreased, and this may be associated with the slight fragility of CE in DMKN-αβγ-/- mice. These findings suggest that DMKN isoforms are essential regulators of barrier function and skin inflammation. DMKN-deficient mice may be useful for evaluating disease pathogenesis and preclinical assessment of treatments aimed at specifically targeting molecular drivers of congenital ichthyosis and psoriasis. Furthermore, recombinant DMKN or a therapeutic strategy to enhance DMKN function may be effective for these skin disorders [44]. Del Rosso et al. [45] found that an application of a ceramide/keratolytic-containing cream and/or cleanser provided significant patient-perceived benefits within two weeks in patients dealing with psoriasis. Moisturizers/barrier repair formulations and keratolytic/desmolytic agents are clinically recognized as valuable topical treatment agents for psoriasis. Ceramide-containing products offer beneficial effects in improving barrier function, reducing TEWL, and maintaining SC hydration. In that study, nearly all patients responded positively to the aesthetic attributes of each formulation (i.e., non-greasy, absorbed quickly and easily) and overall product performance (i.e., skin looks and feels healthier). Additionally, a treatment regimen of twice-daily cream application with twice-weekly cleanser use appeared to provide additional benefits based on the perceptions of the study patients. Patients responded positively regarding the use of both products together, with self-reported improvements in their skin (e.g., improved feel, appearance, and symptom relief), even in those who experienced psoriatic flares. Further clinical studies using the ceramide/keratolytic-containing cream and cleanser regimen in combination with topical therapy in patients with psoriasis would provide clearer insight into the importance of barrier repair in patients with psoriasis and the potential benefit of this approach in reducing flares of the disease [45]. Choi et al. [46] and Motta et al. [47] noted that the major change in ceramide composition in psoriasis was associated with a significant drop in the percentage of phytosphingosine-carrying ceramides (3 and 6I) compared to normal stratum corneum, together with increases in some sphingosine-carrying ceramides (2I, 2II, and 5I). Phytosphingosine-carrying ceramides accounted for 25% of total ceramides in the psoriatic scale versus 44% in normal stratum corneum. In another study, the ceramide fractions and transepidermal water loss in psoriatic and normal stratum corneum were compared. In all types of psoriatic scale, ceramide 1, 3, 4, 5II, and 6I content was decreased, and ceramide 2I, 2II, and 5I content was increased. The mean transepidermal water loss value of scaling psoriatic plaques was 11.5 g/cm^2/h, compared to 4.3 g/cm^2/h in controls. They also compared the total content of the three main intercellular lipids in psoriatic scales and normal human stratum corneum. The molar ratio of free fatty acid/cholesterol/ceramide in normal human stratum corneum was 4.1:1.3:1 compared with 2.2:1.3:1 in psoriatic scales. The relative free fatty acid content was much lower in psoriatic scales compared to normal human stratum corneum, while ceramide and cholesterol content was slightly increased in psoriatic scales compared to normal human stratum corneum. These investigators also identified a change in sphingomyelinase expression in psoriatic skin stratum corneum. In psoriatic lesional skin, immune localization of sphingomyelinase was definitively lowered in the stratum corneum. Taken together, these findings suggest that, in patients with psoriasis, a decrease in prosaposin and sphingomyelinase might lead to a decrease in ceramide 1 and other ceramides, as has been observed in psoriatic plaques [46,47]. Cho et al. [48] mention that the level of Cer [NP] and the Cer [NP]/[NS] ratio are higher in the Striatum corneum (SC) compared to keratinocytes (KCs) in normal human skin and that Cer [NP] is the most abundant Cer subclass in the SC, while Cer [NS] is the most abundant Cer subclass in KCs. Ceramides bearing the moieties of amide-linked non-hydroxy acid, α-hydroxy acid, or ω-hydroxy acid and ester-linked fatty acids on sphingosine provide the driving force for lamellar assembly, and these structural moieties are thought to be important in maintaining the structural integrity of the epidermal barrier against water loss through the

skin. Assessment of the lesional epidermis of psoriasis patients revealed no alteration in the levels of linoleic acid (LA) or other fatty acids compared to the non-lesional epidermis of the same patients. In addition, no relationship was observed between the levels of fatty acids and the PASI score in mild to moderate psoriasis. On the other hand, the level of ceramide synthesis was significantly reduced in the lesional epidermis of patients. These results are in concordance with the results of earlier studies in which decreases in the levels of ceramides, specifically ceramide 1, 4, and 5, have been shown to be associated with increased transepidermal water loss in the psoriatic epidermis. Furthermore, a positive correlation between the percentage reduction in ceramide synthesis in the lesional epidermis and clinical severity was demonstrated in that study [48]. Tessema et al. [49] reported that lecithin-based microemulsions (MEs) were observed to have boosted the penetration of oat CERs in vitro and ex vivo. Moreover, the starch-based nanoparticles (NPs) sustained the release of oat CERs. In both in vitro as well as ex vivo observations, oat CERs from ME gel have shown better degrees of penetration compared to the NP gel. The gel formulations, in general, have shown PhytoCERs targeting into the SC. Therefore, they can be used when localizing the CERs in upper epidermal stratums. To sum up, this analysis gave an insight into the skin permeation profile of oat CERs, which is essential for showing their best use in improving the barrier of affected skin [49]. Egger et al. [50] highlight that caveolae and caveolin-1 (Cav1) are known to be involved in endocytosis. They are flask-shaped invaginations of the cell membrane rich in cholesterol and sphingomyelin. Moreover, Cav1 is extremely stable at the cellular membrane, and only some Cav1 rich vesicles actually become internalized. Cav1 can stabilize cellular membranes and slow down membrane invagination, budding, and vesicle internalization. Cav1 participates in inhibiting keratinocyte differentiation and raises intriguing possibilities for targeting Cav1 in cutaneous disorders manifested by abnormal differentiation and proliferation, such as psoriasis and hypertrophic scarring. Interestingly, Cav1 also locates itself on melanocytes and its expression can be induced by UV exposure, where it leads to changes in cell morphology and increased melanin transfer and skin pigmentation as a result of changes in cAMP production. Soon after, evidence began to emerge demonstrating the connection between downregulated Cav1 and excessive epidermal hyperplasia that is classically seen in psoriasis. Histological analyses of psoriatic skin lesions demonstrated lowered expression of Cav1 compared to unaffected skin. Additionally, one study found markedly decreased expression of Cav1 in different types of psoriasis, including psoriasis vulgaris, localized pustular psoriasis (PP), and erythrodermic psoriasis, with psoriasis vulgaris having the most significant downregulation of Cav1 expression compared to the other two types. There was a significant reduction in Cav1 expression in lesional skin compared to non-lesional skin [50]. Geilen et al. [51] revealed that hydrolysis of approximately 25% of total cellular sphingomyelin was observed after 1α,25-dihydroxyvitamin D treatment, and than SM levels came back to control levels. Similar results were obtained regarding primary keratinocytes. The amount of hydrolyzed SM and the time course for SM hydrolysis are in accordance with results obtained in the leukemic cell line (HL-60). TNFα, another well-known inducer of the SM cycle, also activated SM hydrolysis in keratinocytes and immortalized human keratinocyte cell line (HaCaT) cells. We provide evidence that the SM cycle, a signaling pathway originally described in HL-60 cells, is also found in the immortalized human keratinocyte cell line (HaCaT) and in human keratinocytes. In addition to the known inducers of SM hydrolysis, 1α,25-dihydroxyvitamin D and TNF-α both responded to the antiproliferative, synthetic vitamin D analog calcipotriol. Interestingly, acetylsphingosine, which is a short-chain ceramide similar to the naturally occurring breakdown product of SM hydrolysis, mimicked the effects of calcipotriol and l,25-dihydroxyvitamin D on cell proliferation [51]. Zhang et al. [52] reported that glucose transporter 1 (GLUT1) was also essential for proliferation in human keratinocytes in vitro, indicating that psoriatic lesions have bigger requirements for glucose uptake and metabolism, as evidenced by increased *Glut1* expression and PET scans. Confirmation that glycosylated ceramides and UDP-glucose are essential intermediates for epidermal ceramide maturation, lamellar body

formation, and stratum corneum development has been shown in analyses of epidermal lipids conducted in previous reports. Interestingly, liquid chromatography–mass spectrometry and liquid chromatography–tandem mass spectrometry (LC-MS/MS) revealed that the epidermis of *K14.Glut1* mice demonstrated normal levels of phospholipids, lower levels of free ceramides and sphingoidbases, and increased levels of sphingomyelins. Moreover, while hexosylceramide levels were much lower in keratinocytes from *K14.Glut1* mice, they were not significantly decreased in the epidermis of *K14.Glut1* neonatal mice compared to WT. Specifically, glycosylated ceramides have been essential for the proper formation of an intact stratum corneum, as the deletion of glucosylceramide synthase (*Ugcg*) results in a disruption of normal ceramide metabolism, aberrant stratum corneum development, and perinatal lethality. Despite defects in hexosylceramide synthesis in vitro, it was proven that the skin barrier was intact, indicating that the epidermis is able to maintain sufficient levels of ceramides for the maturation of epidermal ceramides even in the absence of Glut1 [52]. Li et al. [53], in their results of a multicenter evaluator-blinded randomized controlled trial (RCT), demonstrated the superiority of the linoleic acid-ceramide-containing moisturizer (LA-Cer) in continuous improvement of PASI 50 response after topical glucocorticoid (GC) use over the control group. Interestingly, the topical linoleic acid-ceramide moisturizer (LA-Cer) prevented relapses and adverse events (AEs) after the end of corticotherapy [53]. Liu et al. [54] demonstrated that both PC and PS were lowered in the IMQ-induced groups but upregulated by (*R*)-salbutamol treatment, which indicates that (*R*)-salbutamol conferred anti-psoriatic effects by modulating the metabolism of glycerophospholipids. In previous articles, the importance of sphingolipids in innate immunity regulation was shown, especially in T cell differentiation and programming. In that study, it was discovered that (*R*)-salbutamol acted against IMQ-induced psoriasis by regulating the Th17/Treg axis. The metabolomics results suggest that the regulation of Th17/Tregs by (*R*)-salbutamol may participate in sphingolipid metabolism. The biomarkers which were identified in this article, either in IMQ-induced mouse psoriasis or after (*R*)-salbutamol treatment, could be useful in identifying pathways and mechanisms mediating the pathogenesis of psoriasis [54]. Simoni et al. [55] reported that psoriasis coexists with invariant natural killer T (iNK T) cell activation. Additionally, the disease is characterized by elevated CD1d expression in psoriatic lesions. Interestingly, $CD4^+$ iNK T cells infiltrate lesions in psoriasis and might be pathogenic. This suggests that protection or worsening of autoimmune diseases by iNK T cells may be due to disequilibrium between the different subsets. Microbial infections enhance the expression of glucosylceramide synthase, leading to the synthesis of β-glucosylceramide (β-GlcCer). Moreover, this self-glycolipid presented by CD1d activates iNK T cells and promotes their proliferation. iNK T cell function may be activated by boosting the expression of glucosylceramide synthase that increases presentation of self-glycolipids, which are able to activate iNK T cells [55]. Breiden et al. [56] note that the final step of triacylglyceride biosynthesis is the acylation of diacylglyceride by acyl-CoA into diacylglycerol acyltransferase 2 (DGAT 2). This is decreased in human skin affected with psoriasis. DGAT 2 shortages in mice lead to disturbed barrier function with increased transepidermal water loss due to drastically reduced total linoleic acid and acylceramide content [56]. Hong et al. [57] measured the expression of SPT and ceramidase in both psoriatic epidermis and non-lesional epidermis. It was concluded that SPT levels were significantly decreased in psoriatic skin. However, the levels of ceramidase showed no significant difference between psoriatic epidermis and non-lesional epidermis. The relationship between PASI score and decreased levels of SPT was also described to highlight the role of decreased SPT in the severity of psoriasis. The link between the percentage reduction in the ratio of SPT/tubulin in the lesional epidermis and the PASI scores showed a significantly negative correlation. Looking at those results, lowered levels of ceramide in psoriatic skin are responsible for decreased levels of SPT in psoriatic skin lesions, and their levels of reduction are highly related to the clinical severity of psoriasis [57].

