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Katedra i Klinika Dermatologii, Wenerologii i Alergologii

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Aspekty kliniczne i immunologiczne chorych z hidradenitis suppurativa

ROZPRAWA DOKTORSKA

Cykl publikacji powiązanych tematycznie

PROMOTOR:

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Składam najserdeczniejsze wyrazy wdzięczności mojemu promotorowi, Panu prof. dr. hab. n. med. Łukaszowi Matusiakowi za poświęcony czas, cenne wskazówki, sugestie i uwagi oraz nieocenioną pomoc zarówno w działaniach naukowych, jak i w pracy klinicznej.

Pragnę również bardzo podziękować
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Spis treści

1. CYKL PRAC STANOWIĄCYCH ROZPRAWĘ DOKTORSKĄ

1. **Jastrząb B**, Paśnik-Chwalik B, Konopka T, Krajewski PK, Szepietowski JC, Matusiak Ł. The Prevalence of Periodontitis and Assessment of Oral Micro-Biota in Patients with Hidradenitis Suppurativa: A Descriptive Cross-Sectional Study. J Clin Med. 2022 Nov 29;11(23):7065.
   IF = 3,9; Punkty MEiN = 140

2. **Jastrząb B**, Paśnik-Chwalik B, Dębska-Łasut K, Konopka T, Krajewski PK, Szepietowski JC, Matusiak Ł. The Composition of Subgingival Microbiome in Hidradenitis Suppurativa and Periodontitis Patients. Pathogens. 2023 Feb 25;12(3):377.
   IF = 3,7; Punkty MEiN = 100

3. **Jastrząb B**, Szepietowski JC, Matusiak Ł. Hidradenitis suppurativa and follicular occlusion syndrome: Where is the pathogenetic link? Clin Dermatol. 2023 Sep-Oct;41(5):576-583.
   IF = 2,7; Punkty MEiN =100

Sumaryczny IF: **10,3**
Sumaryczna Punktacja Ministerialna: **340 punktów**

2. WYKAZ SKRÓTÓW

AC	Trądzik skupiony (ang. *acne conglobata*)
BMI	Indeks masy ciała (ang. *body mass index)*
CAL	Utrata przyczepu międzyzębowego (ang. *clinical attachment loss*)
CXCL	Rodzina chemokin o motywie C-X-C (ang. *C-X-C motif family chemokine*)
DAMPs	Struktury molekularne związane z uszkodzeniem (ang. *damage associated molecular patterns)*
DC	Rozwarstwiające zapalenie skóry głowy (ang. *dissecting cellulitis*)
FOT	Tetrada mieszka włosowego (ang. *follicular occlusion tetrad*)
HS	Hidradenitis suppurativa
IHS4	Międzynarodowy system oceny ciężkości Hidradenitis Suppurativa (ang. *International Hidradenitis Suppurativa Severity Score System*)
IL	Interleukina (ang. *interleukin*)
IVD	Diagnostyka *in vitro (*ang. *in vitro diagnostic)*
MANOVA	Wieloczynnikowa analiza wariancji (ang. *multivariate analysis of variance*)
PAMPs	Wzorce molekularne związane z drobnoustrojami (ang. *pathogen-associated molecular patterns*)
PC	Torbiel pilonidalna (ang. *pilonidal cyst*)
TBC	Ogólna liczba bakterii (ang. *total bacteria count*)
TNF-α	Czynnik martwicy nowotworów alfa (ang. *tumor necrosis factor* α)

3. OMÓWIENIE ROZPRAWY DOKTORSKIEJ

3.1. Wstęp

Hidradenitis suppurativa (HS, trądzik odwrócony, ropnie mnogie pach) to przewlekła, wyniszczająca, nawracająca, zapalna choroba mieszków włosowych. Prowadzi do powstawania bolesnych zmian zapalnych ze skłonnością do tworzenia przetok i bliznowacenia najczęściej w obrębie pach, pachwin i okolicy anogenitalnej. Zazwyczaj rozpoczyna się po okresie dojrzewania płciowego, częściej u kobiet, osób z otyłością oraz palaczy tytoniu. Choroba ta prowadzi do istotnego pogorszenia jakości życia, a jej leczenie jest długotrwałe, nierzadko frustrujące dla lekarzy i pacjentów. Dokładny patomechanizm HS nie został jeszcze poznany. Obecnie uważa się, że schorzenie to ma złożoną etiologię, a do jego rozwoju przyczyniają się czynniki genetyczne i środowiskowe, styl życia, aspekty hormonalne, oddziaływanie drobnoustrojów oraz czynniki immunologiczne. Zmiany skórne rozwijają się wokół mieszków włosowych zlokalizowanych w obszarach wyprzeniowych. Okluzja mieszka włosowego i lokalne uszkodzenie komórek, do którego przyczynia się między innymi mechaniczne tarcie w obrębie fałdów skórnych, prowadzi do uwalniania struktur molekularnych związanych z uszkodzeniem (DAMPs). DAMPs oraz wzorce molekularne związane z drobnoustrojami (PAMPs) aktywują układ odpornościowy oraz indukują produkcję cytokin (m.in. TNF-α, IL-1β, IL-17, IL-23) i chemokin (m.in. CXCL1, CXCL2, CXCL8) prowadząc do okołonaczyniowego i okołomieszkowego nacieku komórek zapalnych, takich jak neutrofile, makrofagi i komórki dendrytyczne. To z kolei nasila hiperplazję i hiperkeratozę przewodowych keratynocytów skutkując dalszą okluzją mieszka włosowego.

Jak wspomniano powyżej, HS charakteryzuje się przewlekłym przebiegiem z okresami zaostrzeń, co ma negatywny wpływ na jakość życia dotkniętych tą chorobą osób. Dlatego tak ważne jest lepsze zrozumienie złożonych mechanizmów chorobowych i istotnych czynników ryzyka dla rozwoju tej jednostki chorobowej.

Zapalenie przyzębia (*periodontitis*) jest przewlekłą i wieloczynnikową chorobą zapalną związaną z zaawansowaną dysbiozą patogennego biofilmu bakteryjnego w kieszonkach przyzębnych i prowadzącą do postępującej destrukcji aparatu zawieszeniowego zębów. Jej głównymi objawami klinicznymi są krwawienie w czasie sondowania kieszonek, zniszczenie przyczepu łącznotkankowego i utrata kości wyrostka zębodołowego. Do powstawania

zapalenia przyzębia przyczyniają się najczęściej następujące bakterie: *Porphyromonas gingivalis, Treponema denticola, Prevotella intermedia, Aggregatibacter actinomycetemcommitans, Tannarella forsythia, Streptococcus sanguis, Fusobacterium nucleatum*. Do czynników ryzyka zapalenia przyzębia zalicza się między innymi nieprawidłową higienę jamy ustnej, otyłość, cukrzycę, palenie tytoniu i stres. Podnosi się także rolę czynników genetycznych. Do rozwoju choroby dochodzi na skutek zaburzonej odpowiedzi immunologicznej gospodarza na biofilm bakteryjny. Wzmożona produkcja i uwalnianie mediatorów prozapalnych są przyczyną destrukcji tkanek przyzębia oraz rozwoju procesów zapalnych w organizmie. W dotychczasowych badaniach wykazano, że zapalenie przyzębia jest związane z wieloma chorobami zapalnymi o podłożu immunologicznym, takimi jak przewlekła obturacyjna choroba płuc, przewlekłe choroby nerek, reumatoidalne zapalenie stawów oraz łuszczyca.

HS i *periodontitis* wykazują podobieństwo nie tylko w zakresie patogenezy związanej z nieprawidłową odpowiedzią immunologiczną komórek nabłonka i nadmierną produkcją mediatorów zapalnych, ale także w zakresie czynników ryzyka ich wystąpienia. Ponadto dotychczasowe badania mikrobiomu skóry chorych na HS wykazały istotnie zwiększoną względną liczebność gatunków *Porphyromonas*, które stanowią główny patogen w rozwoju zapalenia przyzębia.

3.2. Cel badań i problemy badawcze

Celem badań wchodzących w skład rozprawy doktorskiej jest ocena stanu przyzębia i charakterystyka jego mikrobiomu u osób z HS, określenie prewalencji zapalenia przyzębia u chorych na HS oraz lepsze poznanie patogenezy tych chorób. Dodatkowo skupiono się na podsumowaniu aktualnej wiedzy na temat kluczowego mechanizmu patogenetycznego HS, za jaki uważa się okluzję mieszka włosowego.

3.3. Cele szczegółowe:

3.3.1. Analiza stanu przyzębia i określenie prewalencji zapalenia przyzębia u pacjentów z HS oraz ocena zależności pomiędzy stanem przyzębia a nasileniem HS i czynnikami demograficznymi.

3.3.2. Charakterystyka mikrobiomu przyzębia u pacjentów z HS oraz jego porównanie do mikrobiomu pacjentów z *periodontitis* (bez HS) oraz zdrowej grupy kontrolnej.

3.3.3. Dokonanie przeglądu piśmiennictwa dotyczącego patogenezy HS jako składowej tetrady okluzji mieszka włosowego.

3.4. Materiał i metody

W badaniach będących podstawą pierwszej i drugiej publikacji cyklu dokonano analizy mikrobiomu przyzębia oraz oceniono częstość występowania zapalenia przyzębia w grupie pacjentów z HS.

Do pierwszego badania zostało włączonych 55 pacjentów cierpiących z powodu HS oraz odpowiadająca liczba zdrowych pacjentów stanowiących grupę kontrolną, struktura wieku i płci w obu grupach nie różniła się istotnie. Kryteriami wyłączającymi z badania były następujące: stan psychiczny niepozwalający na świadome wypełnienie kwestionariuszy, ciąża, laktacja oraz antybiotykoterapia lub interwencje terapeutyczne w zakresie jamy ustnej w 3-miesięcznym okresie poprzedzającym badanie.

W drugim badaniu spośród grupy pacjentów z HS wyselekcjonowano 30 osób, u których wykluczono zapalenie przyzębia – stanowili oni pierwszą grupę badaną. Kolejną grupę badaną stanowiło 30 pacjentów z zapaleniem przyzębia bez innych chorób współistniejących. Grupę kontrolną stanowiło 30 osób bez obciążeń zdrowotnych. Ogólne kryteria wykluczenia były zbieżne z badaniem pierwszym.

Od pacjentów włączonych do badania zostały zebrane dane demograficzne, wywiad w kierunku używania produktów zawierających nikotynę, dane dotyczące chorób towarzyszących oraz dotychczasowych sposobów leczenia.

Skóra pacjentów z HS została oceniona klinicznie przez badacza pod kątem lokalizacji, liczby oraz rodzaju zmian chorobowych. Dodatkowo podczas badania ocenione zostało zaawansowanie choroby za pomocą dwóch powszechnie używanych skal: Hurleya oraz IHS4 (ang. International HS Severity Scoring System).

Badanie przyzębia przeprowadzono u wszystkich pacjentów przez periodontologa, przy użyciu sondy periodontologicznej WHO o sile sondowania nie większej niż 20 g. Rozpoznanie zapalenia przyzębia postawiono po pełnym badaniu przyzębia na podstawie głębokości sondowania i oceny utraty przyczepu. Poziom nasilenia zapalenia przyzębia oraz złożoność leczenia oceniano na podstawie zakresu destrukcji tkanek w związku z chorobą przyzębia

(stadium I: początkowe zapalenie przyzębia; stadium II: umiarkowane zapalenie przyzębia; stadium III i IV: ciężkie zapalenie przyzębia), natomiast ryzyko progresji zapalenia przyzębia oceniano na podstawie następujących stopni: stopień A - wolne tempo progresji, stopień B - średnie tempo progresji, stopień C - szybkie tempo progresji. U każdego pacjenta podczas klinicznego badania przyzębia zidentyfikowano najgłębszą kieszonkę przyzębną i pobrano próbki płytki bakteryjnej poddziąsłowej. Przed pobraniem próbki oczyszczono naddziąsłową płytkę bakteryjną sterylnym gazikiem, następnie każdy ząb izolowano za pomocą wacików i dokładnie osuszono. Do wybranych kieszonek przyzębnych wprowadzano na 20 sekund za pomocą pęsety sterylny, papierowy sączek znajdujący się w zestawie diagnostycznym dostarczonym przez producenta testu. Do badań bakteriologicznych wykorzystano test PET Test® plus (MIP Pharma, Niemcy). Analizę próbek przeprowadzono przy użyciu reakcji łańcuchowej polimerazy w czasie rzeczywistym (RT-PCR). Test oparty na PCR umożliwił określenie ilościowe całkowitej liczby bakterii w kieszonce (TBC) oraz jakościowe i ilościowe poszczególnych z dziewięciu kluczowych periopatogenów (*Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia, Prevotella intermedia, Peptostreptococcus micros, Fusobacterium nucleatum, Eubacterium nodatum, Capnocytophaga gingivalis* i *Aggregatibacter actinomycetemcomitans*). Próbki przetwarzane były zgodnie z wewnętrznymi przepisami dotyczącymi przetwarzania, zgodnie z zestawem testowym IVD używanym w laboratorium diagnostycznym w MIP Pharma GmbH, Niemcy. W tym celu próbki zostały najpierw poddane lizie w celu odsłonięcia składników komórkowych. Następnie do późniejszego oczyszczenia DNA zastosowano system MagNA Pure 96 (SN:1128) firmy Roche Diagnostics Deutschland GmbH (Mannheim, Niemcy), łącznie z zestawami do izolacji DNA firmy Roche. Do ilościowej reakcji RT-qPCR mieszaninę reakcyjną odpipetowano na płytkę Hamilton ML STARLet IVD (SN: 4114) od Hamilton Germany Gmbh, (Gräfelfing, Niemcy). Startery, sondy i standardy plazmidowe zakupiono od TibMolBiol GmbH (Berlin, Niemcy). Reakcję RT-qPCR przeprowadzno się przy użyciu Roche LightCycler (SN:270040). W analizie potrójnej równolegle analizowano zawsze 3 patogeny. W trakcie analizy próbki były śledzone i precyzyjnie przypisywane za pomocą systemu kodów kreskowych.