3.5. Sphingolipids in Psoriasis and Obesity and Metabolic Syndrome

Kozłowska et al. [2] reported that lignoceric ceramide (C24:0) and palmitoleic ceramide (C16:1) were inversely correlated with the severity of psoriasis measured by PASI in overweight patients. Lignoceric ceramide is a key factor in maintaining the right epidermal barrier. The negative correlation between C24:0 and inflammatory markers is well known. Ceramide C24:0 inhibits inflammation and the transformation of insulin resistance and maintains the proper homeostasis of the liver. Nervonic ceramide (C24:1) positively correlates with PAS with normal body weight. C24:1 is an inflammatory marker and possesses a prognostic value in predicting the course of psoriasis. There is a positive connection between C24:1 and CRP in both normal weight and obese patients. Ceramide C24:1 is regarded as a protective and anti-inflammatory substance. C24:1 metabolism disturbances may lead to diabetes complications. There was a noticeable decrease in the level of C24:1 in type 1 diabetes, which increased after insulin treatment. In patients with normal weight, an inverse correlation between eicosapentaenoic ceramide (C20:5) and PASI occurs. The amount of ceramides may be altered under eicosapentaenoic acid (EPA) and DHA supplementation [2]. Kozłowska et al. [58] reported that the highest level of S1P was found among normal weight psoriatic patients in comparison to obese psoriatic patients, with an assumption that higher S1P cell uptake exists in obese patients and may lead to reduced insulin sensitivity. Additionally, they reported that there is a well-known connection between metabolic disturbances and Cer profile. In patients with obesity and comorbidities such as type 2 diabetes mellitus (T2DM), an elevated level of ceramides and its subspecies was observed compared to healthy patients. During gastric bypass, lowered plasma levels of C14:0, C16:0, C20:0, and C24:0 in those patients were also observed. The reduction in C24:0 was linked with increased insulin sensitivity and weight reduction. In young obese adults, a positive link between γ-glutamyl transpeptidase and C24 was observed. The levels of C14:0, C16:0, C22:0, and C24:0 were elevated in prediabetic and diabetic nonhuman primates, and the levels of these ceramides correlate with the homeostasis model assessment of insulin resistance (HOMA-R). In conclusion, C24:0 and C14:0 possess a great influence on creating metabolic disturbances, including for patients suffering from psoriasis [58]. Majumdar et al. [59] report that the level of S1P in plasma may be nstable in the insulin-resistant state. High levels of glucose induce sphingosine kinase (Sphk) in vascular endothelial cells in vitro, which generates S1P that subsequently activates vascular endothelial cell growth. It has been proven that a balance between S1P and sphingolipid metabolites is related to cell death and survival, which may lead to the conclusion that those metabolites function as moderators/regulators of insulin resistance and atherogenesis associated with the chronic inflammatory state of obesity [59].

3.6. Sphingolipids in Psoriasis and Liver Diseases

Kozłowska et al. [58] report that C14:0 and C24:0 ceramides are involved in the pathogenesis of liver disease. The level of ceramides correlates directly with alanine aminotransferase (ALT) concentration. Myristic ceramide (C14:0) possesses the strongest correlation, which was observed in relation to ALT level. C14:0 is widely considered as a novel biomarker of hepatosteatosis, independent of obesity. Under those circumstances, the high level of C14:0 recorded in patients suffering from psoriasis may be related to liver disease, and it can inform us about progressing or incoming liver disease. Interestingly, it was observed that total serum Cer concentration in patients with psoriasis did not correlate with the ALT level in serum. The serum concentration of myristic ceramide (C14:0) and sphingosine-1-phosphate was higher in patients with high-level ALT than in healthy controls. The serum concentration of lignoceric ceramide (C24:0) correlates positively with the ALT level. To sum up, patients dealing with psoriasis are susceptible to the evolution and transformation of liver disease. Altering levels of ceramides in patient serum with psoriasis may indicate the triggering liver disease [58].

3.7. Sphingolipids in Psoriasis and Heart Disease

Hadas et al. [60] revealed that increased ceramide levels in heart tissues during acute myocardial infarction (MI) were associated with higher cell death rates in the left ventricle (LV) and deteriorated cardiac function. Ceramidase, the enzyme which hydrolyzes pro-apoptotic ceramide, generates sphingosine, which is phosphorylated by Sphk to create the pro-survival molecule S1P. It is believed that acid ceramidase (AC) overexpression can alleviate the negative effects of elevated ceramide and promote cell survival, thereby providing cardioprotection after myocardial infarction. High amounts of ceramides in plasma concentrations is associated with a higher probability of MI recurrence and death. High cellular ceramide levels may trigger programmed cell death. It is widely known that ceramide levels are high in the heart tissues of rodents and humans during acute MI, and that blocking de novo ceramide synthesis in rodents can improve heart function post MI. Moderate concentrations of ceramidase and sphingosine kinase inhibitors were not toxic to nrCMs (neonatal rat cardiomiocytes) under normal culture conditions. However, incubating nrCM cells with a higher or lower concentrations of the two inhibitors together induced cell death. Restraining these enzymes may have caused ceramide and/or sphingosine to rise to toxic levels. A combination of hypoxia and enzyme inhibition may boost the rate of pro-apoptotic sphingolipid accumulation and cell death. Restraining AC activity in mouse hearts led to elevated cardiac cell death 24 h post MI. Those results show that AC activity is an essential cardioprotective element in ischemic heart disease, enhances heart function post MI, and moderately diminishes the infarct area and inflammation levels following myocardial injury. Inhibiting AC after an MI episode significantly decreases survival, suggesting AC's active role is vital to mouse survival post MI. S1P receptor 2 (S1pr2) or Sphk2 overexpression did not significantly diminish cardiac cell death either in vitro or in vivo. Sphk1 is, thus, effective for preventing apoptotic death but is not redundant in relation to Sphk2 for this function. Sphk1 interacts with TNF receptor-associated factor 2 (TRAF2). and this mutual interaction tends to trigger TRAF2's anti-apoptotic activity. Our pathway analysis for sphingolipid signal transduction revealed upregulated TRAF2 post MI. It has been recently proven that TRAF2 possesses a cardioprotective role [60]. Poss et al. [61] note that the best-characterized ceramide score is CERT1, though most of the ceramide species contained within CERT1 were predictive of CAD. Cer (18:1/24:0) is a good marker of CAD [61]. Kovilakath et al. [62] highlight that S1P signaling components such as S1PR1, sphingosine 1-phosphate receptor 2 (S1PR2), and sphingolipid transporter 2 (SPNS2) are important for cardiomyocyte development and myocardial precursor migration to the ventral midline of the embryo, where they migrate into the primitive heart tube. Proper concentrations of S1P must be maintained for correct development of cardiac valve precursors. Initial studies, including our own, have shown that inhibition of overall sphingolipid biosynthesis prevented cardiac lipotoxicity, suggesting that merely reducing ceramides in the lipotoxic heart may be a "silver bullet". A cardiomyocyte-specific serine palmitoyltransferase long-chain base subunit 2 (SPTLC2) null mouse model showed an exacerbated cardiac phenotype. In addition to ceramides, however, alterations in dihydroceramides, ceramide-1-phopshates, sphingomyelins, and glycosphingolipids likely play disparate roles in cardiac pathology. Long-chain ceramides and very long-chain ceramides and sphingomyelins are associated with severe cardiac complications. Ceramide (d18:1/16:0), (d18:1/18:0), and (d18:1/24:1) levels were associated with major adverse CVD events. Ceramide (d18:1/22:0) was not associated. There was an increased plasma concentration of C16:0 and C18:0 ceramides in participants with heart failure with preserved ejection fraction (HFpEF). Levels of ceramides and sphingomyelins with a 16-carbon acyl chain length were directly associated with higher risks of mortality from CVD. In contrast, it was observed that levels of ceramides with a 22- or 24-carbon acyl chain length and SM with a 20-, 22-, or 24-carbon acyl chain were associated with lower risks of CVD mortality. While these biomarkers and diagnostic indicators represent advances in identifying and diagnosing CVD, there exists a distinction between long chain (i.e., C16–C18) and very long chain (i.e., C20–C24) ceramides, which are generated by different ceramide synthase isoforms

(CERS1/5/6 vs. CerS2/4, respectively). Generally, a lot of circulating lipids are created in the liver, a detailed study of which demonstrates that circulating ceramides but not sphingomyelins come from the endothelium of blood vessels. Endothelia are functionally abnormal in CVDs, which may lead to the plasma sphingolipid profile reported in heart failure [62]. Altekin et al. [63] mention that chronic skin inflammation in patients suffering from psoriasis may lead to atherosclerosis. Interestingly, it was shown that pulse wave velocity (PWV) and the average and maximum carotid intima media thickness (CIMT) values of psoriasis patients were higher than in the healthy group [63]. Shao et al. [23] demonstrated that the ApoB/ApoA1 ratio is a strong and new risk factor for cardiovascular disease (CVD). Data from Indian patients with acute myocardial infarction (AMI) showed that the ApoB/ApoA1 ratio was a better indicator of CAD risk than other lipid ratios, including the TC/HDL-C and LDL/HDL-C ratios. Furthermore, the ApoB/ApoA1 ratio was associated with femoral artery atherosclerosis [23]. Ilanbey et al. [64] note that chitotriosidase (ChT) activity was found to be higher in patients with hypertension than in those with other comorbidities, such as psoriatic arthritis, diabetes mellitus, or hypothyroidism. The higher activity of ChT in hypertension suggests that macrophages may play a greater role in the pathogenesis of hypertension. ChT is an enzyme excreted by activated macrophages and neutrophils as a response to proinflammatory signals [64]. Lasa et al. [65] found twenty-two studies that assessed bradycardia in 9047 patients exposed to an S1P modulator. Selective S1P1 modulators showed a substantially increased risk of bradycardia. Additionally, seventeen studies assessed the atrioventricular (AV) block in 7662 patients exposed to an S1P modulator (fingolimod, ozanimod, siponimod, ponesimod, amiselimod, etrasimod) [65].

The basic characteristics of the original papers in relation to the researched topic are summarized in Tables 1–7 below.

Table 1. Summary of the studies on the role of ceramides in the pathogenesis of psoriasis.

Author	Year	Population	Key Observation
Ceramides—An Overview			
Hannun et al. [1]	2018	Mammalian cells	Ceramides can be produced via the catabolism of sphingomyelin and glycosphingolipids, as well as via de novo biosynthesis starting from the formation of sphingoid bases and their subsequent N-acylation.
Myśliwiec et al. [4]	2017	n1- 85 patients with active plaque psoriasis, (19–79 years); n2- 32 healthy controls	A significantly higher percentage of MUFA and a lower percent of PUFA was demonstrated in both groups of psoriatic patients (with and without obesity) compared to the healthy control subjects.
Lew et al. [9]	2006	n- 5 patients with psoriasis, from 19 to 33 years	Decreased levels of ceramides have been reported in skin conditions involving dryness and barrier disruption, such as psoriasis.
Yokose et al. [10]	2020	Stratum corneum tape-stripping; n1 = 16, healthy control subjects; n2 = 10, PsO patients; n3 = 8, Cer profiles of AD patients	The level of Cer [NP] and the Cer [NP]/[NS] ratio are higher in the SC compared to KCs in normal human skin.
Lee et al. [11]	2009	Keratinocytes; epidermal growth factor, bovine pituitary extract; 5 µg of total RNA antibiotic-antimycotic	RA inhibits keratinocyte differentiation and lipid metabolism associated with the formation of epidermal barrier function.
Alessandrini et al. [12]	2004	n- 5 male subjects with psoriasis vulgaris; skin biopsies from lesional and non-lesional skin	The mRNA expression of GlcCer'ase is decreased in psoriatic epidermis; its level is higher in lesional compared with non-lesional psoriatic skin.

Abbreviations: Cer—ceramides; RA—retinoids; CPE—ceramide phosphoethanolamine; GE—Gentiana lutea extract; ELOVL—elongase; n1—healthy group; n, n2, n3—study group.

Table 2. Summary of the studies on sphingosine 1-phosphate (S1P) involvement in the pathogenesis of psoriasis.

Author	Year	Population	Key Observation
Sphingosine 1-phosphate (S1P) Involvement in Human Diseases			
Kozłowska et al. [2]	2019	n1- 32 healthy controls; n2- 85 patients with active plaque-type psoriasis.	The S1P concentration was higher in psoriatic patients with normal body weight and those overweight than in the control group. In psoriatic patients with normal body weight, nervonic ceramide (C24:1) correlated with PASI.
Jeon et al. [6]	2020	HEKn cells. Eight-week-old mice.	S1P is associated with inhibition of cell proliferation and induction of differentiation in human keratinocytes.
Moskot et al. [13]	2018	NPC1 mice. SPT-cKO mice.	S1P is responsible for angiogenesis, IL-17 uprising, Th17 cell development, T cell migration, and angiogenesis.
Sorokin et al. [14]	2018	n1- 30 healthy controls. n2- 60 psoriasis patients.	Decreased sphingosine-1-phosphate levels developed by excessive sphingosine-1-phosphate lyase activity, which may be associated with the keratinocyte hyperproliferation seen in psoriasis.
Ji et al. [15]	2018	n2- Female KM mice, 6–8 weeks old; n3- Female guinea pigs.	Sy1930, which selectively modulates S1PR1, ameliorates acanthosis and parakeratosis.
Hong et al. [16]	2009	n- Adult female hairless mice, 8–10 weeks of age.	SphK1 activator K6PC-5 influences Ca2 signaling in human keratinocytes as well as epidermal differentiation and proliferation.
Schuster et al. [17]	2020	n- Mice were euthanized and skin samples harvested after 6, 24, or 72 h for further analysis.	Attenuated CCL2 production translates to reduced infiltration of Mφs into the inflamed tissue.
Setyawan et al. [18]	2021	n1- 182,431 patients, IMD cohort; n2- 182,431 patients, non-IMD cohort.	Sphingosine 1-phosphate receptor modulators were associated with decreased rates of TEs.
Rujimongkon et al. [19]	2021	n1 = 5; n2,3,4,5,6 = 5 each, rats with psoriasis.	Sericin reduced SPL expression in psoriatic skin.
Okura et al. [20]	2021	n- murine. Psoriasiform dermatitis was induced by imiquimod application.	Administration of fingolimod ameliorated IMQ-induced psoriatic dermatitis clinically and histologically.
Shin et al. [21]	2020	n- Eight-week-old male C57BL/6 mice.	HWG-35D significantly reduced thickness and scaling in patients with psoriasis.
Bocheńska et al. [22]	2019	HaCaT cell line.	Increased SPHK1 gene activity in psoriatic lesions, resulting in the production of tumor necrosis factor alpha.

Abbreviations: NKT—natural killer T cells; IMD—immune-mediated diseases; HEKn—human neonatal epidermal keratinocyte; SPT-cKO mice—serine palmitoyltransferase–conditional knockout; NPC1—Niemann–Pick disease type C; n1—healthy group; n, n2, n3, n4, n5—study groups.

Table 3. Summary of the studies on phospholipid metabolism in psoriasis.

Author	Year	Population	Key Observation
Phospholipid Metabolism in Psoriasis			
Shao et al. [23]	2021	n1 = 3; n2 = 22, PP; n3 = 13, PRP	Combination of TNF-α and IL-17A is a strong inducer of PLA2G2F, PLA2G4D, and PLA2G4E expression, and these PLA2s play a major role in the proinflammatory effects of IL-17A and TNF-α on the epidermis.

Table 3. *Cont.*

Author	Year	Population	Key Observation
Phospholipid Metabolism in Psoriasis			
Li et al. [24]	2017	n1- 75 healthy volunteers; n2-75 patients with psoriasis vulgaris	Chenodeoxycholic acid in psoriasis vulgaris was lower than in healthy controls; leukotriene D4 and Llukotriene E3 in serum were significantly higher in psoriasis patients.
Farwan-ah et al. [25]	2005	n1- 7 patients; n2- 7 patients with AD; n3- 6 patients with PP	The ceramide amount in the uninvolved skin of atopic dermatitis (15.3 ± 4.0 μg/cm^2) and psoriasis (11.4 ± 3.5 μg/cm^2) patients is reduced when compared to healthy skin (16.2 ± 3.5 μg/cm^2).
Moon et al. [26]	2013	n- 8 patients with psoriasis vulgaris	The sphingosine and sphinganine amounts are significantly elevated in psoriatic epidermis compared to non-lesional epidermis.
Łuczaj et al. [27]	2020	n1- 6 patients; n2- 6, psoriasis vulgaris	The levels of several species of different classes of phospholipids, including PC, PI, PS, and PEo, are reduced in the keratinocytes of patients with psoriasis.
Zeng et al. [28]	2017	n1- 45 patients; n2- 45, psoriasis	LPA and PA are dramatically increased in psoriasis patients compared to healthy controls.
Kim D. et al. [29]	2021	Six-week-old male Balb/c mice; n1- mice; n2- mice, IMQ-vehicle-treated group; n3- mice, IMQ-ki16425-treated group	LPA induced ROCK2 and PI3K/AKT signaling pathway-mediated cell cycle transformation and proliferation in keratinocytes.
Pang et al. [30]	2015	n1- 84 patients; n2- 86 patients with psoriasis	The fasting serum values of TC, HDL-C, LDL-C, and ApoA-I for the patient group were all significantly lower than those in healthy controls. The levels of fasting serum TG and $ApoB_{100}$ did not show any significant difference between the patient group and healthy controls.
Ferretti et al. [31]	2012	n1- 25 patients; n2- 23 patients with psoriasis	Higher levels of lipid hydroperoxides and lower PON1 activity were observed in the serum of patients. Higher levels of Lp(a) in the serum of patients with psoriasis compared with controls.
Tyrrell et al. [32]	2021	n1- 5 patients; n2- 9 patients with psoriasis	ZIC1 may play a central role in upregulating their metabolism in psoriasis.
Gaire et al. [34]	2020	n- Male BALB/c mice, 6 weeks old, Orient Bio, Gyeonggi-do, Korea	Suppressing LPA_5 activity with a pharmacological antagonist alleviated IMQ-induced psoriasis-like symptoms.
Yamamoto et al. [33]	2016	n- Mice (BALB/c background, 8–12-week-old males)	In psoriasis and skin cancer, $sPLA_2$-IIF is upregulated in the thickened epidermis and promotes epidermal hyperplasia through production of the unique P-LPE.
Syed et al. [35]	2020	n- Mice, primary human monocytes from healthy donors	Direct involvement of SPHKs in macrophage NLRP3 inflammasome activation provides a rationale for therapeutic targeting of these kinases in cancer and inflammation.
Ogawa et al. [36]	2011	n- E-FABP-/- mice	E-FABP affects keratinocyte differentiation, which suggests that E-FABP may have a role in the pathogenesis of psoriasis.
Shou et al. [37]	2021	n1- 10 patients; n2- 8 patients with psoriasis; n3- female BALB/c-Mice at 6–8 weeks of age	The pathogenic role of ferroptosis in sensitizing Th22/Th17-type cytokines was described, thereby providing candidate markers of psoriasis aggravation.

Table 3. *Cont.*

Author	Year	Population	Key Observation
Phospholipid Metabolism in Psoriasis			
Utsunomiya et al. [44]	2020	n2- DMKN-βγ-/-mice; n3- DMKN-αβγ-/- mice	Modestly reduced levels of some ceramide species, including EOS (a representative acylCer), were consistent with mild skin barrier dysfunction in DMKN-αβγ-/- mice.

Abbreviations: IMQ-Ki—IMQ with ki16425-treated group; IMQ-Veh—IMQ with vehicle-treated group; n1—healthy group; n, n2, n3, n4, n5—study groups.

Table 4. Summary of the studies on sphingolipid metabolism in psoriasis.

Author	Year	Population	Key Observation
Psoriasis			
Kozłowska et al. [2]	2019	n1- 32 patients; n2- 85 patients with psoriasis	S1P concentration was higher in psoriatic patients with normal body weight and those overweight than in the control group. In psoriatic patients with normal body weight, nervonic ceramide (C24:1) correlated with PASI.
Łuczaj et al. [3]	2020	n1- 6 patients; n2- 6 patients with psoriasis vulgaris	The results showed higher levels of CER[NS], CER[NP], CER[AS], CER[ADS], CER[AP], and CER[EOS] in the keratinocytes of patients with psoriasis, while the CER[NDS] level was lowered compared to the control samples.
Moskot et al. [13]	2018	n2- NPC1 mice; n3- SPT-cKO mice	S1P is responsible for angiogenesis, IL-17 uprising, Th17 cell development, T cell migration, and angiogenesis.
Cho et al. [48]	2004	n- 10 patients with plaque-type psoriasis	The amount of ceramides in the human epidermis is controlled by a stability in the activity of ceramide generating enzymes (for instance β-glucocerebrosidase, serine palmitoyl transferase, sphingomyelinase) and the degradative enzyme (for example ceramidase). Ceramides in the stratum corneum are originally descended from sphingomyelin and β-glucosylceramides.
Holleran et al. [38]	2016	Mammalian skin; FAN-deficient mice; prosaposin-deficient mice	The enzymatic transformation of glucosylceramides to ceramides may be disturbed by reduced levels of prosaposin and saposin in psoriatic skin.
Checa et al. [5]	2017	n1- 32 healthy patients; n2- 32 patients with mild psoriasis; n3- 32 patients with severe psoriasis	Ceramides with chain lengths of 16–24 were higher in severe patients with psoriasis. Circulating levels of the $C_{12:0}$-ceramide were significantly decreased in severe psoriasis and treatment restored levels to normalcy.
Gao et al. [42]	2021	n- 20 BALB/C male mice (8 weeks old)	A successful knockdown of the PLA2G4B gene by siRNA-505 candidates.
Li et al. [24]	2017	n1- 75 healthy patients; n2- 75 patients with psoriasis vulgaris	Chenodeoxycholic acid in psoriasis vulgaris was lower than in healthy controls; leukotriene D4 and leukotriene E3 in serum were significantly higher in psoriasis patients.
Souto-Carneiro et al. [41]	2020	n2- 49 patients with negRA; n3- 73 with PsA	Lipid β-methylenes and lipid α-methylenes can mostly be associated with changes in the levels of lipids in the serum.
Shou et al. [37]	2021	with psoriasis, n2- female BALB/c-Mice at 6–8 weeks of age	Th22/Th17-type cytokines was described, thereby providing candidate markers of psoriasis aggravation.