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

Ostatnią pracą spośród cyklu jest praca poglądowa dotycząca powiązań patogenetycznych HS z innymi chorobami zaliczanymi do tetrady mieszka włosowego (FOT), tj.: trądzik skupiony (AC), rozwarstwiające zapalenie skóry głowy (DS) i torbiel pilonidalna (PC).

3.5. Podsumowanie wyników

U pacjentów z HS istotnie częściej występowało zapalenie przyzębia w porównaniu do pacjentów w grupie kontrolnej (odpowiednio 25/55 [45,5%] vs. 8/55 [14,5%], $p < 0,001$).

W grupie pacjentów z HS, u których zdiagnozowano zapalenie przyzębia najczęstszym stadium było stadium II (10/25 pacjentów, 40%), natomiast stadium III zdiagnozowano u 7 pacjentów (28%). U pacjentów z zapaleniem przyzębia w grupie kontrolnej najczęściej diagnozowano stadium III (4/8 pacjentów, 50%). Stopień C zapalenia przyzębia był najczęstszym stopniem u osób z HS, u których rozpoznano zapalenie przyzębia (17/25 pacjentów, 68%). Dla porównania, grupa kontrolna z zapaleniem przyzębia w większości przypadków (4/8 pacjentów, 50%) prezentowała stopień A zapalenia przyzębia.

U pacjentów z HS stwierdzono wyższe wartości TBC ($2,8 \times 10^8$) w porównaniu z pacjentami w grupie kontrolnej ($1,6 \times 10^8$) ($p < 0,05$). Wśród chorych z HS częściej izolowano bakterie *T. denticola, T. forsythia, P. micros, F. nucleatum* i *C. gingivalis* ($p < 0,01$) w porównaniu do grupy kontrolnej, natomiast nie stwierdzono istotnej różnicy w zakresie występowania *A. actinomycetemcomitans, P. gingivalis, P. intermedia i E. nodatum* w obu badanych grupach.

W grupie HS najczęściej wykrywanymi bakteriami były *T. denticola* (70,9%), *C. gingivalis* (67,3%), *P. micros* (41,8%) i *T. forsythia* (40%), natomiast wśród osób z grupy kontrolnej do najczęściej izolowanych patogenów należały *C. gingivalis* (34,5%), *T. denticola* (20,0%) i *P. micros* (18,2%).

T. denticola, T. forsythia i *P. micros* występowały statystycznie istotnie częściej u palących pacjentów z HS w porównaniu z niepalącymi pacjentami z HS ($p<0,01$). Wśród pacjentów palących z grupy kontrolnej częściej notowano występowanie *C. gingivalis* w porównaniu do osób niepalących z grupy kontrolnej ($p<0,05$). Wieloczynnikowa analiza wariancji (MANOVA) wykazała, że palenie nie wpływało istotnie na liczbę kopii DNA periopatogenów ani na TBC zarówno u pacjentów z HS, jak i w grupie kontrolnej. Nie stwierdzono istotnej zależności pomiędzy całkowitą liczbą bakterii i liczbą kopii DNA periopatogenów a płcią, BMI i wykształceniem. Ponadto, nasilenie HS oceniane zarówno w skali Hurleya, jak i IHS4 również nie wykazało związku z TBC, jak i liczbą patogenów przyzębia.

W drugim badaniu średnia liczba kopii TBC była istotnie wyższa w obu grupach badanych, tj. u pacjentów z HS (bez *periodontitis*) i zapaleniem przyzębia (bez HS) w porównaniu do osób z grupy kontrolnej (p=0,04). Wszystkie badane bakterie periopatogenne z wyjątkiem *A. actinomycetemcomitans* były izolowane statystycznie istotnie częściej w obrębie płytki poddziąsłowej u pacjentów z HS, jak i *periodontitis* w porównaniu do grupy kontrolnej.

Najczęstszym izolowanym patogenem w grupie HS (70%) i w grupie z zapaleniem przyzębia (86,7%) była *T. denticola*, natomiast w grupie kontrolnej najczęstszym drobnoustrojem była *C. gingivalis* (33,2%). Wyniki badań mikrobiologicznych wykazały istotne różnice w częstości występowania periopatogenów pomiędzy grupą pacjentów z HS i zapaleniem przyzębia dotyczące następujących gatunków: *P. gingivalis, T. forsythia, P. intermedia, P. micros* i *F. nucleatum*. Pierwsze cztery wymienione gatunki występowały istotnie częściej u pacjentów z zapaleniem przyzębia, natomiast *F. nucelatum* była wykrywana częściej u osób z HS.

Średnia liczba kopii bakterii *T. denticola, T. forsythia, P. micros* i *C. gingivalis* była istotnie wyższa zarówno w grupie z zapaleniem przyzębia, jak i w grupie HS w porównaniu z grupą kontrolną. U pacjentów z zapaleniem przyzębia ekspresja gatunków *P.gingivalis* i *P. micros* była natomiast wyższa niż u pacjentów z HS. Nie stwierdzono korelacji pomiędzy TBC i liczbą kopii poszczególnych periopatogenów a ciężkością HS ocenianą zarówno skalą Hurleya, jak i IHS4. Podobnie czas trwania choroby nie był skorelowany z TBC, jak i liczbą kopii poszczególnych periopatogenów.

W trzeciej z cyklu pracy podkreślono, że patogeneza hidradenitis suppurativa, trądziku skupionego, rozwarstwiającego zapalenia skóry głowy i torbieli pilonidalnej jest wieloczynnikowa, obejmująca czynniki genetyczne, hormonalne i środowiskowe. Patogeneza tetrady okluzji mieszka włosowego nie została w pełni wyjaśniona, jednak poszczególne jej elementy wydają się być wynikiem połączonej stymulacji wrodzonego i nabytego mechanizmu odpornościowego. Wszystkie te schorzenia mają wiele wspólnych cech patogenetycznych i klinicznych, ale wykazują także wiele różnic. Elementy FOT należy traktować jako odrębne jednostki wymagające indywidualnego podejścia i traktowania.

3.6. Etyka

Projekt pracy doktorskiej opartej na poniższych publikacjach został zatwierdzony przez Komisję Bioetyczną Uniwersytetu Medycznego we Wrocławiu - Nr KB 919/2021. Badanie

przeprowadzono przestrzegając zasad Good Clinical Practice oraz zasad Deklaracji Helsińskiej Światowego Stowarzyszenia Lekarzy przyjętą przez 18 Zgromadzenie Ogólne Światowego Stowarzyszenia Lekarzy (WMA), w Helsinkach w czerwcu 1964 r., a zmienionej przez 64 Zgromadzenie Ogólne WMA, w Brazylii w październiku 2013 r. Badania zostały przeprowadzone z zachowaniem anonimowości uzyskanych danych.

3.7. Wnioski

1. Częstość występowania zapalenia przyzębia oraz patogenów związanych z zapaleniem przyzębia u pacjentów z HS jest istotnie wyższa w porównaniu ze zdrowymi osobami z grupy kontrolnej.

2. Pacjenci z HS i zapaleniem przyzębia wykazują podobieństwa w składzie mikrobiomu poddziąsłowego, a *T. denticola* była najczęściej izolowanym patogenem.

3. U osób z HS konieczne jest wdrożenie podejścia interdyscyplinarnego polegającego między innymi na współpracy między dermatologami i periodontologami.

4. Składowe FOT, do których zalicza się HS, AC, DS i PC należy traktować jako odrębne jednostki wymagające indywidualnego podejścia i traktowania.

4. ARTYKUŁ PIERWSZY:

THE PREVALENCE OF PERIODONTITIS AND ASSESSMENT OF ORAL MICROBIOTA IN PATIENTS WITH HIDRADENITIS SUPPURATIVA: A DESCRIPTIVE CROSS-SECTIONAL STUDY

Journal of
Clinical Medicine

MDPI

Article

The Prevalence of Periodontitis and Assessment of Oral Micro-Biota in Patients with Hidradenitis Suppurativa: A Descriptive Cross-Sectional Study

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Abstract: Periodontitis has been causally connected with the development of other immune-mediated inflammatory disorders previously. Nevertheless, the current literature does not provide knowledge on oral health in hidradenitis suppurativa (HS) individuals. The aim of this study was to assess the prevalence of periodontitis and characterize an oral microbiome in HS patients. Fifty-five patients with HS and fifty-five healthy controls were enlisted in the study. The incidence of periodontitis was assessed in all patients during the periodontal evaluation. RT-PCR tests were used to quantification of bacterial content and assess the number and composition of nine crucial periodontal pathogens. HS patients had a significantly higher prevalence of periodontitis than healthy controls (45.5% versus 14.5%). Significantly higher values of average copy-count numbers of total bacteria were found in HS patients. The majority of periodontal pathogens were more frequently isolated in patients with HS than among controls. The most frequently detected pathogen in the HS group was *Treponema denticola* (70.9%), whereas among controls *Capnocytophaga gingivalis* (34.5%) was the most common isolate. There was no correlation between HS severity and the number of DNA copies of periodontal bacteria. The findings of this research suggest that periodontitis may contribute to the development of HS.

Keywords: hidradenitis suppurativa; periodontitis; oral health; oral microbiota

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1. Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory disorder of the pilosebaceous unit of the intertriginous body regions, characterized by recurrent nodules, abscesses, and tunnels [1]. The greater risk of manifesting HS extends from late adolescence to the fourth decade of life with a female preponderance [2,3]. The etiology is multifaceted and seems to be a synergistic relationship between impaired innate immunity and genetics, hormonal, lifestyle, and microbial factors [4].

Periodontitis is a chronic, inflammatory disease of the tooth-supporting structures that may result in the destruction of alveolar bone and periodontal ligament, leading to tooth loss [5]. The disorder has been reported to affect almost 50% of the adult population in the western world, with the most severe form occurring in 11.2% of the global population [6,7]. The pathogenic mechanisms of the disease involve complex interlinkages among infection with anaerobic bacteria in periodontal pockets, excessive host immune responses, and environmental factors, including smoking [5,8]. Microbial infection in subgingival plaque biofilm with periopathogens (bacterial species that contribute to periodontitis) leads to chronic inflammation in vulnerable individuals [9,10]. Socransky et al. [9] classified oral microbes into several groups (complexes) based on microorganism correlations and their involvement in the etiology of periodontal disorders. The most crucial for periodontal tissues and regarded as a pathogenic consortium in periodontitis is the red complex, which

comprises the following species: *Porphyromonas gingivalis*, *Tannerella forsythia,* and *Treponema denticola*. This complex manifests the strongest correlation with the clinical parameters considered most significant in periodontal diseases such as pocket depth and bleeding on probing [9,11,12]. The orange complex, closely related to the red one, contains *Prevotella intermedia*, *Peptostreptococcus micros*, *Fusobacterium nucleatum,* and *Campylobacter rectus*. The green complex includes *Capnocytophaga gingivalis*, *Campylobacter concisus*, *Eikenella corrodens*, and *Aggregatibacter actinomycetemcomitans* serotype a. The yellow complex consists of various *Streptococci.* Periopathogens such as *Aggregatibacter actinomycetemcomitans* serotype b, *Actinomyces naeslundii genospecies,* and *Selenomonas noxia* are separate microorganisms, and they do not cluster with other species [9].

The staging guidelines of periodontitis divide the classification into staging and grading of the disease. Staging is a measure used to assess the severity and extent of the management required (stage I: initial periodontitis; stage II: moderate periodontitis; stages III and IV: severe periodontitis), whereas grading is based on evidence of progression rate in three categories: slow (grade A), moderate (grade B) and rapid rate of progression (grade C) [5].

Periodontitis has been causally connected with the development of other immune-mediated inflammatory disorders (IMIDs), such as psoriasis, psoriatic arthritis, rheumatoid arthritis, and inflammatory bowel diseases. The dysbiotic biofilm associated with periodontal disease may contribute to these disorders directly or via enhancing the immunological system [13–17]. Although studies on oral health in HS patients are limited and the primary etiology of HS and periodontitis appears different, both diseases seem to share several pathogenetic features [18–22]. Confirming this relationship is important and could result in early periodontal management and prevent teeth loss, as well as may provide a good starting point for further investigation on unraveling new pathogenetic pathways common to both disorders.

The primary purpose of this study was to characterize an oral microbiome in patients with HS in comparison to healthy controls and investigate the potential association between HS and periodontitis.

2. Materials and Methods

2.1. Study Population

Between December 2021 and May 2022, 55 consecutive adult HS individuals (27 females and 28 males, aged 19–61 years, mean age = 36.22, SD = 10.97) attending the outpatient unit at the Department of Dermatology, Venereology and Allergology of Wroclaw University Hospital, were enlisted to the study. The corresponding number of healthy controls was matched with HS patients in terms of age and gender. Before the study commencement, the protocol was accepted by the local ethical committee (Consent no. 919/2021, date: 26 November 2021). The study was conducted according to the principles of Helsinki's Declaration, and a written participation agreement was obtained from each study subject after elucidating the purpose and nature of the investigation. The exclusion criteria for this study were the following: being under the age of 18, pregnancy, breastfeeding, and use of any systemic antimicrobials within 3 months prior to study entry.

2.2. Clinical Evaluation

Detailed information on demographics, lifestyle, comorbidities, and previous treatment in both groups was collected and analyzed. HS severity stage was assessed in all patients during the dermatological evaluation using the Hurley staging system, and the clinical severity of HS was determined with International Hidradenitis Suppurativa Severity Score System (IHS4) [23–25].