Table 4. *Cont.*

Author	Year	Population	Key Observation
		Psoriasis	
Myśliwiec et al. [40]	2019	n1- 32 healthy patients; n2- 54 active plaque-type psoriasis; n2a- 40 without PsA; n2b- 14 with PsA	An abnormal FA profile with a higher SFA/UFA ratio in PsA compared to psoriasis without arthritis; lower concentration of PUFA and higher concentration of MUFA in psoriasis and PsA compared to healthy control.
Del Rosso et al. [45]	2017	n- 33 with a history of mild-to-moderate psoriasis	In this study, application of a ceramide/keratolytic-containing cream showed benefits within two weeks in patients with psoriasis.
Choi et al. [46]	2005	Comparison of the lipid structure of the skin in atopic dermatitis, psoriasis, and healthy controls	A major alteration to ceramide composition in psoriasis was associated with a significant decrease in the percentage of phytosphingosine-carrying ceramides.
Cho et al. [48]	2004	n- 10 psoriatic patients	The level of ceramide synthesis is significantly reduced in the lesional epidermis, which is sensitive enough to make an inverse correlation with clinical severity in mild to moderate status psoriasis.
Tessema et al. [49]	2018	Soybean GlcCER (> 99% by TLC)	ME was shown to improve the penetration of oat CERs in vitro as well as ex vivo compared to the other formulations. On the other hand, the NPs sustained the release of oat CERs.
Egger et al. [50]	2020	Patients with psoriasis and without psoriasis; Cav1-null mice	There was a significant reduction in Cav1 expression in lesional skin compared to non-lesional skin.
Geilen et al. [51]	1996	HaCaT cells, human keratynocytes	The known inducers of SM hydrolysis, 1 a,25_dihydroxyvitamin D and TNFa, both responded to the antiproliferative, synthetic vitamin D analog, calcipotriol.
Zhang et al. [52]	2018	Glut1fl/fl mice	GLUT1 was also essential for proliferation in human keratinocytes in vitro.
Li et al. [53]	2020	n- 178 patients with mild-to-moderate psoriasis vulgaris	LA-Cer moisturizer alleviated psoriasis by maintaining and prolonging the improvement achieved by topical GC treatment.
Liu et al. [54]	2020	8–11 weeks-old BALB/c female mice weighing 20–25 g	Demonstrates a significant anti-psoriasis effect by (R)-salbutamol.
Simoni et al. [55]	2013	Mice- no data available, patients with psoriasis, MS, SLE, RA	$CD4^+$ iNK T cells infiltrate lesions in psoriasis and atherosclerosis and might be pathogenic.
Bæiden et al. [56]	2014	Mice- no data available	Transepidermal water loss is due to the drastically reduced content of total linoleic acid and acylceramides.
Motta et al. [47]	1994	n1- 6 healthy patients; n2- 6 psoriatic patients	In all types of psoriatic scale, CER 1, 3, 4, 5n, and 6 content was decreased, while CER 2h 2n, and 5 content was increased.
Hong et al. [57]	2007	n- 24 patients with psoriasis	Levels of SPT expression in the lesional epidermis were significantly lower than those in the non-lesional epidermis.
Tawada et al. [43]	2014	n1- 22 healthy patients; n2- 15 psoriatic patients; n3- 15 with AD patients	IFN-γ downregulates ELOVL1 and CERS3, which in turn reduces the levels of CERs with long-chain fatty acids in human skin.

Abbreviations: SPT-cKO mice—serine palmitoyltransferase-conditional knockout; NPC1—Niemann-Pick disease type C; FAN—factor associated with neutral sphingomyelinase activity-deficient mice; n1—healthy group; n, n2, n2a, n2b, n3, n4, n5—study groups.

Table 5. Summary of the studies on sphingolipids in psoriasis and obesity and metabolic syndrome.

Author	Year	Population	Key Observation
		Obesity	
Kozłowska et al. [2]	2019	n1- 32 healthy patients; n2- 85 psoriatic patients	In overweight patients, the concentration of lignoceric ceramide (C24:0) correlated inversely with the severity of the disease.
Kozłowska et al. [58]	2021	n1- 32 healthy patients; n2- 85 psoriatic patients	The reduction in C24:0 was linked with increased insulin sensitivity and weight reduction. In young obese adults, a positive link was observed between γ-glutamyl transpeptidase and C24. The levels of C14:0, C16:0, C22:0, and C24:0 were elevated in prediabetic and diabetic nonhuman primates, and the levels of these ceramides correlate with the HOMA-R.
Majumdar et al. [59]	2012	n1- 15 healthy patients; n2- 30 psoriatic patients	A high level of glucose induces Sphk in vascular endothelial cells in vitro and leads to synthesis of S1P, which subsequently activates vascular endothelial cell growth.

Abbreviations: n1—healthy group; n2—study group.

Table 6. Summary of the studies on sphingolipid metabolism in psoriasis and liver disease.

Author	Year	Population	Key Observation
		Liver Diseases	
Kozłowska et al. [58]	2021	n1- 32 healthy patients; n2- 85 psoriatic patients	Lignoceric ceramide positively correlated with ALT level in psoriatic patients.

Abbreviations: n1—healthy group; n2—study group.

Table 7. Summary of the studies on sphingolipids in psoriasis and cardiovascular diseases.

Author	Year	Population	Key Observation
		Heart Diseases	
Hadas et al. [60]	2020	CFW male and female mice, modRNA, sphingolipids	AC overexpression is sufficient and necessary to induce cardioprotection post MI.
Poss et al. [61]	2020	n1- 212 healthy patients; n2- 462 individuals with familial CAD	Cer (18:1/24:0) is a good marker of CAD. Ceramide concentrations were shown to be elevated among individuals with heart events.
Kovilakath [62]	2020	Mice, zebrafish	There were increased plasma concentrations of C16:0 and C18:0 ceramides in participants with HFpEF.
Altekin et al. [63]	2012	n1- 60 healthy patients; n2- 75 plaque-type psoriasis patients	PWV and the average and maximum CIMT values of psoriasis patients were higher than in the healthy group.
Wang et al. [39]	2022	n2- 136 PsA patients; n3- 152 PsO patients	PsA patients had a higher ApoB/ApoA1 ratio than PsO patients. ApoB was positively associated with concomitant arthritis, diabetes, and hypertension.
Ilanbey et al. [64]	2021	n1- 52 healthy patients; n2- 53 psoriatic patients	ChT activity was found to be higher in patients with hypertension than in those with other comorbidities.
Lasa et al. [65]	2021	n- 9604 patients who were exposed to an S1P modulator	Transient cardiovascular events (such as bradycardia and AV block) are increased with S1P modulators.

Abbreviation: ApoA1—apolipoprotein A1; ApoB—apolipoprotein B; CFW—Swiss Webster; HF—heart failure; n1—healthy group; n, n2, n3—study groups.

4. Conclusions

In recent times we have experienced quickly growing interest in the topic of sphingolipids metabolism in human diseases. The discoveries made in recent years have

proven the huge role that altered levels of ceramides play in psoriatic skin, which leads to anti-apoptotic and pro-proliferative states, the over-proliferation of keratinocytes, and the development of skin lesions. Patients suffering from psoriasis with higher S1P serum concentrations may be predisposed to the development of metabolic syndrome. Finally, ceramides are measured as markers of recurrence and mortality after myocardial infarction, coronary artery disease, and acute coronary syndrome. Although sphingolipid metabolism in human diseases has been broadly researched, further research studies are still needed to evaluate the effect of individual ceramides on the course of various diseases. These studies may help us discover new prognostic factors and new treatment modalities.

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References

1. Hannun, Y.A.; Obeid, L.M. Sphingolipids and their metabolism in physiology and disease. *Nat. Rev. Mol. Cell Biol.* **2017**, *19*, 175–191. [CrossRef] [PubMed]
2. Kozłowska, D.; Harasim-Symbor, E.; Myśliwiec, H.; Milewska, A.; Chabowski, A. Serum sphingolipid level in psoriatic patients with obesity. *Adv. Dermatol. Allergol.* **2019**, *36*, 714–721. [CrossRef]
3. Łuczaj, W.; Wroński, A.; Domingues, P.; Rosário Domingues, M.; Skrzydlewska, E. Lipidomic Analysis Reveals Specific Differences between Fibroblast and Keratinocyte Ceramide Profile of Patients with Psoriasis Vulgaris Molecules. *Clin. Immunol.* **2020**, *214*, 108397. [CrossRef]
4. Myśliwiec, H.; Baran, A.; Harasim-Symbor, E.; Myśliwiec, P.; Milewska, A.J.; Chabowski, A.; Flisiak, I. Serum fatty acid profile in psoriasis and its comorbidity. *Arch. Dermatol. Res.* **2017**, *309*, 371–380. [CrossRef]
5. Checa, A.; Xu, N.; Sar, D.G.; Haeggström, J.Z.; Ståhle, M.; Wheelock, C.E. Circulating levels of sphingosine-1-phosphate are elevated in severe, but not mild psoriasis and are unresponsive to anti-TNF-α treatment. *PLoS ONE* **2019**, *14*, e0216963. [CrossRef] [PubMed]
6. Jeon, S.; Song, J.; Lee, D.; Kim, G.-T.; Park, S.-H.; Shin, D.-Y.; Shin, K.-O.; Park, K.; Shim, S.-M.; Park, T.-S. Inhibition of sphingosine 1-phosphate lyase activates human keratinocyte differentiation and attenuates psoriasis in mice. *J. Lipid Res.* **2020**, *61*, 20–32. [CrossRef] [PubMed]
7. Liberati, A.; Altman, D.G.; Tetzlaff, J.; Mulrow, C.; Gøtzsche, P.C.; Ioannidis, J.P.; Clarke, M.; Devereaux, P.J.; Kleijnen, J.; Moher, D. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *Ann. Intern. Med.* **2009**, *151*, W65–W94. [CrossRef] [PubMed]
8. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, n71. [CrossRef]
9. Lew, B.-L.; Cho, Y.; Kim, J.; Sim, W.-Y.; Kim, N.-I. Ceramides and Cell Signaling Molecules in Psoriatic Epidermis: Reduced Levels of Ceramides, PKC-α, and JNK. *J. Korean Med. Sci.* **2006**, *21*, 95–99. [CrossRef] [PubMed]
10. Yokose, U.; Ishikawa, J.; Morokuma, Y.; Naoe, A.; Inoue, Y.; Yasuda, Y.; Tsujimura, H.; Fujimura, T.; Murase, T.; Hatamochi, A. The ceramide [NP]/[NS] ratio in the stratum corneum is a potential marker for skin properties and epidermal differentiation. *BMC Dermatol.* **2020**, *20*, 6. [CrossRef]
11. Lee, D.-D.; Stojadinovic, O.; Krzyzanowska, A.; Vouthounis, C.; Blumenberg, M.; Tomic-Canic, M. Retinoid-responsive transcriptional changes in epidermal keratinocytes. *J. Cell. Physiol.* **2009**, *220*, 427–439. [CrossRef] [PubMed]
12. Alessandrini, F.; Pfister, S.; Kremmer, E.; Gerber, J.-K.; Ring, J.; Behrendt, H. Alterations of Glucosylceramide-β-Glucosidase Levels in the Skin of Patients with Psoriasis Vulgaris. *J. Investig. Dermatol.* **2004**, *123*, 1030–1036. [CrossRef] [PubMed]
13. Moskot, M.; Bocheńska, K.; Jakóbkiewicz-Banecka, J.; Banecki, B.; Gabig-Cimińska, M. Abnormal Sphingolipid World in Inflammation Specific for Lysosomal Storage Diseases and Skin Disorders. *Int. J. Mol. Sci.* **2018**, *19*, 247. [CrossRef]
14. Sorokin, A.V.; Domenichiello, A.F.; Dey, A.K.; Yuan, Z.-X.; Goyal, A.; Rose, S.M.; Playford, M.P.; Ramsden, C.E.; Mehta, N.N. Bioactive Lipid Mediator Profiles in Human Psoriasis Skin and Blood. *J. Investig. Dermatol.* **2018**, *138*, 1518–1528. [CrossRef] [PubMed]

15. Ji, M.; Xue, N.; Lai, F.; Zhang, X.; Zhang, S.; Wang, Y.; Jin, J.; Chen, X. Validating a Selective S1P1 Receptor Modulator Syl930 for Psoriasis Treatment. *Biol. Pharm. Bull.* **2018**, *41*, 592–596. [CrossRef]
16. Hong, J.H.; Youm, J.-K.; Kwon, M.J.; Park, B.D.; Lee, Y.-M.; Lee, S.-I.; Shin, D.M.; Lee, S.H. K6PC-5, a Direct Activator of Sphingosine Kinase 1, Promotes Epidermal Differentiation Through Intracellular Ca2+ Signaling. *J. Investig. Dermatol.* **2008**, *128*, 2166–2178. [CrossRef]
17. Schuster, C.; Huard, A.; Sirait-Fischer, E.; Dillmann, C.; Brüne, B.; Weigert, A. S1PR4-dependent CCL2 production promotes macrophage recruitment in a murine psoriasis model. *Eur. J. Immunol.* **2020**, *50*, 839–845. [CrossRef]
18. Setyawan, J.; Mu, E.; Yarur, A.; Zichlin, M.L.; Yang, H.; Fernan, C.; Billmyer, E.; Downes, N.; Azimi, N.; Strand, V. Risk of Thromboembolic Events and Associated Risk Factors, Including Treatments, in Patients with Immune-mediated Diseases. *Clin. Ther.* **2021**, *43*, 1392–1407.e1. [CrossRef]
19. Rujimongkon, K.; Ampawong, S.; Reamtong, O.; Buaban, T.; Aramwit, P. The therapeutic effects of Bombyx mori sericin on rat skin psoriasis through modulated epidermal immunity and attenuated cell proliferation. *J. Tradit. Complement. Med.* **2021**, *11*, 587–597. [CrossRef]
20. Okura, I.; Kamata, M.; Asano, Y.; Mitsui, A.; Shimizu, T.; Sato, S.; Tada, Y. Fingolimod ameliorates imiquimod-induced psoriasiform dermatitis by sequestrating interleukin-17-producing ?d T cells in secondary lymph nodes. *J. Dermatol. Sci.* **2021**, *102*, 116–125. [CrossRef]
21. Shin, S.-H.; Kim, H.-Y.; Yoon, H.-S.; Park, W.-J.; Adams, D.; Pyne, N.; Pyne, S.; Park, J.-W. A Novel Selective Sphingosine Kinase 2 Inhibitor, HWG-35D, Ameliorates the Severity of Imiquimod-Induced Psoriasis Model by Blocking Th17 Differentiation of Naïve CD4 T Lymphocytes. *Int. J. Mol. Sci.* **2020**, *21*, 8371. [CrossRef]
22. Bocheńska, K.; Moskot, M.; Malinowska, M.; Jakóbkiewicz-Banecka, J.; Szczerkowska-Dobosz, A.; Purzycka-Bohdan, D.; Pleńkowska, J.; Słomiński, B.; Gabig-Cimińska, M. Lysosome Alterations in the Human Epithelial Cell Line HaCaT and Skin Specimens: Relevance to Psoriasis. *Int. J. Mol. Sci.* **2019**, *20*, 2255. [CrossRef] [PubMed]
23. Shao, S.; Chen, J.; Swindell, W.R.; Tsoi, L.C.; Xing, X.; Ma, F.; Uppala, R.; Sarkar, M.K.; Plazyo, O.; Billi, A.C.; et al. Phospholipase A2 enzymes represent a shared pathogenic pathway in psoriasis and pityriasis rubra pilaris. *JCI Insight* **2021**, *6*, e151911. [CrossRef] [PubMed]
24. Li, L.; Lu, C.; Han, L.; Deng, J.; He, Z.; Yan, Y.; Zhang, Z. Untargeted serum metabonomics study of psoriasis vulgaris based on ultra-performance liquid chromatography coupled to mass spectrometry. *Oncotarget* **2017**, *8*, 95931–95944. [CrossRef] [PubMed]
25. Farwanah, H.; Raith, K.; Neubert, R.H.H.; Wohlrab, J. Ceramide profiles of the uninvolved skin in atopic dermatitis and psoriasis are comparable to those of healthy skin. *Arch. Dermatol. Res.* **2005**, *296*, 514–521. [CrossRef]
26. Moon, S.-H.; Kim, J.-Y.; Song, E.-H.; Shin, M.-K.; Cho, Y.-H.; Kim, N.-I. Altered Levels of Sphingosine and Sphinganine in Psoriatic Epidermis. *Ann. Dermatol.* **2013**, *25*, 321–326. [CrossRef] [PubMed]
27. Łuczaj, W.; Dobrzyńska, I.; Wroński, A.; Domingues, M.R.; Domingues, P.; Skrzydlewska, E. Cannabidiol-Mediated Changes to the Phospholipid Profile of UVB-Irradiated Keratinocytes from Psoriatic Patients. *Int. J. Mol. Sci.* **2020**, *21*, 6592. [CrossRef] [PubMed]
28. Zeng, C.; Wen, B.; Hou, G.; Lei, L.; Mei, Z.; Jia, X.; Chen, X.; Zhu, W.; Li, J.; Kuang, Y.; et al. Lipidomics profiling reveals the role of glycerophospholipid metabolism in psoriasis. *GigaScience* **2017**, *6*, 1–11. [CrossRef] [PubMed]
29. Kim, D.; Kim, H.-J.; Baek, J.-O.; Roh, J.-Y.; Jun, H.-S. Lysophosphatidic Acid Mediates Imiquimod-Induced Psoriasis-like Symptoms by Promoting Keratinocyte Proliferation through LPAR1/ROCK2/PI3K/AKT Signaling Pathway. *Int. J. Mol. Sci.* **2021**, *22*, 10777. [CrossRef]
30. Pang, X.; Lin, K.; Liu, W.; Zhang, P.; Zhu, S. Characterization of the abnormal lipid profile in Chinese patients with psoriasis. *Int. J. Clin. Exp. Pathol.* **2015**, *8*, 15280–15284.
31. Ferretti, G.; Bacchetti, T.; Campanati, A.; Simonetti, O.; Liberati, G.; Offidani, A. Correlation between lipoprotein(a) and lipid peroxidation in psoriasis: Role of the enzyme paraoxonase-1. *Br. J. Dermatol.* **2011**, *166*, 204–207. [CrossRef]
32. Tyrrell, V.J.; Ali, F.; Boeglin, W.E.; Andrews, R.; Burston, J.; Birchall, J.C.; Ingram, J.R.; Murphy, R.C.; Piguet, V.; Brash, A.R.; et al. Lipidomic and transcriptional analysis of the linoleoyl-omega-hydroxyceramide biosynthetic pathway in human psoriatic lesions. *J. Lipid Res.* **2021**, *62*, 100094. [CrossRef] [PubMed]
33. Yamamoto, K.; Miki, Y.; Sato, H.; Nishito, Y.; Gelb, M.H.; Taketomi, Y.; Murakami, M. Expression and Function of Group IIE Phospholipase A2 in Mouse Skin. *J. Biol. Chem.* **2016**, *291*, 15602–15613. [CrossRef] [PubMed]
34. Gaire, B.P.; Lee, C.-H.; Kim, W.; Sapkota, A.; Lee, D.Y.; Choi, J.W. Lysophosphatidic Acid Receptor 5 Contributes to Imiquimod-Induced Psoriasis-Like Lesions through NLRP3 Inflammasome Activation in Macrophages. *Cells* **2020**, *9*, 1753. [CrossRef]
35. Syed, S.N.; Weigert, A.; Brüne, B. Sphingosine Kinases are Involved in Macrophage NLRP3 Inflammasome Transcriptional Induction. *Int. J. Mol. Sci.* **2020**, *21*, 4733. [CrossRef]
36. Ogawa, E.; Owada, Y.; Ikawa, S.; Adachi, Y.; Egawa, T.; Nemoto, K.; Suzuki, K.; Hishinuma, T.; Kawashima, H.; Kondo, H.; et al. Epidermal FABP (FABP5) Regulates Keratinocyte Differentiation by 13(S)-HODE-Mediated Activation of the NF-κB Signaling Pathway. *J. Investig. Dermatol.* **2011**, *131*, 604–612. [CrossRef]
37. Shou, Y.; Yang, L.; Yang, Y.; Xu, J. Inhibition of keratinocyte ferroptosis suppresses psoriatic inflammation. *Cell Death Dis.* **2021**, *12*, 1–10. [CrossRef] [PubMed]
38. Holleran, W.M.; Takagi, Y.; Uchida, Y. Epidermal sphingolipids: Metabolism, function, and roles in skin disorders. *Am. J. Clin. Dermatol.* **2003**, *4*, 107–129. [CrossRef]