The diagnosis of periodontitis was made in accordance with the new classification and case definition of periodontitis revised in 2018 [26]. Participants from study and control groups were examined by a periodontist and identified as periodontitis cases in the context of clinical care if interdental clinical attachment loss (CAL) was detectable at two or more

non-adjacent teeth or if buccal or oral CAL no less than 3 mm with pocketing more than 3 mm was detectable at two or more teeth [26].

2.3. Sample Collection and Processing

The deepest periodontal pocket was selected for examination, and gingival sulcus samples were collected from every study subject. Prior to the procedure, supragingival bacterial plaque was removed, and the examined sites were carefully dried using sterile cotton swaps. Next, with sterile tweezers, the paper point from the diagnostic kit was inserted full depth in periodontal pockets for 20 seconds. In the event of bleeding, collecting samples was repeated.

The samples were packed into labeled test tubes, located in a transportation set, and sent to a MIP Pharma Laboratory for bacterial culture and count.

2.4. Bacterial Identification

Microbiological analysis was accomplished by using a real-time polymerase chain reaction (RT-PCR). Diagnostic kit PET Test® plus (MIP Pharma, Blieskastel, Germany) was used for quantification of bacterial content and to assess the number and composition of nine following periopathogens: *Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia* from the red complex, *Prevotella intermedia, Peptostreptococcus micros, Fusobacterium nucleatum* from the orange complex, *Eubacterium nodatum* from the orange-associated complex, *Capnocytophaga gingivalis* from the green complex, and *Aggregatibacter actinomycetemcomitans.*

2.5. Statistical Analysis

The processing and statistical analyses of the obtained data were performed using BM SPSS Statistics v. 26 (SPSS INC., Chicago, IL, USA) software. All data were tested for parametric or non-parametric distribution. The minimum, maximum, mean, and standard deviation numbers were calculated. Analyzed quantitative variables were compared using Mann–Whitney U test and Spearman correlation, while for qualitative data, test Chi^2 was used. Alterations between HS patients with a Hurley score from I to III and IHS4 mild, moderate, and severe were evaluated by Kruskal–Wallis 1-way analysis of variance on ranks. Effects of more than one independent variable on oral microflora were assessed with the use of Multivariate analysis of variance (MANOVA). A two-sided p value ≤ 0.05 was interpreted to indicate statistical significance.

3. Results

The study groups' characteristics are presented in Table 1. A comparable age and gender structure was noticed in both groups. A remarkably higher number of active smokers was observed among HS individuals ($p < 0.001$).

Table 1. Patients' characteristics.

	HS Group (n = 55)	Control Group (n = 55)
Age in years (mean ± SD)	36.22 ± 10.97 (19–61)	34.45 ± 10.29 (20–58)
Sex (Male, %)	28 (50.91)	26 (47.27)
Smokers (%)	39 (70.91)	7 (12.73)

HS: hidradenitis suppurativa; SD: standard deviation.

HS patients had a significantly higher prevalence of periodontitis than healthy controls (45.5% versus 14.5%, $p < 0.001$, Figure 1). The assessment of periodontitis severity in both groups is presented in Table 2. Grade C was the most frequent grade in HS individuals diagnosed with periodontitis (68%). In comparison, controls with periodontitis presented with grade A in most cases (50%). The most frequent stage in HS patients with periodontitis was stage II (40%), while among controls with periodontitis, stage III (50%) was most commonly diagnosed.

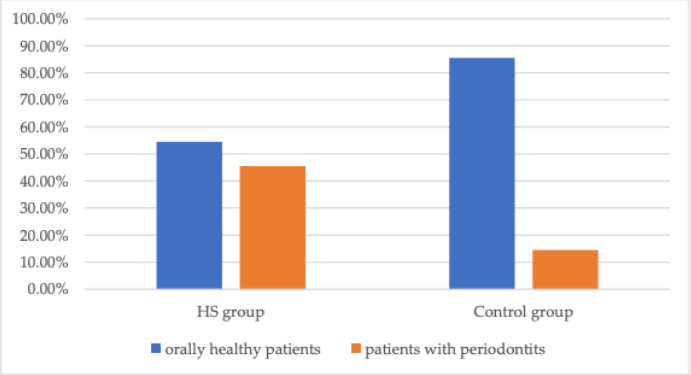

Figure 1. Prevalence of periodontitis in HS and control groups. $p < 0.001$, HS: hidradenitis suppurativa.

Table 2. Staging and grading of periodontitis in HS and control groups.

	No (%) of Patients	
	HS Patients with Periodontitis (n = 25)	**Controls with Periodontitis (n = 8)**
Stage I	2 (8%)	0
Stage II	10 (40%)	3 (37.5%)
Stage III	7 (28%)	4 (50%)
Stage IV	6 (24%)	1 (12.5%)
Grade A	6 (24%)	4 (50%)
Grade B	2 (8%)	2 (25%)
Grade C	17 (68%)	2 (25%)

HS: hidradenitis suppurativa.

Figure 2 exposes the average copy-count numbers of total bacteria in both groups. The statistically significant higher values were found in HS patients (2.8×10^8 average total bacteria count) compared to healthy controls (1.6×10^8 average total bacteria count) ($p < 0.05$).

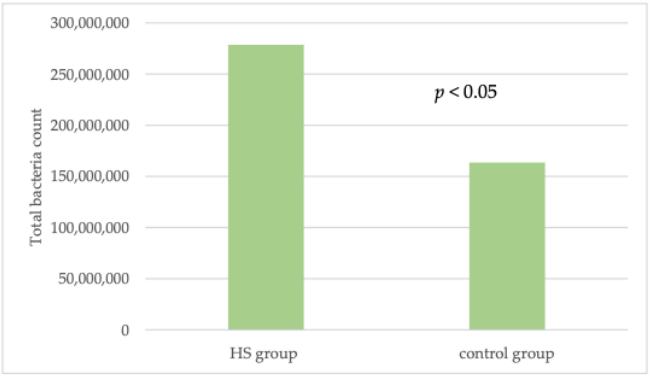

Figure 2. Average copy-counts number of total bacteria in the HS group and the control group. HS: hidradenitis suppurativa.

The majority of periopathogens tested were expressed at variable levels in the study and in the control group (Table 3). While *T. denticola*, *T. forsythia*, *P. micros*, *F. nucleatum*, and *C. gingivalis* were more frequently isolated in patients with HS ($p < 0.01$), no significant difference was identified in *A. actinomycetemcomitans*, *P. gingivalis*, *P. intermedia*, and *E. nodatum* preponderance among the two studied groups (Table 3).

Table 3. Comparison of the copy number of pathogens collected from gingival sulci and the percentage of patients with particular bacteria in the HS group and the control group.

	Mean ± SD			No (%) of Infected Patients		
Periopathogens Tested	**Subjects with HS**	**Control Group**	***p***	**Subjects with HS**	**Control Group**	***p***
A. actinomycetemcomitans	$2.7 \times 10^2 \pm 1.5 \times 10^3$	$2.3 \times 10^3 \pm 9.4 \times 10^3$	0.332	4 (7.3%)	7(12.7%)	0.340
P.gingivalis	$3.3 \times 10^4 \pm 1.2 \times 10^5$	$2.7 \times 10^4 \pm 1.3 \times 10^5$	0.635	6 (10.9%)	8 (14.5%)	0.567
T. denticola	$1.8 \times 10^4 \pm 3.0 \times 10^4$	$8.3 \times 10^3 \pm 3.1 \times 10^4$	<0.001 *	39 (70.9%)	11 (20.0%)	<0.001 *
T. forsythia	$7.0 \times 10^5 \pm 5.0 \times 10^6$	$6.2 \times 10^3 \pm 4.3 \times 10^4$	0.001 *	22 (40.0%)	6 (10.9%)	<0.001 *
P. intermedia	$2.7 \times 10^4 \pm 9.9 \times 10^4$	$3.7 \times 10^4 \pm 1.4 \times 10^5$	0.381	12 (21.8%)	8 (14.5%)	0.323
P. micros	$1.8 \times 10^3 \pm 8.9 \times 10^3$	$1.0 \times 10^3 \pm 4.5 \times 10^3$	0.010 *	23 (41.8%)	10 (18.2%)	0.007 *
F. nucleatum	$5.9 \times 10^2 \pm 3.0 \times 10^3$	10 ± 55	0.007 *	11 (20.0%)	2 (3.6%)	0.008 *
E. nodatum	$1.5 \times 10^3 \pm 1.1 \times 10^4$	$54 \pm 3.1 \times 10^2$	0.625	3 (5.5%)	2 2 (3.6%)	0.647
C. gingivalis	$2.9 \times 10^3 \pm 8.0 \times 10^3$	$3.8 \times 10^3 \pm 1.2 \times 10^4$	0.003 *	37 (67.3%)	19 (34.5%)	0.001 *
Total bacteria count	$2.8 \times 10^8 \pm 4.3 \times 10^8$	$1.6 \times 10^8 \pm 2.6 \times 10^8$	0.023 *	55(100%)	55(100%)	NA

* $p < 0.05$, statistically significant differences between groups, HS: hidradenitis suppurativa, SD: standard deviation.

The most common bacteria detected in the HS group were *T. denticola* (70.9%), *C. gingivalis* (67.3%), *P. micros* (41.8%), and *T. forsythia* (40.0%), whereas among healthy controls, *C. gingivalis* (34.5%), *T. denticola* (20.0%), and *P. micros* (18.2%) were the most frequently isolated pathogens. Table 4 compares the prevalence of periodontal pathogens between smokers and non-smokers in both groups. Noteworthy, *T. denticola*, *T. forsythia*, and *P. micros* were statistically significantly more frequently found in smoking patients with HS ($p < 0.01$, Table 4). Interestingly, among smoking controls, *C. gingivalis* was more abundant ($p < 0.05$, Table 4). Importantly, MANOVA showed that smoking did not significantly influence the number of DNA copies of periopathogens or total bacteria count in both patients and controls. In addition, there was no correlation between total bacterial count as well as number of DNA copies of periopathogens and gender, body mass index, and education. Furthermore, HS severity assessed both with Hurley and IHS4 scales showed no relationship with copy numbers of total bacteria and quantity of periodontal pathogens (Table 5).

Table 4. Comparison of the prevalence of periodontal pathogens among smokers and non-smokers.

	HS Group			Control Group		
Periopathogens Tested	**No (%) of Infected Smokers (n = 39)**	**No (%) of Infected Non-smokers (n = 16)**	***p***	**No (%) of Infected Smokers (n = 7)**	**No (%) of Infected Non-smokers (n = 48)**	***p***
A. actinomycetemcomitans	3 (7.69) %	1 (6.25) %	NS	0%	7 (14.58) %	NS
P.gingivalis	5 (12.82) %	1 (6.25) %	NS	2 (28.57) %	6 (12.5) %	NS
T. denticola	31 (79.49) %	8 (50.0) %	0.029	3 (42.85) %	8 (16.67) %	NS
T. forsythia	19 (48.72) %	3 (18.75) %	0.039	1 (14.29) %	5 (10.42) %	NS
P. intermedia	10 (25.64) %	2 (12.5) %	NS	1 (14.29) %	7 (14.58) %	NS

Table 4. *Cont.*

Periopathogens Tested	HS Group			Control Group		
	No (%) of Infected Smokers (n = 39)	No (%) of Infected Non-smokers (n = 16)	p	No (%) of Infected Smokers (n = 7)	No (%) of Infected Non-smokers (n = 48)	p
P. micros	21 (53.85) %	2 (12.5) %	0.005	2 (28.57) %	8 (16.67) %	NS
F. nucleatum	7 (17.95) %	4 (25.0) %	NS	1 (14.29) %	1 (2.08) %	NS
E. nodatum	1 (2.56) %	2 (12.5) %	NS	1 (14.29) %	1 (2.08) %	NS
C. gingivalis	23 (58.97) %	14 (87.5) %	NS	5 (71.43) %	14 (29.17) %	0.028

$p < 0.05$, statistically significant differences between groups, HS: hidradenitis suppurativa, NS: no statistically significant difference.

Table 5. Spearman correlation coefficient (r_S) between Hurley and IHS4 scores and DNA copy number of periopathogens and total bacteria.

Periopathogens Tested		Hurley Score	IHS4
A. actinomycetemcomitans	r_S	0.024	0.058
	p	0.866	0.685
P.gingivalis	r_S	0.116	0.076
	p	0.412	0.596
T. denticola	r_S	0.230	0.211
	p	0.101	0.136
T. forsythia	r_S	0.257	0.212
	p	0.066	0.135
P. intermedia	r_S	−0.057	−0.090
	p	0.686	0.530
P. micros	r_S	0.229	0.162
	p	0.102	0.257
F. nucleatum	r_S	−0.049	0.039
	p	0.729	0.784
E. nodatum	r_S	0.152	−0.026
	p	0.282	0.854
C. gingivalis	r_S	−0.199	−0.186
	p	0.158	0.191
Total bacteria count	r_S	0.030	−0.025
	p	0.833	0.861

IHS4: International Hidradenitis Suppurativa Severity Score System.

4. Discussion

In the present study, HS was associated with a higher prevalence of periodontitis compared with healthy subjects. Oral health may have an importance in the pathogenesis of many autoimmune skin conditions. Periodontal disease could play a role in the development and prognosis of psoriasis, pemphigoid, pemphigus, and lichen planus [14,27–29]. The more frequent prevalence of periodontitis in HS patients suggests that periodontal care and its impact on the oral microbiome might act as a modifiable risk factor for this entity.

Recent studies support the association between periodontitis and IMIDs, demonstrating the similarities in the imbalance of inflammatory cytokine network in these diseases.

Th17 cells, their crucial cytokine interleukin 17 (IL-17), and interleukin 23 (IL-23) have been reported to play key roles in the pathogenesis of IMIDs as well as periodontitis [18,19].