39. Wang, B.; Deng, H.; Hu, Y.; Han, L.; Huang, Q.; Fang, X.; Yang, K.; Wu, S.; Zheng, Z.; Yawalkar, N.; et al. The difference of lipid profiles between psoriasis with arthritis and psoriasis without arthritis and sex-specific downregulation of methotrexate on the apolipoprotein B/apolipoprotein A-1 ratio. *Arthritis Res. Ther.* **2022**, *24*, 1–9. [CrossRef] [PubMed]
40. Myśliwiec, H.; Harasim-Symbor, E.; Baran, A.; Szterling-Jaworowska, M.; Milewska, A.; Chabowski, A.; Flisiak, I. Abnormal serum fatty acid profile in psoriatic arthritis. *Arch. Med. Sci.* **2019**, *15*, 1407–1414. [CrossRef] [PubMed]
41. Souto-Carneiro, M.; Tóth, L.; Behnisch, R.; Urbach, K.; Klika, K.D.; Carvalho, R.; Lorenz, H.-M. Differences in the serum metabolome and lipidome identify potential biomarkers for seronegative rheumatoid arthritis versus psoriatic arthritis. *Ann. Rheum. Dis.* **2020**, *79*, 499–506. [CrossRef] [PubMed]
42. Gao, Y.; Lu, J.; Bao, X.; Yi, X.; Peng, C.; Chen, W.; Zhen, T.; Shi, Y.; Xing, K.; Zhu, S.; et al. Inhibition of phospholipases suppresses progression of psoriasis through modulation of inflammation. *Exp. Biol. Med.* **2021**, *246*, 1253–1262. [CrossRef]
43. Tawada, C.; Kanoh, H.; Nakamura, M.; Mizutani, Y.; Fujisawa, T.; Banno, Y.; Seishima, M. Interferon-γ Decreases Ceramides with Long-Chain Fatty Acids: Possible Involvement in Atopic Dermatitis and Psoriasis. *J. Investig. Dermatol.* **2014**, *134*, 712–718. [CrossRef] [PubMed]
44. Utsunomiya, A.; Chino, T.; Utsunomiya, N.; Luong, V.H.; Tokuriki, A.; Naganuma, T.; Arita, M.; Higashi, K.; Saito, K.; Suzuki, N.; et al. Homeostatic Function of Dermokine in the Skin Barrier and Inflammation. *J. Investig. Dermatol.* **2019**, *140*, 838–849.e9. [CrossRef]
45. Del Rosso, J.Q. Ceramide- and Keratolytic-containing Body Cleanser and Cream Application in Patients with Psoriasis: Outcomes from a Consumer Usage Study. *J. Clin. Aesthetic Dermatol.* **2019**, *12*, 18–21.
46. Choi, M.J.; Maibach, H.I. Role of Ceramides in Barrier Function of Healthy and Diseased Skin. *Am. J. Clin. Dermatol.* **2005**, *6*, 215–223. [CrossRef] [PubMed]
47. Motta, S.; Monti, M.; Sesana, S.; Mellesi, L.; Ghidoni, R.; Caputo, R. Abnormality of Water Barrier Function in Psoriasis. Role of ceramide fractions. *Arch. Dermatol.* **1994**, *130*, 452–456. [CrossRef]
48. Cho, Y.; Lew, B.-L.; Seong, K.; Kim, N.-I. An Inverse Relationship Between Ceramide Synthesis and Clinical Severity in Patients with Psoriasis. *J. Korean Med. Sci.* **2004**, *19*, 859–863. [CrossRef]
49. Tessema, E.N.; Gebre-Mariam, T.; Paulos, G.; Wohlrab, J.; Neubert, R.H. Delivery of oat-derived phytoceramides into the stratum corneum of the skin using nanocarriers: Formulation, characterization and in vitro and ex-vivo penetration studies. *Eur. J. Pharm. Biopharm.* **2018**, *127*, 260–269. [CrossRef] [PubMed]
50. Egger, A.N.; Rajabi-Estarabadi, A.; Williams, N.M.; Resnik, S.R.; Fox, J.D.; Wong, L.L.; Jozic, I. The importance of caveolins and caveolae to dermatology: Lessons from the caves and beyond. *Exp. Dermatol.* **2019**, *29*, 136–148. [CrossRef]
51. Geilen, C.C.; Bektas, M.; Wieder, T.; Orfanos, C.E. The vitamin D_3 analogue, calcipotriol, induces sphingomyelin hydrolysis in human keratinocytes. *FEBS Lett.* **1996**, *378*, 88–92. [CrossRef] [PubMed]
52. Zhang, Z.; Zi, Z.; Lee, E.E.; Zhao, J.; Contreras, D.C.; South, A.P.; Abel, E.D.; Chong, B.F.; Vandergriff, T.; Hosler, G.A.; et al. Differential glucose requirement in skin homeostasis and injury identifies a therapeutic target for psoriasis. *Nat. Med.* **2018**, *24*, 617–627. [CrossRef] [PubMed]
53. Li, X.; Yang, Q.; Zheng, J.; Gu, H.; Chen, K.; Jin, H.; He, C.; Xu, A.; Xu, J.; Zhang, J.; et al. Efficacy and safety of a topical moisturizer containing linoleic acid and ceramide for mild-to-moderate psoriasis vulgaris: A multicenter randomized controlled trial. *Dermatol. Ther.* **2020**, *33*, e14263. [CrossRef]
54. Liu, F.; Wang, S.; Liu, B.; Wang, Y.; Tan, W. (R)-Salbutamol Improves Imiquimod-Induced Psoriasis-Like Skin Dermatitis by Regulating the Th17/Tregs Balance and Glycerophospholipid Metabolism. *Cells* **2020**, *9*, 511. [CrossRef]
55. Simoni, Y.; Diana, J.; Ghazarian, L.; Beaudoin, L.; Lehuen, A. Therapeutic manipulation of natural killer (NK) T cells in autoimmunity: Are we close to reality? *Clin. Exp. Immunol.* **2012**, *171*, 8–19. [CrossRef] [PubMed]
56. Breiden, B.; Sandhoff, K. The role of sphingolipid metabolism in cutaneous permeabilitybarrier formation. *Biochim. et Biophys. Acta (BBA)-Mol. Cell Biol. Lipids* **2014**, *1841*, 441–452. [CrossRef]
57. Hong, K.-K.; Cho, H.-R.; Ju, W.-C.; Cho, Y.; Kim, N.-I. A Study on Altered Expression of Serine Palmitoyltransferase and Ceramidase in Psoriatic Skin Lesion. *J. Korean Med. Sci.* **2007**, *22*, 862–867. [CrossRef]
58. Kozłowska, D.; Harasim-Symbor, E.; Myśliwiec, H.; Milewska, A.; Chabowski, A.; Flisiak, I. Lipid profile disturbances may predispose psoriatic patients to liver dysfunction. *Adv. Dermatol. Allergol.* **2021**, *38*, 310–318. [CrossRef] [PubMed]
59. Majumdar, I.; Mastrandrea, L.D. Serum sphingolipids and inflammatory mediators in adolescents at risk for metabolic syndrome. *Endocrine* **2012**, *41*, 442–449. [CrossRef]
60. Hadas, Y.; Vincek, A.S.; Youssef, E.; Żak, M.M.; Chepurko, E.; Sultana, N.; Sharkar, M.T.K.; Guo, N.; Komargodski, R.; Kurian, A.A.; et al. Altering Sphingolipid Metabolism Attenuates Cell Death and Inflammatory Response After Myocardial Infarction. *Circulation* **2020**, *141*, 916–930. [CrossRef] [PubMed]
61. Poss, A.M.; Maschek, J.A.; Cox, J.E.; Hauner, B.J.; Hopkins, P.N.; Hunt, S.C.; Holland, W.L.; Summers, S.A.; Playdon, M.C. Machine learning reveals serum sphingolipids as cholesterol-independent biomarkers of coronary artery disease. *J. Clin. Investig.* **2020**, *130*, 1363–1376. [CrossRef] [PubMed]
62. Kovilakath, A.; Jamil, M.; Cowart, L.A. Sphingolipids in the Heart: From Cradle to Grave. *Front. Endocrinol.* **2020**, *11*. [CrossRef] [PubMed]

63. Altekin, E.R.; Koç, S.; Karakaş, M.S.; Yanıkoğlu, A.; Başarıcı, I.; Demir, I.; Alpsoy, E. Determination of subclinical atherosclerosis in plaque type psoriasis patients without traditional risk factors for atherosclerosis. *Turk Kardiyol. Dern. Ars.* **2012**, *40*, 574–580. [CrossRef] [PubMed]
64. Ilanbey, B.; Elmas, F.; Sözmen, E.Y.; Günay, Ü.; Demirbaş, A.; Atasoy, M.; Türsen, Ü.; Lotti, T. A novel marker of systemic inflammation in psoriasis and related comorbidities: Chitotriosidase. *Turk. J. Med. Sci.* **2021**, *51*, 2318–2323. [CrossRef]
65. Lasa, J.S.; Olivera, P.A.; Bonovas, S.; Danese, S.; Peyrin-Biroulet, L. Safety of S1P Modulators in Patients with Immune-Mediated Diseases: A Systematic Review and Meta-Analysis. *Drug Saf.* **2021**, *44*, 645–660. [CrossRef]

Rozdział 6. Streszczenie w języku polskim

Łuszczyca jest przewlekłą zapalną chorobą immunologiczną, która jest szeroko rozpowszechniona na całym świecie. Występuje ona częściej u dorosłych niż u dzieci, a jej globalna częstość występowania w tej pierwszej grupie szacowana jest na 0.27% - 11.4%. Najbardziej klasycznymi objawami łuszczycy plackowatej są rumieniowe, dobrze odgraniczone zmiany skórne, które są zazwyczaj pokryte srebrzystymi łuskami. W typowych łuszczycowych zmianach skórnych zaburzone jest różnicowanie keratynocytów naskórka (parakeratoza i akantoza) oraz naciekanie komórek odpornościowych do głębszych warstw skóry. Łuszczyca zajmuje nie tylko skórę, ale także stawy i mogą jej towarzyszyć różne schorzenia ogólnoustrojowe. Głównie ze względu na prozapalną etiologię łuszczycy może ona współwystępować z różnorodnymi składnikami zespołu metabolicznego, np. hiperlipidemią, nadciśnieniem tętniczym, otyłością. Z upływem czasu schorzenia te mogą prowadzić do rozwoju T2DM, choroby miażdżycowej, CAD lub MI.

Celem pierwszej z prac wchodzących w skład niniejszej rozprawy doktorskiej, była ocena stężenia wybranych sfingolipidów tzn. S1P, SFO, SFA, SFA1P, CERs w skórze zajętej i niezajętej chorobowo u pacjentów z łuszczycą.

Do badania włączono 15 pacjentów (7 mężczyzn i 8 kobiet) z aktywną łuszczycą plackowatą o różnym nasileniu oraz 17 osób do grupy kontrolnej (11 mężczyzn i 6 kobiet). Średni czas trwania łuszczycy wynosił 24 lata.

Stężenia wszystkich badanych sfingolipidów (S1P, SFO, SFA, SFA1P, CERs) były wyższe w skórze zmienionej chorobowo, w porównaniu do skóry niezajętej u pacjentów z łuszczycą oraz do skóry osób zdrowych. W skórze klinicznie niezmienionej pacjentów z łuszczycą obserwowano wyższe stężenie CERs i SFO w stosunku do skóry osób zdrowych.

Dodatkowo, wykazano statystycznie istotne dodatnie korelacje między naciekiem w obrębie zmian skórnych a SFA oraz SFA1P upacjentów z łuszczycą.

Celem drugiej z prac wchodzących w skład rozprawy doktorskiej była ocena korelacji pomiędzy sfingolipidami obecnymi w skórze pacjentów a analogicznymi metabolitami w surowicy pacjentów z łuszczycą. Badaniem objęto 20 pacjentów z łuszczycą i 28 osób zdrowych. Wykazano, iż stężenia S1P, SFO, SFA, SFA1P w surowicy pacjentów z łuszczycą były znacznie podwyższone ($p<0,05$) w porównaniu do poziomów tych samych sfingolipidów u osób zdrowych. Wykazano ujemne korelacje Pearsona między różnymi zmiennymi w skórze niezajętej chorobowo i surowicy pacjentów z łuszczycą. W szczególności korelacje obejmują SFO w tkance do SFO w surowicy, CERs w tkance do SFA w surowicy, CERs w tkance do SFO w surowicy, i SFO w tkance do SFA w surowicy. Natomiast dodatnia korelacja Pearsona była widoczna między CERs w tkance do CERs w surowicy, SFA w tkance do CERs w surowicy, oraz SFO w tkance do CERs w surowicy. Nie stwierdzono istotnych korelacji między sfingolipidami w skórze i surowicy grupy kontrolnej.

W pracy przeglądowej podsumowano dotychczasową wiedzę na temat roli sfingolipidów w patogenezie łuszczycy. Wyniki wielu badań wskazują, że u pacjentów z łuszczycą zaburzony metabolizm sfingolipidów, może być czynnikiem łączącym patogenezę rozwoju łuszczycy z ogólnoustrojowymi chorobami towarzyszącymi np. zespołem metabolicznym, chorobami sercowo-naczyniowymi, chorobami wątroby.

Wnioski

1. Pacjenci z łuszczycą pospolitą mają odmienny profil sfingolipidowy w skórze zmienionej (wyższe stężenie CERs, S1P, SFO, SFA, SFA1P) w porównaniu do skóry niezmienionej chorobowo oraz do skóry osób zdrowych.

2. W skórze niezmienionej chorobowo u pacjentów z łuszczycą stwierdzono wyższe stężenia sfingolipidów (CERs, SFO) w porównaniu do skóry osób zdrowych. Wskazuje to, na występowanie zaburzeń i nieprawidłowości metabolizmu lipidów nawet w klinicznie pozornie niezmienionej skórze.

3. Zaobserwowane korelacje między wybranymi bioaktywnymi sfingolipidami w skórze zmienionej chorobowo a poziomem tych samych związków w surowicy pacjentów z łuszczycą, mogą wskazywać na wpływ zaburzeń metabolizmu lipidów skóry na zmiany ogólnoustrojowe.

4. Nieprawidłowy metabolizm sfingolipidów u pacjentów z łuszczycą, może wpływać na występowanie i przebieg schorzeń współistniejących z łuszczycą np. otyłości, zespołu metabolicznego, schorzeń wątroby oraz chorób sercowo-naczyniowych.

Rozdział 7. Streszczenie w języku angielskim.

Psoriasis is a chronic inflammatory immune-mediated disease that is widespread worldwide. Its global prevalence is between 0.27% and 11.4% in adults and appears more frequently in adults than in children. The most classic symptoms of plaque psoriasis are erythematous, well-demarcated lesions generally covered by silvery scales. In typical psoriatic skin lesions, deregulated differentiation of epidermal keratinocytes (parakeratosis and acanthosis) and infiltration of immune cells into the deeper layers of the skin may be observed.

Psoriasis is a chronic inflammatory autoimmune disease that commonly affects both the skin and joints. Primarily driven by its pro-inflammatory nature, psoriasis often coexists with various components of metabolic syndrome, such as hyperlipidemia, hypertension, and obesity. Over time, these conditions may contribute to the onset of type 2 diabetes mellitus (T2DM), atherosclerotic disease, ischemic heart disease, or myocardial infarction.

The objective of the primary original article, "The Interplay between Bioactive Sphingolipids in Psoriatic Skin and the Severity of the Disease," which serves as the basis for this dissertation, is to evaluate the levels of specific sphingolipids—namely, CERs, SFA1P, SFA, SFO, and S1P—in both unaffected and psoriasis-affected skin tissue among patients with psoriasis.

The study included 17 healthy patients (11 men and 6 women) and 15 patients (7 men and 8 women) with active plaque psoriasis of varying severity. The mean duration of psoriasis was 24 years.

All the sphingolipid levels analyzed in this study (S1P, SFO, SFA, SFA1P, CERs) exhibited higher concentrations in psoriasis-affected skin compared to non-lesional skin in patients with psoriasis. Elevated levels of CER and SFO were also noted in the clinically unaffected skin of psoriasis patients compared to that of healthy individuals.

In the second original paper, titled "Crosstalk between Serum and Skin Sphingolipids in Psoriasis," we evaluated the correlation between sphingolipids present in the skin of psoriatic patients and those found in the serum of patients with psoriasis. The study comprised 20 patients with psoriasis and 28 healthy subjects. It demonstrated that serum levels of S1P, SFO, SFA, and SFA1P in psoriatic patients were significantly elevated ($p<0.05$) compared to the levels of these same sphingolipids in the serum of healthy subjects.

We observed negative Pearson's correlations between various variables in non-lesional psoriatic skin and the serum of psoriatic patients, all of which were statistically significant. Specifically, the correlations include tissue SFO vs. serum SFA, tissue SFO vs. serum SFO, tissue CERs vs. serum SFO, and tissue CERs vs. serum SFA.

A positive Pearson's correlation was evident between several variables in lesional psoriatic skin and the serum of psoriatic patients. Specifically, statistically significant associations were observed between tissue CERs and serum CERs, SFO in tissue and serum CERs, and SFA in tissue and serum CERs. There were no significant correlations between serum and skin sphingolipids in the healthy skin and serum of the control group.

The review article summarizes the current knowledge regarding the role of sphingolipids in the pathogenesis of psoriasis. The findings of numerous studies indicate that disrupted sphingolipid metabolism in psoriatic patients may serve as a connecting factor linking the pathogenesis of psoriasis with systemic comorbidities such as metabolic syndrome, cardiovascular diseases, and liver diseases.

Conclusions:

1. Patients with psoriasis vulgaris exhibit a distinct sphingolipid profile in affected skin (elevated levels of CERs, S1P, SFO, SFA, SFA1P) compared to unaffected skin and healthy individuals' skin.

2. Higher concentrations of sphingolipids (CERs, SFO) were found in the unaffected skin of psoriasis patients compared with the skin of the control group. This indicates the presence of lipid metabolism disorders and abnormalities even in clinically seemingly unaffected skin.

3. The observed correlations between selected bioactive sphingolipids in lesional skin and their levels in the serum of psoriatic patients, may suggest the influence of abnormal skin lipid metabolism on systemic changes.

4. Dysregulated sphingolipid metabolism in individuals with psoriasis may impact the occurrence and progression of comorbidities such as obesity, metabolic syndrome, liver disease, and cardiovascular disease.

Rozdział 8. Spis piśmiennictwa

1. Parisi, R.; Symmons, D.P.M.; Griffiths, C.E.M.; Ashcroft, D.M. Global epidemiology of psoriasis: A systemic review of incidence and prevalence. J. Invest. Dermatol. 2013, 133, 377–385.

2. Parisi, R.; Iskander, I.Y.K.; Kontopantelis, E.; Augustin, E.; Griffiths, C.E.M.; Ashcroft, D.M. National, regional, and worldwide epidemiology of psoriasis: Systemic analysis and modeling study. BMJ 2020, 369, m1590.

3. Zheng, M.; Jullien, D.; Eyerich, E. The prevalence and Disease Characteristics of generalized Pustular Psoriasis. Am. J. Clin. Dermatol. 2022, 23 (Suppl. S1), 5–12.

4. Lowes, M.A.; Bowcock, A.M.; Krueger, J.G. Pathogenesis and therapy of psoriasis. Nature 2007, 445, 866–873.

5. Laporte, M.; Galand, P.; Fokan, D.; de Graef, C.; Heenen, M. Apoptosis in established and healing psoriasis. Dermatology 2000, 200, 314–316.

6. Wrone-Smith, T.; Mitra, R.S.; Thompson, C.B.; Jasty, R.; Castle, V.P.; Nickoloff, B.J. Keratinocytes derived from psoriatic plaques are resistant to apoptosis compared with normal skin. Am. J. Pathol. 1997, 151, 1321–1329.

7. Chiricozzi, A.; Raimondo, A.; Lembo, S.; Fausti, F.; Dini, V.; Costanzo, A.; Monfrecola, G.; Balato, N.; Ayala, F.; Romanelli, M.; et al. Crosstalk between skin inflammation and adipose tissue-derived products: Pathogenic evidence linking psoriasis to increases adiposity. Expert. Rev. Clin. Immunol. 2016, 12, 1299–1308.

8. Fernández-Armenteros, J.M.; Gómez-Arbonés, X.; Buti-Soler, M.; Betriu-Bars, A.; Sanmartin-Novell, V.; Ortega-Bravo, M.; Martínez-Alonso, M.; Garí, E.; Portero-Otín, M.; Santamaria-Babi, L.; et al. Psoriasis, metabolic syndrome and cardiovascular risk factors. A population-based study. J. Eur. Acad. Dermatol. Venereol. 2019, 33, 128–135.

9. Nakhwa, Y.C.; Rashmi, R.; Basavaraj, K.H. Dyslipidemia in Psoriasis: A Case Controlled Study. Int. Sch. Res. Not. 2014, 2014, 729157.

10. Hannun, Y.A.; Obeid, L.M. Sphingolipids and their metabolism in physiology and disease. Nat. Rev. Mol. Cell Biol. 2018, 19, 175–191.

11. Moskot, M.; Bochenska, K.; Jakobkiewiczc-Baniecka, J.; Banecki, B.; Gabig-Ciminska, M. Abnormal Sphingolipid World in Inflammation Specific for Lysosomal Storage Disease and Skin Disorders. Int. J. Mol. Sci. 2018, 19, 247.

12. Checa, A.; Xu, N.; Sar, D.G.; Haeggstrom, J.Z.; Stahle, M.; Wheelock, C.E. Circulating levels of sphingosine-1-phosphate are elevated in severe, but not mild psoriasis and are unresponsive to anti-TNF-_ treatment. Sci. Rep. 2015, 5, 12017.

13. Mysliwiec, H.; Baran, A.; Harasim-Symbor, E.; Choromanska, B.; Mysliwiec, P.; Justyna Milewska, A.; Chabowski, A.; Flisiak, I. Increase in circulating sphingosine-1-phosphate and decrease in ceramide levels in psoriatic patients. Arch. Dermatol. Res. 2017, 309, 79–86.

14. Herzinger, T.; Kleuser, B.; Schäfer-Korting, M.; Christian Korting, H. Sphingosine-1-phosphate signaling and the skin. Am. J. Clin. Dermatol. 2007, 8, 329–336.

15. Sung-Hyuk, M.; Kim, J.Y.; Song, E.H.; Shin, M.K.; Cho, Y.H.; Kim, N.I. Altered Levels of Sphingosine and Sphinganine in Psoriatic Epidermis. Ann. Dermatol. 2013, 25, 321–326.

16. Kozłowska, D.; Harasim-Symbor, E.; My´sliwiec, H.; Milewska, A.; Chabowski, A. Serum sphingolipid level in psoriatic patients with obesity. Adv. Dermatol. Allergol. 2019, 36, 714–721.

17. Majumdar, I.; Mastrandrea, L.D. Serum sphingolipids and inflammatory mediators in adolescents at risk for metabolic syndrome. Endocrine 2012, 41, 442–449.

18. Kovilakath, A.; Jamil, M.; Cowart, L.A. Sphingolipids in the Heart: From Cradle to Grave. Front. Endocrinol. 2020, 11.

19. Farwanah H, Raith K, Neubert RH, Wohlrab J. Ceramide profiles of the uninvolved skin in atopic dermatitis and psoriasis are comparable to those of healthy skin. Arch Dermatol Res. 2005 May;296(11):514-21.

20. Tawada C, Kanoh H, Nakamura M, Mizutani Y, Fujisawa T, Banno Y, Seishima M. Interferon-γ decreases ceramides with long-chain fatty acids: possible involvement in atopic dermatitis and psoriasis. J Invest Dermatol. 2014 Mar;134(3):712-718.