IL-17 is a proinflammatory cytokine that is mainly derived from activated CD4+ helper T cells [30]. By promoting fibroblast upregulation of granulocyte colony-stimulating factor and CXC chemokines, this cytokine may influence bone marrow production and secretion of neutrophils and their chemotactic recruitment to the periodontal tissues [31]. In addition, IL-17 exhibits potent pro-osteoclastogenic capability that may also contribute to the development of periodontitis [32]. IL-17 increases receptor activator of nuclear factor kappa-B ligand (RANKL) expression via osteoblasts, synovial cells, and mesenchymal cells [33]. Moreover, IL-17 may enhance the synthesis of matrix metalloproteinases in endothelial cells, epithelial cells, and fibroblasts, resulting in the destruction of connective tissue as well as the underlying bone [34].

IL-23 is a crucial cytokine involved in the differentiation and expansion of the Th17 subset [30]. Significantly higher tissue levels of IL-23 have been detected in periodontal lesions compared to control sites, suggesting that the IL-23/IL-17 axis plays a key role in the pathogenesis of periodontitis [35,36].

The IL-23/IL-17 signaling pathway also has pivotal importance in the development of chronic inflammation in HS [20,30,37]. IL-17 level has been shown to be significantly increased among HS patients and positively correlated with disorder severity [38,39]. The supplementary abundant expression of IL-23 by macrophages has been found in HS, indicating that the IL-23-induced Th17 pathways are involved in the disease process [20].

The majority of periodontopathic bacteria species were more frequently identified in the HS group in comparison to healthy controls. Importantly, *T. denticola*, which is one of the pivotal pathogens in periodontitis, was the most common isolated periopathogen among the HS group, affecting 70.9% of individuals. The total bacteria count and average number of copies of particular pathogens, such as *T. denticola*, *T. forsythia*, *P. micros,* and *F. nucleatum* tended to be higher in the HS group than in the control group.

The human microbiome may have major importance in autoimmunity. When self-tolerance mechanisms fail, residing microorganisms might elicit exaggerated immune responses [40]. The progression of periodontitis might be modulated by the interactions between periodontopathic microorganisms and host immunity. Periopathogens may damage the periodontum; nevertheless, an excessive and inappropriate host immune response stimulated by the bacteria might result in more severe and chronic destruction. Toll-like receptors (TLRs), which play an important role in the innate immune system via recognizing pathogen-associated molecular patterns, are involved in host innate immune responses to periopathogens and in the induction of adaptive immunity [21].

Recent studies provide evidence that HS may be associated with specific alterations in the cutaneous microbiome [4]. Various bacteria have been isolated from the abscesses and draining sinus tracts, including *Porphyromonas* species [41]. The increased expression of TLR2 at both the mRNA and the protein level has been reported in HS lesions compared with healthy skin [42]. Impaired Notch signaling, an essential part of HS pathogenesis, triggers the immune cascade and results in increased TLR- stimulated inflammatory responses [22].

Excessive immune activation due to microbial antigens observed in both periodontitis and HS may indicate a shared genetic predisposition and shared pathogenic pathways affecting dendritic cells and TLRs expression. Periopathogens can modulate IL-17 secretion by exploiting the resulting inflammatory milieu to access nutrients from tissue breakdown products as well as heme-containing molecules [32]. As IL-17 is one of the pivotal players in the pathogenesis of periodontitis and HS, increased expression of the cytokine might result in the progression of both diseases.

Apart from similar etiopathogenetic mechanisms, these entities share a common risk factor, which is smoking [43,44]. Smoking has been well-recognized as a risk factor for periodontitis progression [45]. Nevertheless, there are conflicting reports about the extent to which smoking influences the composition of the subgingival microbiome. Several

investigations demonstrated that smoking patients with periodontitis have a higher prevalence and abundance of periodontitis-associated pathogens than non-smokers [46–48]. On the other hand, some studies could not corroborate those results [49,50]. In the present study, we revealed that mean DNA probe counts of pathogens species evaluated in current cigarette smokers did not significantly vary from those in non-smokers. Members of the red and orange complexes, including *T. denticola*, *T. forsythia*, and *P. micros*, were more prevalent among smoking patients with HS than in non-smoking patients from the study group. *C. gingivalis*, the member of the green complex, was more frequently found in smoking controls compared with non-smokers from the control group. The positive correlation between cigarette smoking and the higher prevalence of *T. denticola* and *P. micros* species has been previously reported [46]. Smoking is also a well-established risk factor for HS development [1,43]. It depletes normal commensal cutaneous microflora and may induce bacterial propagation and biofilm formation in HS lesions [51,52]. Biofilm harbored in sinus tracts can irreversibly attach to the epithelium, contributing to further inflammation [53].

This study has some limitations. First of all, the design of a descriptive cross-sectional study does not allow the detection of temporal interactions between HS and periodontal disease. Furthermore, the prevalence of HS is various, ranging from 0.00033 to 4.1% [54], and underdiagnosis or inadequate diagnosis is a common event, leading to difficulty in patient recruitment. This present research should be considered as a pilot study for further investigation of the association between HS and periodontitis. Therefore, the number of patients involved in our study (n = 55) seems to be appropriate, approximating that suggested to be optimal for this type of research [55].

5. Conclusions

To the best of our knowledge, this is the first study assessing oral health in patients with HS. In the present research, we revealed the higher prevalence of periodontitis and periodontitis-associated pathogens in HS patients compared to healthy controls. Therefore, a multidisciplinary interaction between dermatologists and periodontists is needed in HS individuals. HS management should include regular periodontal exams and appropriate treatment when required. Further studies on HS and periodontitis are crucial to shed light on potential mechanisms underlying the correlations between these conditions.

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Institutional Review Board Statement: This study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Wroclaw Medical University Ethics Committee (Consent no. 919/2021, date: 26 November 2021).

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

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

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

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5. ARTYKUŁ DRUGI:

THE COMPOSITION OF SUBGINGIVAL MICROBIOME IN HIDRADENITIS SUPPURATIVA AND PERIODONTITS PATIENTS

pathogens

MDPI

Article

The Composition of Subgingival Microbiome in Hidradenitis Suppurativa and Periodontitis Patients

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Abstract: Hidradenitis suppurativa (HS) is a chronic inflammatory disorder of the pilosebaceous unit of the intertriginous body areas. Recent findings have suggested the association between periodontitis and HS. This investigation aimed to characterize and compare the composition of subgingival microbiome between HS, periodontitis, and control patients. The nine crucial perio-pathogenic species and total bacteria were analyzed using RT-PCR based tests in samples collected from 30 patients with periodontitis, 30 patients with HS and 30 controls. Patients with HS were excluded if they had periodontitis and patients with periodontitis were excluded if they had HS. The mean total bacteria count was significantly higher in HS and periodontitis samples than in control samples ($p < 0.05$). The majority of perio-pathogens tested were more frequently detected in HS and periodontitis groups than among controls. *Treponema denticola* was the most common pathogen in individuals with HS (70%) and periodontitis (86.7%), while among controls *Capnocytophyga gingivalis* was the most frequently detected isolate (33.2%). The results of the present investigation demonstrated that HS and periodontitis patients share some similarities in their subgingival microbiome composition.

Keywords: hidradenitis suppurativa; periodontitis; subgingival microbiome; oral microbiota; periodontal health

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1. Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory dermatosis that is characterized by deep-seated nodules and abscesses that rupture and lead to sinus tracts formation and scarring. The estimated prevalence of HS ranges from under 1% to 4%. These numbers may be underestimated as underdiagnosis or inadequate diagnosis are common events. The age of onset of the disease is usually between puberty and the fourth decade of life, most commonly from age 21 to 29 [1]. This condition most commonly involves the intertriginous skin of the axillary, inguinal, inframammary and genital regions of the body [2]. Because of the physical appearance, painful flare-ups and malodorous discharge, this condition may have a negative psychosocial impact on affected individuals [1,2].

The pathogenic mechanisms underlying HS are not fully elucidated, but genetic predisposition, environmental factors, host-microbe interactions, and immune dysregulation seem to be involved in the disease development [3].

Periodontitis is a multifactorial inflammatory disorder caused by dysbiotic microflora and excessive host response, resulting in progressive destruction of the tooth-supporting apparatus. In the course of the disease, the gingival sulcus is deepened to form a periodontal pocket colonized by perio-pathogens [4]. Although more than 700 different types of bacteria reside in the oral cavity, only a small portion of these microorganisms may trigger the destruction of periodontal tissues [5]. Periodonto-pathogenic species were first grouped by Socransky [6] in five colorimetrically coded complexes—green, yellow, orange, red

and purple. The particular dental plaque bacteria colonize the gingival sulcus in the specified order via cell-to-cell coaggregation [7]. Oral Streptococci are the dominant species of the oral cavity and the pioneer colonizers of tooth surfaces [8]. Streptococcus species provide additional binding sites for the subsequent deposition of secondary colonizers. The primary as well as secondary colonizers are considered early colonizers and involve green, yellow and violet complexes and *Actinomyces* [9]. The growth of these species groups leads to the proliferation of mainly gram-negative anaerobic bridging and late colonizers. The bridging colonizers form the orange complex and enable the multiplication of late colonizers including the red complex species [10].

The association between periodontitis and various autoimmune skin diseases has been recognized previously [11–16]. Several cross-sectional investigations reported a higher incidence of periodontitis and more advanced periodontal disease involvement among patients with psoriasis than among controls. This association was positively correlated with psoriasis severity [11,12]. Moreover, a bi-directional relationship between psoriasis and periodontitis has been suggested, with psoriasis contributing to periodontitis, and vice versa [11,12,17]. Psoriasis has also been demonstrated to be associated with characteristics of salivary microbiota and salivary levels of inflammation-related proteins, which differ from those of individuals with periodontitis and controls [18]. Noteworthy, a significantly higher number of missing teeth and lower radiographic bone level were noticed in psoriasis cases compared to control group [11]. Patients with oral pemphigus vulgaris and mucous membrane pemphigoid appear to be more susceptible to periodontitis, that in turn can potentially induce bullous disorders [19]. Individuals with mucous membrane pemphigoid have more gingival inflammation and worse periodontal status than a control population [13]. Significantly higher values of plaque index, probing depth and clinical attachment level were noticed in pemphigus vulgaris patients than among healthy subjects. Several studies revealed significantly worse periodontal status in patients with lichen planus compared to healthy controls [20,21]. Another study showed that increased plaque and calculus deposits are connected with a significantly higher prevalence of atrophic-erosive gingival lesions in individuals with oral lichen planus [22].

Periodontitis has also been linked with the development of other immune-mediated inflammatory disorders, such as inflammatory bowel diseases (IBD), psoriatic arthritis and rheumatoid arthritis [23–25]. Several studies demonstrated a high prevalence of periodontitis in patients with IBD [25,26]. Furthermore, IBD patients harbored higher levels of pathogenic bacteria in inflamed subgingival sites compared to patients with periodontitis [26]. The strict association between rheumatoid arthritis and periodontitis has been revealed. Individuals with rheumatoid arthritis were significantly more frequently diagnosed with periodontitis. This prevalence has been reported to be higher in patients at the earliest stages of the disease and in seropositive subjects [24]. Compelling epidemiological evidence confirms that the risk of periodontal disease is elevated for psoriatic arthritis. Periodontitis severity, as defined by clinical attachment level, was higher in the patients with psoriatic arthritis than in the reference group [12,23].

However, the current knowledge on oral health and periodontal status in HS patients is limited. Recent findings suggested that periodontal disease may be linked with HS [27]. In this study, periodontitis was significantly more frequently diagnosed in patients with HS than among controls. HS and periodontitis seem to share some pathogenic similarities. The IL-23/IL-17 axis plays an essential role in the development and progression of periodontitis as well as HS [28,29]. Several studies provide evidence that HS can be associated with specific alterations in the skin microbiome and toll-like receptors (TLRs) act as important factors in the development of both entities [30–32]. Although common inflammatory pathways are implicated in the pathogenesis of these disorders, the exact mechanism of relationship between them is unknown.

The primary objective of the present study was to characterize the composition of periodontal pathogens and evaluate the quantity of salivary microbiota in HS patients.

We compared these data to those in patients with periodontitis and healthy controls, to examine the association between HS and periodontitis.

2. Materials and Methods

2.1. Study Groups

A cross-sectional study was performed from December 2021 until May 2022. Individuals with HS were recruited at the Department of Dermatology, Venereology, and Allergology, Wroclaw Medical University, while individuals with clinical features typical of periodontitis were recruited at the Department of Periodontology, Wroclaw Medical University. A total of 30 healthy controls, 30 HS patients and 30 periodontitis patients were enlisted in the study. The general exclusion criteria were as follows: other systemic diseases, pregnancy, breast-feeding, being under the age of 18, and the use of local and systemic antimicrobials $\leq$3 months prior to the study baseline. Subjects with HS were excluded if they had periodontitis, and subjects with periodontitis were excluded if they had concomitant HS. The study was approved by the local ethical committee (consent no. 919/2021, date: 26 November 2021). The objective of the study was clarified and written informed consent was received from each participant before the commencement of the study.

2.2. Periodontal Evaluation

Periodontal examination was conducted in all patients by a single examiner using the WHO periodontal probe with a probing force of not more than 20 g. The dentition was divided into sextants, and each sextant was examined only if there were two or more teeth present and not indicated for extraction. Diagnosis of periodontitis was established after a complete periodontal inspection using probing depth and attachment loss evaluation. In the current study, periodontitis was defined as the presence of interdental clinical attachment loss (CAL) at two or more non-adjacent teeth or the presence of oral or buccal CAL no less than 3 mm with pocketing >3 mm at $\geq$two teeth [33]. The severity and extent of the management required were assessed using the staging (stage I: initial periodontitis; stage II: moderate periodontitis; stages III and IV: severe periodontitis), while the progression rate of the periodontitis was assessed using the grading (grade A: slow; grade B: moderate; grade C: rapid rate of progression) [34].

2.3. Dermatological Evaluation

All participants in the study were evaluated by a dermatologist for systemic status, cutaneous and mucosal lesions. Patients diagnosed with HS without any other concomitant skin, periodontal or systemic disorder were enrolled in the HS group. In addition, patients from periodontitis and control groups were excluded if they were diagnosed with any chronic cutaneous or systemic disease. HS severity stage was assessed in patients from HS group using the Hurley staging system and International Hidradenitis Suppurativa Severity Score System (IHS4). In addition, after establishment of the IHS4 score, the subjects were subsequently divided into 3 groups (mild, moderate, and severe disease). Cut-off points were employed for mild ($\leq$3 points), moderate (>3 and $\leq$10 points) and severe HS (>10 points) [35,36].

2.4. Subgingival Plaque Sample Collection

The deepest periodontal pocket was identified for every study subject during the clinical periodontal examination and subgingival bacterial plaque samples were obtained. Before sampling, the supragingival bacterial plaque was cleaned, and then each tooth was isolated with cotton rolls and dried thoroughly with an air syringe. A sterile paper point included in the diagnostic kit was introduced inside each gingival sulcus for 20 s using tweezers. The samples were loaded into test tubes and shipped to the MIP International Pharma Research GmbH Laboratory located in Germany, where sample processing was performed.

2.5. Microbiological Analysis

PET Test® plus is a CE-certified medical device, that is manufactured by MIP Pharma GmbH. The exact protocol for the microbiological examination procedure is confidential to the company. Sample analysis was conducted using a real-time polymerase chain reaction (RT-PCR). The PCR-based test allowed detection and quantification of nine crucial perio-pathogens (*Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, *Prevotella intermedia*, *Peptostreptococcus micros*, *Fusobacterium nucleatum*, *Eubacterium nodatum*, *Capnocytophaga gingivalis* and *Aggregatibacter actinomycetemcomitans*) in the study's samples. Free strand sections of DNA were obtained from lysed bacterial cells and were subsequently subjected to amplification and hybridization using fluorescence-stained starters characteristic of particular periodontal pathogens. The quantitative analysis of the samples was carried out with a reader that measures fluorescence intensity compared to that in reference specimens. According to information from the manufacturer, the threshold determination for all analyzed perio-pathogens was approximately 10^3 bacteria.

2.6. Statistical Analysis

Statistical analysis of the obtained results was performed with the use of the IBM SPSS Statistics v. 26 (SPSS INC., Chicago, IL, USA) software. All data was assessed for normal or abnormal distribution. The minimum, maximum, mean, and standard deviation were calculated. Differences in quantitative variables between two groups, depending on the normality, were evaluated using the t-Student test or Mann–Whitney U test. Correlation between quantitative data were assessed, depending on normality, with Pearson's and Spearman's correlations. For qualitative data, the Chi-squared test was used. Differences in number of copies of perio-pathogens between more than two groups were assessed, depending on the normality, with the use of the one-way analysis of variance on ranks (ANOVA) or Kruskal-Wallis test with the adjustment according to the Bonferroni correction. A two-sided p of less than 0.05 was considered statistically significant.

3. Results

The HS, periodontitis and control groups consisted of 12 males and 18 females aged 36.1 ± 11.64 (range, 20–75) years, 12 males and 18 females aged 41.5 ± 9.78 (range, 27–53) years, and 10 males and 20 females aged 33.5 ± 7.40 (range, 20–52) years, respectively.

The severity of the disease in the HS group in the majority of patients (14 patients, 46.6%) was assessed as Hurley stage II, in eight patients (26.7%) as Hurley stage I, and in eight patients (26.7%) as Hurley stage III. As for IHS4, 12 patients (40.0%) presented with moderate HS, 12 patients (40.0%) presented with severe HS, and six patients (20.0%) presented with mild HS. The mean IHS4 score among HS patients was assesed as 19 ± 22.28 points.

The periodontitis stage in the periodontits group in the majority of individuals (14 patients, 46.6%) was assessed as stage IV, in 12 patients (40.0%) as stage III, in three patients (10.0%) as stage II, and in one patient (3.4%) as stage I. The most frequent grade was grade B (17 patients, 56.7%), while grade C was present in 13 individuals (43.3%), and none of the patients with periodontitis presented with grade A.

The average copy-count number of total bacteria was significantly higher in the HS and periodontitis samples than in the control samples ($p = 0.04$) (Figure 1).

Statistically significant differences in the prevalence of periopathogens between groups were found for all bacterial species except *A. actinomycetemcomitans* (Figure 2).

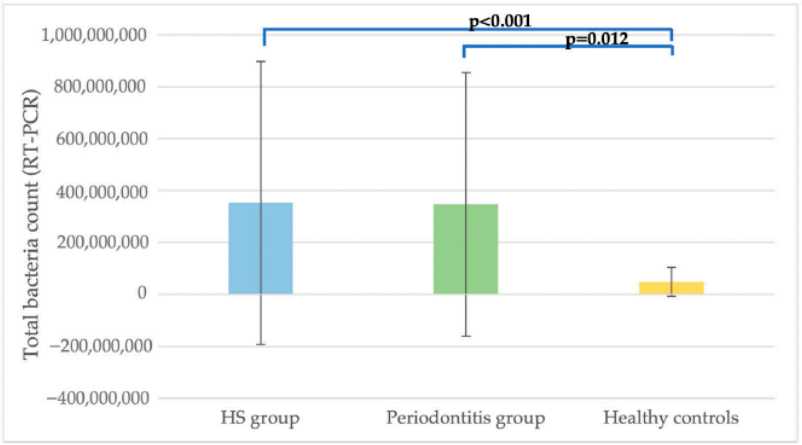

Figure 1. A comparison of the average copy number of total bacteria in the HS, periodontitis and control groups. HS: hidradenitis suppurativa, RT-PCR: real-time polymerase chain reaction.

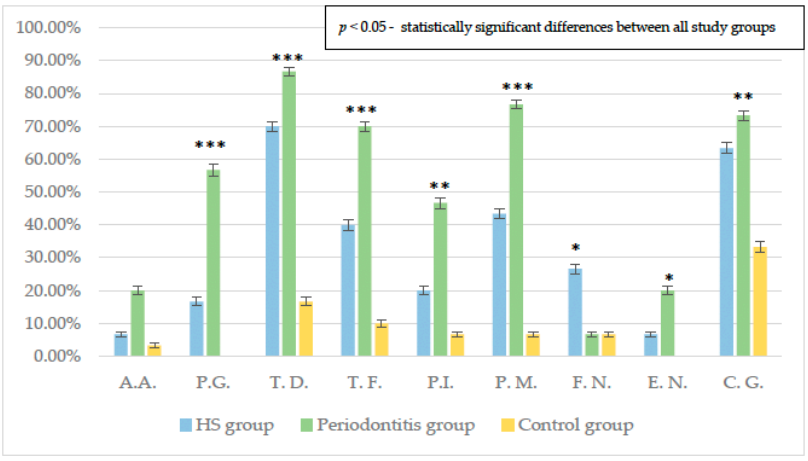

Figure 2. Percentages of patients in the HS, periodontitis and control groups with particular -. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, HS: hidradenitis suppurativa, A.A.: *Aggregatibacter actinomycetemcomitans*, P.G.: *Porphyromonas gingivalis*, T.D.: *Treponema denticola*, T.F.: *Tannerella forsythia*, P.I.: *Prevotella intermedia*, P.M.: *Peptostreptococcus micros*, F.N.: *Fusobacterium nucleatum*, E.N.: *Eubacterium nodatum*, C.G.: *Capnocytophaga gingivalis*.

Most perio-pathogenic bacteria were more frequently detected in the subgingival plaque both in HS and periodontitis patients than in healthy controls (Tables 1 and 2).

Table 1. The prevalence and the copy number of oral microorganisms in patients with periodontitis and controls.

	Number (%) of Infected Individuals			Average Copy Number of Bacteria (RT-PCR) (Mean ± SD)		
Periopathogens Tested	**Patients with Periodontitis (*n* = 30)**	**Controls (*n* = 30)**	***p***	**Patients with Periodontitis**	**Controls**	***p***
Total bacteria	30 (100%)	30(100%)	NA	$3.5 \times 10^8 \pm 5.1 \times 10^8$	$4.9 \times 10^7 \pm 5.6 \times 10^7$	<0.001
Aggregatibacter actinomycetemcomitans	6 (20.0%)	1 (3.3%)	0.044	$2.0 \times 10^3 \pm 7.7 \times 10^3$	18 ± 97	NS
Porphyromonas gingivalis	17 (56.7%)	0 (0.0%)	<0.001	$9.1 \times 10^4 \pm 3.5 \times 10^5$	0	<0.001
Treponema denticola	26 (86.7%)	5 (16.7%)	<0.001	$3.6 \times 10^4 \pm 8.4 \times 10^4$	$2.4 \times 10^3 \pm 9.7 \times 10^3$	<0.001
Tanerella forsythia	21 (70.0%)	3 (10.0%)	<0.001	$2.7 \times 10^4 \pm 6.5 \times 10^4$	$4.6 \times 10^2 \pm 2.2 \times 10^3$	<0.001
Prevotella intermedia	14 (46.7%)	2 (6.7%)	<0.001	$4.8 \times 10^4 \pm 1.3 \times 10^5$	$50 \pm 2.6 \times 10^2$	0.001
Peptostreptococcus micros	23 (76.7%)	2 (6.7%)	<0.001	$4.2 \times 10^3 \pm 6.9 \times 10^3$	$30 \pm 1.2 \times 10^2$	<0.001
Fusobacterium nucleatum	2 (6.7%)	2 (6.7%)	NS	20 ± 79	$3.6 \times 10^2 \pm 19$	NS
Eubacterium nodatum	6 (20.0%)	0 (0.0%)	0.010	$1.5 \times 10^3 \pm 6.4 \times 10^3$	0	0.021
Capnocytophaga gingivalis	22 (73.3%)	10 (33.2%)	0.002	$8.1 \times 10^3 \pm 1.5 \times 10^4$	$1.2 \times 10^3 \pm 4.3 \times 10^3$	0.001

NS: Not statistically significant, NA: Not applicable, SD: standard deviation.

Table 2. The prevalence and the copy number of oral microorganisms in patients with HS and controls.

	Number (%) of Infected Individuals			Average Copy Number of Bacteria (RT-PCR) (Mean ± SD)		
Periopathogens Tested	**Patients with HS (*n* = 30)**	**Controls (*n* = 30)**	***p***	**Patients with HS**	**Controls**	***p***
Total bacteria	30 (100%)	30(100%)	NA	$3.5 \times 10^8 \pm 5.4 \times 10^8$	$4.9 \times 10^7 \pm 5.6 \times 10^7$	0.012
Aggregatibacter actinomycetemcomitans	2 (6.7%)	1 (3.3%)	NS	$28 \pm 1.2 \times 10^2$	18 ± 97	NS
Porphyromonas gingivalis	5 (16.7%)	0 (0.0%)	0.020	$4.8 \times 10^4 \pm 1.6 \times 10^5$	0	NS
Treponema denticola	21 (70.0%)	5 (16.7%)	<0.001	$1.8 \times 10^4 \pm 2.7 \times 10^4$	$2.4 \times 10^3 \pm 9.7 \times 10^3$	<0.001
Tanerella forsythia	12 (40.0%)	3 (10.0%)	0.007	$1.3 \times 10^6 \pm 6.8 \times 10^6$	$4.6 \times 10^2 \pm 2.2 \times 10^3$	0.042
Prevotella intermedia	6 (20.0%)	2 (6.7%)	NS	$3.6 \times 10^4 \pm 1.2 \times 10^5$	$50 \pm 2.6 \times 10^2$	NS
Peptostreptococcus micros	13 (43.3%)	2 (6.7%)	0.001	$2.7 \times 10^3 \pm 1.2 \times 10^4$	$30 \pm 1.2 \times 10^2$	0.033
Fusobacterium nucleatum	8 (26.7%)	2 (6.7%)	0.038	$9.8 \times 10^2 \pm 4.0 \times 10^3$	$3.6 \times 10^2 \pm 19$	NS
Eubacterium nodatum	2 (6.7%)	0 (0.0%)	NS	$1.2 \times 10^2 \pm 4.8 \times 10^2$	0	NS
Capnocytophaga gingivalis	19 (63.3%)	10 (33.2%)	0.020	$3.7 \times 10^3 \pm 1.0 \times 10^4$	$1.2 \times 10^3 \pm 4.3 \times 10^3$	0.032

NS: Not statistically significant, NA: Not applicable, SD: standard deviation, HS: hidradenitis suppurativa.

T.denticola was the most frequently isolated pathogen in individuals with HS (70%) and periodontitis (86.7%), whereas among controls *C. gingivalis* was the most common microorganism (33.2%). The microbiological results revealed significant differences in the prevalence of periopathogens between HS and periodontitis groups concerned the following species: *P.gingivalis*, *T. forsythia*, *P. intermedia*, *P. micros* and *F. nucleatum*. The first four above-mentioned species were significantly more common among periodontitis patients, while *F. nucleatum* was identified more frequently in HS individuals (Table 3).

Table 3. The prevalence and the copy number of oral microorganisms in patients with HS and periodontitis.