21. Utsunomiya, A.; Chino, T.; Utsunomiya, N.; Luong, V.H.; Tokuriki, A.; Naganuma, T.; Arita, M.; Higashi, K.; Saito, K.; Suzuki, N.; et al. Homeostatic Function of Dermokine in the Skin Barrier and Inflammation. J. Investig. Dermatol. 2019, 140, 838–849.e9.

22. Del Rosso, J.Q. Ceramide- and Keratolytic-containing Body Cleanser and Cream Application in Patients with Psoriasis: Outcomes from a Consumer Usage Study. J. Clin. Aesthetic Dermatol. 2019, 12, 18–21.

23. Choi, M.J.; Maibach, H.I. Role of Ceramides in Barrier Function of Healthy and Diseased Skin. Am. J. Clin. Dermatol. 2005, 6, 215–223.

24. Motta, S.; Monti, M.; Sesana, S.; Mellesi, L.; Ghidoni, R.; Caputo, R. Abnormality of Water Barrier Function in Psoriasis. Role of ceramide fractions. Arch. Dermatol. 1994, 130, 452–456.

25. Yokose U, Ishikawa J, Morokuma Y, Naoe A, Inoue Y, Yasuda Y, Tsujimura H, Fujimura T, Murase T, Hatamochi A. The ceramide [NP]/[NS] ratio in the stratum corneum is a potential marker for skin properties and epidermal differentiation. BMC Dermatol. 2020 Aug 31;20(1):6.

26. Hadas, Y.; Vincek, A.S.; Youssef, E.; Z˙ ak, M.M.; Chepurko, E.; Sultana, N.; Sharkar, M.T.K.; Guo, N.; Komargodski, R.; Kurian, A.A.; et al. Altering Sphingolipid Metabolism Attenuates Cell Death and Inflammatory Response After Myocardial Infarction. Circulation 2020, 141, 916–930.

27. Poss, A.M.; Maschek, J.A.; Cox, J.E.; Hauner, B.J.; Hopkins, P.N.; Hunt, S.C.; Holland, W.L.; Summers, S.A.; Playdon, M.C. Machine learning reveals serum sphingolipids as cholesterol-independent biomarkers of coronary artery disease. J. Clin. Investig. 2020, 130, 1363–1376.

28. Kozłowska, D.; Harasim-Symbor, E.; My´sliwiec, H.; Milewska, A.; Chabowski, A.; Flisiak, I. Lipid profile disturbances may predispose psoriatic patients to liver dysfunction. Adv. Dermatol. Allergol. 2021, 38, 310–318.

Rozdział 9. Oświadczenie współautorów.

Informacja o charakterze udziału współautorów w publikacjach wraz z szacunkowym określeniem procentowego wkładu:

Matwiejuk, M.; Mysliwiec, H.; Lukaszuk, B.; Lewoc, M.; Malla, H.; Mysliwiec, P.; Dadan, J.; Chabowski, A.; Flisiak, I. The Interplay between Bioactive Sphingolipids in the Psoriatic Skin and the Severity of the Disease. Int. J. Mol. Sci. 2023, 24, 11336. doi.org/10.3390/ijms241411336

Imię i nazwisko współautora	Charakter udziału	Procentowy udział
Doktorant – Mateusz Matwiejuk	Planowanie badania, włączenie pacjentów, wykonywanie badań, tworzenie bazy danych, analiza otrzymanych wyników, współtworzenie manuskryptu.	60%
Dr hab. n. med. Hanna Myśliwiec	Współtworzenie i ocena manuskryptu, opieka merytoryczna.	20%
Dr n. med. Bartłomiej Łukaszuk	Tworzenie bazy danych, analiza wyników, ocena manuskryptu.	5%
Lek. Marta Lewoc	Włączanie pacjentów.	2%
Lek. Hend Malla	Włączanie pacjentów.	2%
Prof. dr hab. n. med. Piotr Myśliwiec	Analiza i ocena manuskryptu, opieka merytoryczna.	2%

Prof dr hab. n. med. Jacek Dadan	Analiza i ocena manuskryptu, opieka merytoryczna.	2%
Prof. dr hab. n. med. Adrian Chabowski	Analiza i ocena manuskryptu, opieka merytoryczna.	5%
Prof dr hab. n. med. Iwona Flisiak	Analiza i ocena manuskryptu, opieka merytoryczna.	2%

Oświadczam, że wszyscy współautorzy wyrazili zgodę na wykorzystanie powyższej publikacji w pracy doktorskiej lek. Mateusza Matwiejuka.

Podpis kandydata

Potwierdzam opisany powyżej merytoryczny wkład kandydata w powstanie publikacji wchodzącej w skład rozprawy doktorskiej.

Podpis promotora

Informacja o charakterze udziału współautorów w publikacjach wraz z szacunkowym określeniem procentowego wkładu:

Matwiejuk, M.; Myśliwiec, H.; Lukaszuk, B.; Lewoc, M.; Malla, H.; Myśliwiec, P.; Dadan, J.; Chabowski, A.; Flisiak, I. Crosstalk between Serum and Skin Sphingolipids in Psoriasis. Int. J. Mol. Sci. 2023, 24, 14872. https://doi.org/ 10.3390/ijms241914872

Imię i nazwisko współautora	Charakter udziału	Procentowy udział
Doktorant – Mateusz Matwiejuk	Planowanie badania, włączenie pacjentów, wykonywanie badań, tworzenie bazy danych, analiza otrzymanych wyników, współtworzenie manuskryptu.	60%
Dr hab. n. med. Hanna Myśliwiec	Współtworzenie i ocena manuskryptu, opieka merytoryczna.	20%
Dr n. med. Bartłomiej Łukaszuk	Tworzenie bazy danych, analiza wyników, ocena manuskryptu.	5%
Lek. Marta Lewoc	Włączanie pacjentów.	2%
Lek. Hend Malla	Włączanie pacjentów.	2%
Prof. dr hab. n. med. Piotr Myśliwiec	Analiza i ocena manuskryptu, opieka merytoryczna.	2%
Prof dr hab. n. med. Jacek Dadan	Analiza i ocena manuskryptu, opieka merytoryczna.	2%

Prof. dr hab. n. med. Adrian Chabowski	Analiza i ocena manuskryptu, opieka merytoryczna.	5%
Prof. dr hab. n. med. Iwona Flisiak	Analiza i ocena manuskryptu, opieka merytoryczna.	2%

Oświadczam, że wszyscy współautorzy wyrazili zgodę na wykorzystanie powyższej publikacji w pracy doktorskiej lek. Mateusza Matwiejuka.

Podpis kandydata

Mateusz Matwiejuk

Potwierdzam opisany powyżej merytoryczny wkład kandydata w powstanie publikacji wchodzącej w skład rozprawy doktorskiej.

Podpis promotora

Informacja o charakterze udziału współautorów w publikacjach wraz z szacunkowym określeniem procentowego wkładu:

Matwiejuk, M.; Mysliwiec, H.; Chabowski, A.; Flisiak, I. The Role of Sphingolipids in the Pathogenesis of Psoriasis. Metabolites 2022, 12, 1171. https://doi.org/10.3390/metabo12121171.

Imię i nazwisko współautora	Charakter udziału	Procentowy udział
Doktorant – lek. Mateusz Matwiejuk	Współtworzenie manuskryptu, poszukiwanie i analiza piśmiennictwa.	70%
Dr hab. n. med. Hanna Myśliwiec	Koncepcja pracy, współtworzenie i ocena manuskryptu oaz opieka merytoryczna.	20%
Prof. dr hab. n. med. Adrian Chabowski	Analiza i ocena manuskryptu, opieka merytoryczna	5%
Prof. dr hab. n. med. Iwona Flisiak	Analiza i ocena manuskryptu, opieka merytoryczna	5%

Oświadczam, że wszyscy współautorzy wyrazili zgodę na wykorzystanie powyższej publikacji w pracy doktorskiej lek. Mateusza Matwiejuka.

Podpis kandydata

Potwierdzam opisany powyżej merytoryczny wkład kandydata w powstanie publikacji wchodzącej w skład rozprawy doktorskiej.

Podpis promotora

Dr hab. n. med. Hanna Myśliwiec

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Białystok, 27.05.2024r.

Oświadczenie

Oświadczam, iż mój udział w przygotowaniu publikacji:

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Oświadczenie

Oświadczam, iż mój udział w przygotowaniu publikacji:

"Crosstalk between Serum and Skin Sphingolipids in Psoriasis" autorów: Mateusz Matwiejuk, Hanna Mysliwiec, Bartłomiej Lukaszuk, Marta Lewoc, Hend Malla, Piotr Mysliwiec, Jacek Dadan, Adrian Chabowski, Iwona Flisiak opublikowanej w „Psoriatic Arthritis and Skin Diseases: Pathogenesis and Therapies" International Journal of Molecular Sciences. 2023, 24(19), 14872 wchodzącej w skład rozprawy doktorskiej lek. Mateusza Matwiejuka, pt. „Ocena stężenia wybranych sfingolipidów w zmianach skórnych oraz surowicy pacjentów z łuszczycą" wynoszący 2% polegał na włączaniu pacjentów.

Jednocześnie wyrażam zgodę na wykorzystanie przez lek. Mateusza Matwiejuka publikacji w postępowaniu o nadanie stopnia doktora nauk medycznych.

Podpis

Marta Lewoc-Magnuszewska

Rozdział 10. Zgoda komisji bioetycznej

KOMISJA BIOETYCZNA
PRZY UNIWERSYTECIE MEDYCZNYM W BIAŁYMSTOKU
ul. Jana Kilińskiego 1
15-089 Białystok
tel. 85 748 54 07, fax 85 748 55 08
komisjabioetyczna@umb.edu.pl

Białystok, 16.12.2021 r.

Uchwała nr: APK.002.500.2021

Na podstawie art. 29 ust. 2 i 14 ustawy dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty (t.j. Dz. U z 2020, poz. 514 ze zm.), Komisja Bioetyczna przy Uniwersytecie Medycznym w Białymstoku, po zapoznaniu się z projektem badania zgodnie z zasadami GCP/ Guidelines for Good Clinical Practice /- **w y r a ż a z g o d ę** na prowadzenie tematu badawczego: „Ocena stężenia ceramidów, wolnych kwasów tłuszczowych oraz wybranych białkowych transporterów kwasów tłuszczowych w zmianach skórnych pacjentów z łuszczycą" przez dr hab. Hannę Myślwiec wraz z zespołem badawczym z UMB.

Planowany okres realizacji od 16.12.2021 r. do grudnia 2024 r.

Przewodnicząca Komisji Bioetycznej przy UMB

prof. dr hab. Otylia Kowal-Bieleeka

Pouczenie:
1. Odwołanie od uchwały komisji bioetycznej wyrażającej opinię może wnieść:
1) wnioskodawca;
2) kierownik podmiotu, w którym eksperyment medyczny ma być przeprowadzony;
3) komisja bioetyczna właściwa dla ośrodka, który ma uczestniczyć w wieloośrodkowym eksperymencie medycznym.
2. Odwołanie, o którym mowa w ust. 1, wnosi się za pośrednictwem komisji bioetycznej, która podjęła uchwałę, do Odwoławczej Komisji Bioetycznej w terminie 14 dni od dnia doręczenia uchwały wyrażającej opinię.