	Number (%) of Infected Individuals			Average Copy Number of Bacteria (RT-PCR) (Mean ± SD)		
Periopathogens Tested	**Patients with HS (n = 30)**	**Patients with Periodontitis (n = 30)**	***p***	**Patients with HS**	**Patients with Periodontitis**	***p***
Total bacteria	30 (100%)	30 (100%)	NA	$3.5 \times 10^8 \pm 5.4 \times 10^8$	$3.5 \times 10^8 \pm 5.1 \times 10^8$	NS
Aggregatibacter actinomycetemcomitans	2 (6.7%)	6 (20.0%)	NS	$28 \pm 1.2 \times 10^2$	$2.0 \times 10^3 \pm 7.7 \times 10^3$	NS
Porphyromonas gingivalis	5 (16.7%)	17 (56.7%)	0.001	$4.8 \times 10^4 \pm 1.6 \times 10^5$	$9.1 \times 10^4 \pm 3.5 \times 10^5$	0.003
Treponema denticola	21 (70.0%)	26 (86.7%)	NS	$1.8 \times 10^4 \pm 2.7 \times 10^4$	$3.6 \times 10^4 \pm 8.4 \times 10^4$	NS
Tanerella forsythia	12 (40.0%)	21 (70.0%)	0.02	$1.3 \times 10^6 \pm 6.8 \times 10^6$	$2.7 \times 10^4 \pm 6.5 \times 10^4$	NS
Prevotella intermedia	6 (20.0%)	14 (46.7%)	0.028	$3.6 \times 10^4 \pm 1.2 \times 10^5$	$4.8 \times 10^4 \pm 1.3 \times 10^5$	NS
Peptostreptococcus micros	13 (43.3%)	23 (76.7%)	0.008	$2.7 \times 10^3 \pm 1.2 \times 10^4$	$4.2 \times 10^3 \pm 6.9 \times 10^3$	0.033
Fusobacterium nucleatum	8 (26.7%)	2 (6.7%)	0.038	$9.8 \times 10^2 \pm 4.0 \times 10^3$	20 ± 79	NS
Eubacterium nodatum	2 (6.7%)	6 (20.0%)	NS	$1.2 \times 10^2 \pm 4.8 \times 10^2$	$1.5 \times 10^3 \pm 6.4 \times 10^3$	NS
Capnocytophaga gingivalis	19 (63.3%)	22 (73.3%)	NS	$3.7 \times 10^3 \pm 1.0 \times 10^4$	$8.1 \times 10^3 \pm 1.5 \times 10^4$	NS

NS: Not statistically significant, NA: Not applicable, SD: standard deviation, HS: hidradenitis suppurativa.

The average copy number of all periopathogenic bacteria except *A.actinomycetemcomitans* differed significantly between groups (Figure 3).

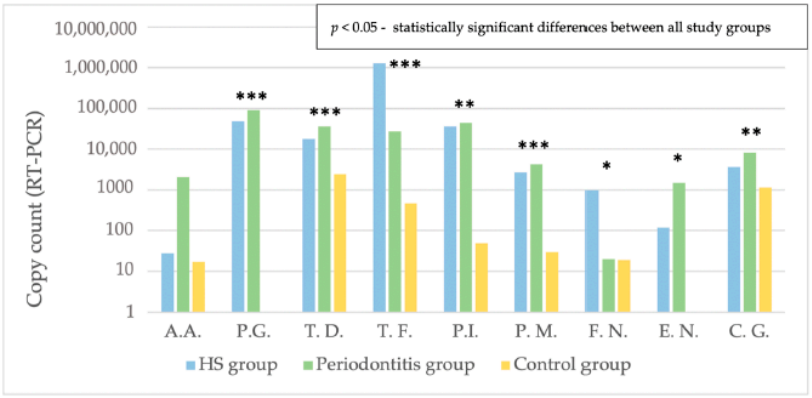

Figure 3. A comparison of the average copy number of perio-pathogens in the HS, periodontitis and control groups. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, HS: hidradenitis suppurativa, A.A.: *Aggregatibacter actinomycetemcomitans*, P.G.: *Porphyromonas gingivalis*, T.D.: *Treponema denticola*, T.F.: *Tannerella forsythia*, P.I.: *Prevotella intermedia*, P.M.: *Peptostreptococcus micros*, F.N.: *Fusobacterium nucleatum*, E.N.: *Eubacterium nodatum*, C.G.: *Capnocytophaga gingivalis*.

The average copy-count number of *T. denticola*, *T. forsythia*, *P. micros* and *C. gingivalis* was significantly higher in both periodontitis and HS groups compared to controls (Tables 1 and 2). *P.gingivalis* and *P. micros* species were expressed at higher level in periodontitis patients than in HS patients (Table 3).

Noteworthy, there was no correlation between total bacterial count as well as quantity of particular periopathogens and HS severity assessed both with Hurley and IHS4 scales

in the HS group. Similarly, the duration of the disease was not correlated with the copy number of periodontal pathogens.

4. Discussion

Dental plaque plays a crucial role in the patho-etiology of periodontal disease [37]. Many studies in the literature focus on whether various autoimmune disorders contribute to periodontitis, and conversely, whether periodontitis may influence systemic diseases' development and spread [25,38–40]. The current knowledge on periodontal status in HS is limited. Recent data showed a higher prevalence of periodontitis among HS patients, suggesting possible links between these entities [27].

Our study revealed that HS patients, similarly to periodontitis patients, tended to be more frequently infected with perio-pathogenic bacteria compared to orally healthy controls. Furthermore, the total bacteria count and the DNA copies number of a large portion of perio-pathogenic species were significantly higher in HS and periodontitis groups than among controls. These findings suggest that HS may influence oral homeostasis and HS individuals might be more prone to periodontal disease. On the other hand, periodontal pathogens may also enhance HS progression by promoting an inflammatory milieu.

Bacteria genera that were increased in occurrence in HS patients without periodontal disease compared to orally healthy controls were *P.gingivalis*, *T. denticola*, *T. forsythia*, *P. micros*, *F. nucleatum* and *C. gingivalis*. The three first species mentioned above form the red complex that acts as a pathogenic consortium in periodontitis. *P. micros and F. nucleatum* constitute the orange complex, while *C. gingivalis* belongs to the green complex [6].

P.gingivalis is a gram-negative, non-motile, anaerobic bacterium of the oral cavity [41]. This bacterial species has been recognized for its role in the regulation of distant inflammatory responses connected with chronic conditions and autoimmune diseases [42]. Several investigations reported that *P.gingivalis* exposure might be linked to systemic diseases such as rheumatoid arthritis (RA), inflammatory bowel diseases, diabetes mellitus and atherosclerosis [43–46]. *P. gingivalis* has been referred to as a master of immune subversion, utilizing unique and intricate sabotage techniques to evade and weaken the host's immune system [47]. It modifies the functions of various innate immune signaling cascade components such as the complement system, toll-like receptors (TLRs), macrophages, neutrophils, dendritic cells, and T cells [48]. The lipopolysaccharide (LPS) of *P. gingivalis* exhibits two isoforms responsible for the dual inflammatory response via TLRs modulation. The penta-acylated LPS induces TLR4 and TLR2 when tetra-acylated LPS is a TLR4 antagonist and TLR2 an agonist [49]. *P. gingivalis* triggers the release of IL-1, IL-6, IL-8, and TNF-α, acting by TLR4/TLR2 in host cells [50]. IL-1β production, maturation, and secretion are tightly modulated by TLR signaling as well as inflammasome activation [51]. *P. gingivalis* stimulated innate immune cells by the nucleotide-binding domain-like receptor protein 3 (NLRP3) inflammasome. The NLRP3 inflammasome and the following response from the IL-1 family might play an important role in periodontal disease triggered via *P. gingivalis* challenge through sustained inflammatory milieu [52,53].

T. denticola is a motile oral spirochete, while *T. forsythia* is a non-motile, rod-shaped microorganism [54–57]. A recent study examined the correlation between systemic lupus erythematosus (SLE) disease activity and severity and perio-pathogenic bacteria and reported that abundance of *T. denticola* and *T. forsythia* was increased in SLE-active periodontal sites compared to that of SLE-inactive and controls [58]. Moreover, serum antibody titers against *T. denticola*, *P. gingivalis*, *A. actinomycetemcomitans* and *C. ochracea* species were positively correlated with anti-dsDNA titers and reduced complement levels in SLE patients [59]. The study on the association of RA with periodontopathic bacterial infection revealed that serum and synovial fluid antibodies to *T. forsythia*, *P. gingivalis*, *P. intermedia*, and *Prevotella melaninogenica* were detected in RA patients [60]. Several studies showed that *T. denticola* enhances the synthesis of various cytokines, including IL-1β, IL-6, IL-8, and TNF-α from different cell types [61–64]. Conversely, it has also been demonstrated that *T. denticola* suppresses IL-8 production [65].

The gram-positive anaerobic coccus *P. micros* was found to be above the detection threshold in RA patients [66]. This bacterium has been reported to induce intracellular signaling mechanisms, resulting in an increased production of pro-inflammatory cytokines such as TNF- α, IL-1beta and IL-6 and chemokines through macrophages [6,67,68]. Noteworthy, *C. gingivalis*, which is a gram-negative rod, has also been shown to induce the release of IL-6 [69,70].

F. nucleatum was the only perio-pathogenic bacterium that was more prevalent among HS individuals than among periodontitis patients. This gram-negative pathogen has been reported to be associated with many systemic diseases, including atherosclerosis, adverse pregnancy outcomes, polycystic ovary syndrome, colorectal cancer and RA [71–75]. *F. nucleatum* induces a spectrum of host immune responses and acts as a potent stimulator of inflammatory cytokines. Chronic local infection of *F. nucleatum* initiates the up-regulation of inflammatory pathways. It stimulates various cytokines, such as IL-6, IL-8 and TNF-α [76,77]. Moreover, chronic inflammation caused by *F. nucleatum* contributes to the progression of various systemic diseases via modulation of TLRs and promoting CD4+ T cell proliferation and differentiation in Th1 and Th17 [78–80].

The role of dysbiosis in HS development is not fully elucidated [32]. The profile of skin microbiota changes with the progression of the disease, but it remains to be determined if this is a primary or secondary event [81]. The preponderance of *Staphylococcus* was noted in early HS lesions, while gram-negative anaerobic bacteria such as *Porphyromonas* and *Prevotella* were predominantly identified in HS tunnels and chronic suppurating lesions [81,82]. Patients affected with HS present elevated levels of pro-inflammatory cytokines, including TNF-α, IL-1β and IL-6, which are also implicated in perio-pathogens-induced immune responses [2,50,67,68]. The expression of IL-1β was significantly increased in the HS lesional and perilesional skin compared with uninvolved HS skin or healthy control skin [83]. TNF-α inhibitors have demonstrated a significant efficacy in individuals with moderate to severe HS [84]. Studies revealed increased serum IL-6 levels in Hurley II and III HS individuals, indicating that IL-6 may participate in the development of HS [85,86]. Moreover, TLRs and NLRP3 inflammasome, which are involved in periodontal bacteria pathogenicity, play also a role in the pathogenesis of HS [87,88].

Some limitations apply to the study. The first concerns the relatively low number of included individuals with HS, resulting from the single-center setting. Nevertheless, as significant differences in the composition of subgingival microbiota were noted, the number of participants might have been sufficient. Furthermore, the lack of follow-up examinations is another limitation and should be considered in future studies.

5. Conclusions

In conclusion, data from the present investigation prove that HS and periodontitis patients share similarities in their subgingival microbiome composition. Further studies are needed to understand the relationship between oral dysbiosis, immune dysregulation and HS pathogenesis. Future investigation should incorporate larger patient populations to confirm the initial results. In addition, the evaluation of the relationship between HS and periodontitis using the selected markers of inflammation would allow an understanding of interlinkage mechanisms.

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6. ARTYKUŁ TRZECI:

HIDRADENITIS SUPPURATIVA AND FOLLICULAR OCCLUSION SYNDROME: WHERE IS THE PATHOGENETIC LINK?

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Hidradenitis suppurativa and follicular occlusion syndrome: Where is the pathogenetic link?

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Abstract The follicular occlusion tetrad complex encompasses several entities (hidradenitis suppurativa, acne conglobata, dissecting cellulitis of the scalp, and pilonidal cyst) that share common clinical features, risk factors, and pathophysiology. Follicular occlusion is a crucial triggering mechanism in the etiology in each of these disorders, leading to development of distinctive skin lesions such as deep-seated nodules, abscesses, comedones, and draining sinuses, often with accompanying scarring. Despite the fact that the follicular occlusion tetrad components manifest multiple similarities, they also exhibit many differences among themselves and require individual approaches and treatment.

Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory disorder of the hair follicle characterized by recurrent nodules, abscesses, and pus-discharging sinus tracts in the flexural regions.[1] The pathogenesis is multifactorial. Genetic, hormonal, and lifestyle factors, as well as microbial components, seem to be involved.[2] Endogenous genetic predisposition and changes in hormonal levels, as well as external agents such as mechanical stimulation and smoking, contribute to occlusion of the hair follicle, which is considered the initiating event in HS.[3] Continuing obstruction of the follicular infundibulum results in its rupture and extrusion of follicular contents into the surrounding dermis. The diffusion of released molecules from the pilosebaceous unit elicits a strong chemotactic inflammatory response, leading to affluence of neutrophils, lymphocytes, and histiocytes. Chronic inflammation in association with microbial infiltration of the subcutaneous tissue induces sinus tracts and fistula formation.[4,5]

Follicular occlusion is also an essential triggering factor in the etiology of other cutaneous disorders. In 1940, William H. Goeckerman (1884-1954)[6] first described the pathogenesis similarities between HS, acne conglobata (AC), and dissecting cellulitis of the scalp (DC; perifolliculitis capitis abscedens et suffodiens). In 1956, Donald M. Pillsbury (1902-1980)[7] named the complex comprising these entities the follicular occlusion triad. Nearly two decades later, the addition of pilonidal cyst (PC) formed the follicular occlusion tetrad (FOT).[8] In 1989, Gerd Plewig (1939) and Ronald Marks[9] (1935-2020) proposed the term "acne inversa" to replace the term HS, accentuating the follicular origin of the disorder.

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Epidemiology

The age of onset of HS ranges from the late teen years to the fourth decade of life.[10] Epidemiologic data indicate a female predominance with a 2:1 to 3:1 sex ratio.[2,11] AC is an infrequent form of acne and may occur from infancy to adulthood, but the onset is usually in early adulthood (20-30 years). This disorder tends to develop more commonly in men than women.[12,13] DC principally affects African American patients. The greater risk of manifesting DC seems to occur during the second and third decades of life, with a male preponderance.[14,15] Men are twice as likely as women to be diagnosed with PC. The peak of incidence is between 15 and 30 years of age.[16]

Clinical features

The disorders forming the FOT are characterized by similar clinical features. The course of these diseases is chronic and usually severe. Deep-seated nodules, abscesses, and draining sinuses, often with accompanying scarring, dominate in their clinical presentation.[1,17-19]

DC is a primary neutrophilic cicatricial alopecia, typically occurring on the scalp with a predilection for the vertex region.[15,20,21] The presence of multifocal disease process may result in cerebriform appearance of the scalp.[22] Infrequently, the beard area could be also affected.[21]

The clinical picture of AC, apart from cystic nodules, pustules, abscesses, and sinus tracts, is determined by numerous comedones. Lesions tend to involve the face, neck, upper shoulders, arms, chest, gluteal region, and proximal parts of lower extremities.[17] Secondary bacterial infection with Gram-positive microorganisms is common and may impart scar formation.[23]

PC is defined as suppurative condition generally affecting the sacrococcygeal region.[24] Lesions are usually found on the top of intergluteal cleft, but occasionally could involve other parts of the body such as the umbilicus, groin, axilla, or interdigital spaces of the hand and feet.[25] The clinical presentation is varied from an abscess to a chronically discharging sinus tract with intermittent drainage.[24]

HS presents as painful deep-seated nodules, abscesses, and pus-discharging tunnels that result in scar formation. Lesions have predilection for the intertriginous skin, especially on the axillary, inguinal, and anogenital regions of the body.[26] Interwoven scars located in the skin folds could interfere with movement and lead to social impairment.[27]

Risk factors

Both genetics and hormonal factors seem to play an important role in the pathology of HS, AC, DC, and PC.[13,16,28,29]

Approximately one-third of patients diagnosed with HS have a positive family history of the disease.[30] Several investigations of mutations of the genes responsible for the gamma secretase production have supplied evidence supporting the role of genetic susceptibility in HS.[31-35] Gamma secretase is a high molecular weight membrane-embedded protease complex composed of four protein subunits: presenilin, presenilin enhancer-2, nicastrin, and anterior pharynx-defective-1. These hydrophobic protein components are encoded by the following genes: PSEN1/PSEN2, PSENEN, NCSTN, and APH1A/APH1B, respectively.

Gamma secretase complex catalyzes sequential cleavages of type-1 transmembrane proteins, including the Notch receptors, which seem to be involved in the HS pathogenesis. Heterozygous mutations in the NCSTN, PSENEN, and PSEN1 genes resulting in alterations in Notch signaling pathways have been reported as causative for the development of HS, especially in patients with familial HS.[36-39] The possible association of HS with AC in individuals with gamma secretase mutations has been also highlighted.[34] The mutation in the NCSTN gene has been found in one family with dominantly inherited AC.[40]

Other genetic factors are also known to influence the pathogenesis and clinical phenotype of HS. Missense mutations in the connexin-26, fibroblast growth factor-receptor 2, inositol polyphosphate-5-phosphatase 1, and IL-12Rb1 genes have been related to HS.[41] The link between single nucleotide polymorphisms at the promoter region of the tumor necrosis factor (TNF) gene and predisposition to HS has been demonstrated.[42] Further studies revealed that an elevated number of DEFB4 and DEFB103 genes leading to enhanced expression of beta defensin 2 and 3 proteins plays a role in genetic susceptibility to HS.[43] In addition, the correlation between polymorphism in the myeloid differentiation primary response gene 88 and predisposition to develop severe HS has been established.[44]

Chromosomal aberration of XXY karyotype has been linked to a severe form of AC.[13] Additionally, several cases of familial AC support a genetic background.[40,45-47] Hereditary implications of DC and PC have also been reported.[48-51]

The role of hormones in the development of HS remains unclear. The link between obesity and HS is presumably bidirectional, with obesity contributing to HS and HS promoting obesity. Obesity is a complex disease connected with variable degrees of low-grade chronic inflammation, leading to cardiovascular diseases and alterations in insulin resistance via the production of proinflammatory adipokines and cytokines.[52] Individuals with obesity have increased serum levels of inflammatory cytokines, such as TNF-α, interleukin (IL) 6, and IL-18.[52,53] TNF-α, which is also a pivotal cytokine in HS pathogenesis, exerts metabolic dysregulation by altering adipose tissue function and blocking insulin signaling.[54] Released soluble factors from skin and adipose tissue cells may diffuse across the lipid portion of the plasma membrane into systemic circulation as well as spread directly between dermal and adipose milieus. This mutual exchange of

inflammatory signals might facilitate both the progression of HS and metabolic dysregulation.[2,52,54]

Adipose tissue excess may also influence the disease by mechanical factors as well as hormonal alterations. Overlapping skin folds in overweight patients contribute to increased friction, occlusion, and maceration, resulting in local cell damage and penetration of microorganisms into the skin. In addition, hormonal derangements associated with obesity lead to relative androgen excess.[1,5]

HS affects women more frequently than men, and variations in severity of the disease seem to be related to the menstrual cycle.[55,56] Worsening of HS have been noted during menstruation and the luteal phase of the menstrual cycle, suggesting androgens as possible pathogenic factor.[57] Antiandrogen therapy has been reported to improve HS lesions.[58]

Several studies have shown the lack of evidence for elevated plasma levels of testosterone or dehydroepiandrosterone sulfate in patients with HS, proposing that the local effect of androgens plays a decisive role.[59-61]

AC has been linked to abuse of anabolic-androgenic steroids or iatrogenic administration of testosterone.[62,63] The male predominance of DC in conjunction with predilection for the vertex region indicates a hormonal risk factor.[15] PC has been related to hormone alterations causing modifications of hair follicles with subsequent obstruction of pilosebaceous glands in the sacrococcygeal region.[64]

Other risk factors for HS include smoking and specific microbiota composition.[65-67] Nicotine depletes normal commensal cutaneous flora and favors the growth and colonization of *Staphylococcus aureus*.[68,69] In addition, cholinergic stimulation by nicotinic receptors encourages infundibular epithelial hyperplasia, which may result in follicular plugging.[70,71] Nicotine could enhance biofilm formation and bacterial propagation via inducing initial adhesion and intracellular aggregation of these microorganisms.[72] Biofilm harbored in fistulas and sinus tracts might permanently bind to epithelium, promoting further inflammation.[68]

The most commonly cultured microorganisms in HS lesions are anaerobes, such as *Prevotella* and *Porphyromonas*, coagulase-negative *Staphylococcus*, and *S. aureus*.[73] Interestingly, clinically unaffected intertriginous skin in patients with HS is characterized by alterations in the microbiome associated with higher abundance of anaerobic bacteria in comparison to healthy controls.[74] Host immunity also has the potential to influence the skin flora variations. Several studies have shed light on the role of upregulation of toll-like receptors (TLRs) and cytokine signaling in microbiome changes and formation of proinflammatory milieu.[2,75] It remains to be clarified whether the cutaneous dysbiosis is of primary etiological significance or secondary to the disease.

Cutibacterium acnes, which is a key pathogen in acne vulgaris, is thought to be also involved in pathogenesis of AC. Changes in reactivity to bacterial antigens may exert strong immune responses, resulting in a chronic inflammatory environment.[13,17]

Bacterial motifs might also play a role as alloantigens in the etiology of DC. A hypersensitive immune response to microbial antigens in the hair follicle can cause inflammatory activation and promote development of the disease.[15]

The microbiology of PC is generally polymicrobial with an anaerobic bacteria preponderance. Anaerobes dominate in the progression of follicular infection and abscess development.[76] The exact mechanism of the impact of microflora on the pathology of PC remains unknown.

Pathogenesis

FOT complex encompasses several entities that share common clinical features and pathophysiology. The pathogenesis of HS, DC, AC, and PC has yet to be entirely elucidated, but follicular occlusion process in apocrine gland bearing skin is considered the initiating pathogenic event in each of these disorders. The occlusion is a result of infundibular keratosis and hyperplasia of the follicular epithelium, which leads to stasis and dilatation.[23,77] External follicular occlusion-promoting factors include mechanical friction, obesity, and smoking. The follicular obstruction could also be triggered by endogenous factor in patients harboring a genetic predisposition toward altered keratinocyte differentiation and proliferation.[1,78] The occluded follicles rupture, causing subsequent significant expression of inflammatory mediators and tissue destruction.[41,79] The accumulation of bacteria in obstructed and ruptured hair follicle units increases inflammation and results in a pus-containing discharge. This initiates the distinctive skin manifestations, such as deep-seated nodules, abscesses, comedones, and sinus tract formation.[77,80,81]

Clinical investigations targeting immune mediators in HS provide insight for understanding the mechanism of key signaling cells in immune response pathways.

The aforementioned events engender the dilation of follicular portion of the folliculopilosebaceous unit followed by its rupture.[82] The dispersion of released molecules, such as keratin fibers, sebum products, and hair shafts into the surrounding tissue may act as damage-associated molecular patterns, provoking immune dysregulation, inflammation, and dermal tunnel formation.[83] The constant activation of an immune response is due primarily to activation of neutrophils, macrophages, CD3+ T cells (CD4+ and CD8+), and B lymphocytes.[41] Recruited neutrophils and T helper cells produce IL-17, which together with TNF-α are the key cytokines in etiology of HS.[2,41]

Interleukin 17 is a proinflammatory cytokine that is produced predominantly by activated CD4+ helper T cells.[84] IL-17 levels have been found to be significantly elevated in HS individuals and positively correlated with severity of the disease.[85] IL-23 induces the production of IL-17A via stimulating the development and differentiation of Th17 cells.[84,86] The IL-23/IL-17 signaling pathway is known to play a pivotal role in development of chronic inflammation in HS.[84,87] IL-

1β also enhances Th17 cells differentiation through a mechanism involving the nucleotide-binding domain-like receptor protein 3 (NLRP3) inflammasome.[87,88] The NLRP3 inflammasome is a multimeric protein complex that detects a broad range of microorganisms and mediates host innate immune defense against infection.[89]

NLRP3 activation is driven by pathogen-associated molecular patterns (PAMPs) as well as by damage-associated molecular patterns and smoking. Inflammasome-induced caspase-1 release induces the production of IL-1β and IL-18, which activates the secretion of IL-17A.[87,88]

Serum levels of TNF-α in patients with HS markedly exceeded those observed in healthy controls and were closely associated with disease severity.[90,91] Notch signaling mediated TNF-α–induced cytokine production has been shown to be an essential part of HS pathogenesis. The Notch pathway has crucial importance for regulating cell differentiation and development of the hair shaft, inner root sheath, and skin adnexa.[92,93] Impaired Notch signaling leads to the transformation of hair follicles to epidermal cysts and alteration of apocrine gland homoeostasis and increases TLR-stimulated inflammatory responses. A deficiency in the Notch signaling pathway is a key factor not only for triggering immune cascade but also for maintaining chronic inflammation by insufficient feedback inhibition. Upregulation of TLRs on macrophages and dendritic cells results in an increased production of proinflammatory cytokines, including TNF-α and IL-1β.[93]

In addition, the association between anti-TNF-α therapy and significant reduction of Th17 cells has been demonstrated, indicating that TNF-α plays an important role in promoting IL-17 production in HS lesions.[86]

Several studies indicate an association between certain single-nucleotide polymorphisms of TLR4 and protection against the occurrence of AC.[94,95] Anti-TNF-α monoclonal antibodies such as adalimumab and infliximab have been shown to have efficacy in refractory AC, additionally suggesting that TNF-α is involved in the pathogenesis of the disease.[96-98] TNF inhibitors also have been effectively used for severe and recalcitrant cases of DC.[99-101] Proof of increased production of TNF-α and other cytokines that participate in HS development is lacking for DC and PC.

Treatment

HS, AC, DC, and PC partially share similar therapeutic strategies. The treatment options include both pharmacologic and nonpharmacologic approaches.

Antimicrobials

Topical clindamycin and systemic antimicrobials, such as the tetracyclines, rifampin-clindamycin combination, and ertapenem, have been shown to be helpful for HS management. Monotherapy might be appropriate for the initial treatment of a mild disease. In moderate to severe HS, polytherapy is more frequently used.[102]

Similarly, the variety of oral antimicrobials that include tetracyclines, macrolides, quinolones, rifampin and clindamycin combination, metronidazole, trimethoprim-sulfamethoxazole, and dapsone have demonstrated efficacy in treating DC. Topically administered clindamycin may also be an option in DC management.[103]

Systemic antimicrobials (tetracyclines, azithromycin, and dapsone) alone may not result in a significant improvement of AC. Despite the fact that some benefits can be derived by using them in high doses, the effects are not completely satisfactory due to drug resistance.[17]

There are no final data on antimicrobial use in patients with PC, but if antimicrobials are administered, their spectrum of activity should include both aerobic and anaerobic bacteria.[76,104]

Retinoids

The efficacy of the use of retinoids in HS remains questionable.[102] Isotretinoin is not a recommended therapy for the treatment of HS; nevertheless, some success may be achieved in patients with the frictional furuncle type of disease.[105] The mechanistic target of rapamycin complex 1 (mTORC1) activity has been suggested to be responsible for the outcome of isotretinoin in individuals with HS.[106] mTORC1 is an important regulator of cell growth and proliferation.[107] Forkhead box class O transcription factor-1 (FoxO1), which is also an essential regulator of cellular homeostasis, suppresses the activity of mTORC1.[108,109] mTORC1 signaling seems to be involved in HS pathogenesis by promoting Th17 differentiation.[110] Isotretinoin has the potential to increase the levels of nuclear FoxO1, leading to downregulation of mTORC1 and attenuated production of IL-17.[106,110,111]

Several studies have demonstrated the effectiveness of acitretin among patients with HS.[112-114] Acitretin activates specific nuclear retinoic acid receptors (RARs) and retinoid X receptors (RXRs) located in the epidermis, hair follicles, sebaceous glands, and the immune system, resulting in alterations of intracellular metabolism of natural retinoids. Due to frequent side effects, acitretin usage is often limited.[115,116]

Oral isotretinoin is a first-line agent for AC.[13] Isotretinoin has minimal or no capability to attach to cellular retinol-binding proteins or RARs and RXRs, but it might act as a prodrug that is transformed intracellularly to metabolites that interfere with RAR and RXR nuclear receptors.[117] This signaling pathway stimulates FoxO gene expression and inhibits mTORC1, contributing to sebocyte apoptosis, which is a crucial pharmacologic mechanism of isotretinoin in acne.[111,118]

Similarly, oral isotretinoin is the treatment of choice for moderate to severe refractory DC.[14] Common relapses after the discontinuation of isotretinoin may occur.[15]

Biologic therapy

Adalimumab is the first and only Food and Drug Administration–approved biologic treatment for moderate to severe HS.[102] In addition to the TNF-α blocking effect described and the entire cascade of immunologic processes associated with adalimumab, its effectiveness also may be linked to mTORC1 signaling, which has significance for Th17 differentiation and innate and adaptive immunity.[119] Infliximab provides another effective treatment option for patients with HS.[90] Variable outcomes have been reported with the use of other biologics in HS, including etanercept, anakinra, ustekinumab, secukinumab, and IFX-1.[120]

Successful treatment of AC and DC using TNF-α inhibitors, that is, adalimumab and infliximab, has also been demonstrated.[14,97]

Others

Another therapeutic approach of HS includes the use of intralesional corticosteroids, anti-androgenic hormonal therapy, laser hair removal, photodynamic therapy, and surgery.[102,121]

Oral steroids, carbon dioxide laser, and external beam radiation have been effectively used to treat some cases of AC.[13] Oral and intralesional corticosteroids, photodynamic therapy, hair-removal lasers, and surgical excision have been proven to be effective in the management of DC.[103,122]

Surgical intervention is a first-line treatment for PC; however, several nonsurgical methods comprising phenol injection, fibrin glue, laser treatment, and cryotherapy are also a possible therapeutic option.[76]

Conclusions

The pathogenesis of HS, AC, DS, and PC is multifactorial, including genetic, hormonal, and environmental factors. The pathogenesis of FOT has not been fully explained; nonetheless, propagation of its components seems to be a result of the combined stimulation of an innate and adaptive immune mechanism. All entities share multiple pathogenetic and clinical features, but they also exhibit many differences among themselves. FOT components should be considered as separate entities requiring an individual approach and treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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7. STRESZCZENIE W JĘZYKU POLSKIM

Rozprawa doktorska oparta jest o cykl trzech monotematycznych artykułów opublikowanych w międzynarodowych czasopismach naukowych indeksowanych w bazie PubMed i uwzględnionych na liście Journal Citation Reports oraz znajdujących się w wykazie czasopism naukowych Ministerstwa Edukacji i Nauki (MEiN). Artykuły wchodzące w skład rozprawy doktorskiej zostały zaakceptowane do publikacji w międzynarodowych czasopismach o łącznym współczynniku wpływu (Impact Factor – IF) 10,3 oraz punktacji MEiN 340 punktów. We wszystkich artykułach jestem pierwszym i wiodącym autorem.

W badaniach będących podstawą pierwszej i drugiej publikacji cyklu dokonano analizy mikrobiomu przyzębia oraz oceniono częstość występowania zapalenia przyzębia w grupie pacjentów z hidradenitis suppurativa (HS).

Do pierwszego badania zostało włączonych 55 pacjentów chorujących z powodu HS oraz odpowiadająca im liczba zdrowych pacjentów stanowiących grupę kontrolną.

W drugim badaniu spośród grupy pacjentów z HS wyselekcjonowano 30 osób, u których wykluczono zapalenie przyzębia – stanowili oni pierwszą grupę badaną. Kolejną grupę badaną stanowiło 30 pacjentów z zapaleniem przyzębia bez innych chorób współistniejących. Grupę kontrolną stanowiło 30 osób bez obciążeń zdrowotnych.

Od pacjentów włączonych do badania zostały zebrane dane demograficzne, wywiad w kierunku używania produktów zawierających nikotynę, dane dotyczące chorób towarzyszących oraz dotychczasowych sposobów leczenia.

Zaawansowanie HS zostało ocenione za pomocą dwóch powszechnie używanych skal: Hurleya oraz IHS4 (ang. International HS Severity Scoring System). U każdego pacjenta przeprowadzono badanie periodontologiczne, podczas którego oceniano obecność zapalenia przyzębia oraz jego nasilenie. Ponadto pobrano próbki poddziąsłowej płytki bakteryjnej w celu wykonania badań mikrobiologicznych. Do oceny bakteriologicznej wykorzystano test PET Test® plus (MIP Pharma, Niemcy). Test oparty na reakcji łańcuchowej polimerazy w czasie rzeczywistym (RT-PCR) umożliwił określenie ilościowe całkowitej liczby bakterii w kieszonce (TBC) oraz jakościowe i ilościowe poszczególnych z dziewięciu kluczowych periopatogenów (*Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia, Prevotella intermedia, Peptostreptococcus micros, Fusobacterium nucleatum, Eubacterium nodatum, Capnocytophaga gingivalis i Aggregatibacter actinomycetemcomitans*).

W pierwszym badaniu wykazano zwiększoną częstość występowania zapalenia przyzębia w grupie pacjentów z HS w porównaniu z grupą kontrolną (45,5% w porównaniu z 14,5%, p<0,001). W grupie osób z HS stwierdzono wyższe wartości TBC ($2,8 \times 10^8$) w porównaniu z pacjentami w grupie kontrolnej ($1,6 \times 10^8$) ($p < 0,05$). Dodatkowo u pacjentów z HS częściej izolowano bakterie *T. denticola, T. forsythia, P. micros, F. nucleatum* i *C. gingivalis* ($p < 0,01$) w porównaniu do grupy kontrolnej, natomiast nie stwierdzono istotnej różnicy w zakresie występowania *A. actinomycetemcomitans, P. gingivalis, P. intermedia i E. nodatum* w obu badanych grupach. Nasilenie HS oceniane zarówno w skalach Hurleya, jak i IHS4 nie wykazało istotnego związku z TBC i ilością patogenów przyzębia.

W drugim badaniu średnia liczba kopii TBC była wyższa w obu grupach badanych, tj. u pacjentów z HS (bez *periodontitis*) i zapaleniem przyzębia (bez HS) w porównaniu do osób z grupy kontrolnej (p=0,04). Wszystkie badane bakterie periopatogenne z wyjątkiem *A. actinomycetemcomitans* były izolowane statystycznie istotnie częściej w obrębie płytki poddziąsłowej u pacjentów z HS, jak i *periodontitis* w porównaniu do grupy kontrolnej. Najczęściej izolowanym patogenem w grupie HS (70%) i w grupie z zapaleniem przyzębia (86,7%) była *T.denticola*, natomiast w grupie kontrolnej najczęstszym drobnoustrojem była *C. gingivalis* (33,2%). Ponownie nie stwierdzono istotnej zależności pomiędzy TBC i liczbą poszczególnych periopatogenów a ciężkością HS.

W ostatniej z cyklu pracy, będącej pracą poglądową, omówiono patogenezę HS oraz powiązania tego schorzenia z innymi jednostkami chorobowymi zaliczanymi do tetrady mieszka włosowego (FOT). Zespół ten wraz z HS tworzą trądzik skupiony, rozwarstwiające zapalenie skóry głowy i torbiel pilonidalna. Patogeneza tych chorób jest wieloczynnikowa i nie została jeszcze w pełni wyjaśniona, niemniej poszczególne jej elementy wydają się być wynikiem połączonej stymulacji wrodzonego i nabytego mechanizmu odpornościowego. Wszystkie te schorzenia mają wiele wspólnych cech patogenetycznych i klinicznych, ale wykazują także wiele różnic. Elementy FOT należy traktować jako odrębne jednostki wymagające indywidualnego podejścia i traktowania.

Podsumowując, hidradenitis suppurativa jest ciężką, przewlekłą jednostką chorobową, której dokładne podłoże patogenetyczne pozostaje nie do końca wyjaśnione. Wyniki prac zawartych w rozprawie doktorskiej wskazują na zwiększoną częstość występowania dodatkowych schorzeń w tej grupie chorych, takich jak zapalenie przyzębia oraz pozostałych składowych FOT, co warunkuje potrzebę interdyscyplinarnego podejścia do pacjenta. Podkreślają również konieczność prowadzenia dalszych badań mających na celu lepsze poznanie mechanizmów warunkujących rozwój tej jednostki chorobowej.

8. STRESZCZENIE W JĘZYKU ANGIELSKIM

The doctoral dissertation consists of a series of three monothematic articles published in international scientific journals indexed in the MEDLINE database and included in the Journal Citation Reports by Web of Science list, as well as in the list of scientific journals of the Ministry of Education and Science (MEiN). The total impact factor (IF) of the articles included in the doctoral dissertation is 10.3, and the MEiN score is 340 points. In all articles, I am the first and lead author.

The research underlying the first and second publications of the series analyzed the periodontal microbiome and assessed the incidence of periodontitis in a group of patients with hidradenitis suppurativa (HS).

The first study included 55 patients suffering from HS and a corresponding number of healthy control patients.

In the second study, 30 patients were selected from the group of HS patients in whom periodontitis was excluded: they constituted the first study group. The next study group consisted of 30 patients with periodontitis without other comorbidities. The control group consisted of 30 people with no health problems.

Demographic data, history of use of nicotine-containing products, data on comorbidities and previous treatment methods were collected from patients included in the study.

The severity of HS was assessed using two commonly used scales: Hurley and IHS4 (International HS Severity Scoring System). Each patient underwent a periodontal examination, during which the presence of periodontitis and its severity were assessed. Additionally, samples of subgingival bacterial plaque were taken for microbiological tests. The PET Test® plus test (MIP Pharma, Germany) was used for bacteriological evaluation. The real-time polymerase chain reaction (RT-PCR) test allowed for the quantitative determination of the total bacterial count (TBC) and the qualitative and quantitative assessment of the nine key periopathogens (*Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia, Prevotella intermedia, Peptostreptococcus micros, Fusobacterium nucleatum, Eubacterium nodatum, Capnocytophaga gingivalis* and *Aggregatibacter actinomycetemcomitans*).

The first study showed an increased incidence of periodontitis in the group of patients with HS compared to the control group (45.5% vs 14.5%, $p<0.001$). Higher TBC values were found in the HS group (2.8×10^8) compared to patients in the control group (1.6×10^8) ($p< 0.05$). Additionally, *T. denticola, T. forsythia, P. micros, F. nucleatum* and *C. gingivalis* were more frequently isolated in HS patients ($p<0.01$) compared to the control group, while no significant

difference was found in the occurrence of *A.actinomycetemcomitans, P. gingivalis, P. intermedia* and *E. nodatum* in both study groups. The severity of HS assessed by both the Hurley and IHS4 scales did not show any relationship with TBC and the number of periodontal pathogens.

In the second study, the average copy-count number of total bacteria was significantly higher in both HS and periodontitis patients compared to healthy controls (p=0.04). All tested periopathogenic bacteria, except *A.actinomycetemcomitans*, were isolated statistically significantly more often in the subgingival plaque in patients with HS and periodontitis compared to the control group. The most frequently isolated pathogen in the HS group (70%) and in the periodontitis group (86.7%) was *T. denticola*, while in the control group the most common microorganism was *C. gingivalis* (33.2%). There was no relationship between TBC as well as the quantity of particular periopathogens and the severity of HS.

The last work in the series, which is a review work, discusses the pathogenesis of HS and the relationship between this disease and other disorders included in the follicular occlusion tetrad (FOT). This syndrome together with HS constitutes acne conglobata, dissecting cellulitis and pilonidal cyst. The pathogenesis of these diseases is multifactorial and has not yet been fully elucidated; however, its individual elements seem to be the result of combined stimulation of the innate and adaptive immune mechanisms. All these diseases have many common pathogenetic and clinical features, but they also show many differences. FOT elements should be treated as separate units requiring individual approach and treatment.

In conclusion, hidradenitis suppurativa is a severe, chronic disease whose pathogenesis is not fully understood. The results of the work included in the doctoral dissertation indicate an increased incidence of concomitant diseases such as periodontitis and other FOT elements in this group of patients and the need for an interdisciplinary approach to the patient. They also emphasize the need to conduct further research to better understand the mechanisms that determine the development of HS.

9. OPINIA KOMISJI BIOETYCZNEJ

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

OPINIA KOMISJI BIOETYCZNEJ Nr KB – 919/2021

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

dr Joanna Birecka (psychiatria)

dr Beata Freier (onkologia)

dr hab. Tomasz Fuchs (ginekologia, położnictwo)

prof. dr hab. Dariusz Janczak (chirurgia naczyniowa, transplantologia)

dr hab. Krzysztof Kaliszewski (chirurgia endokrynologiczna)

dr prawa Andrzej Malicki (prawo)

dr hab. Marcin Mączyński, prof. UMW (farmacja)

Urszula Olechowska (pielęgniarstwo)

prof. dr hab. Leszek Szenborn (pediatria, choroby zakaźne)

prof. dr hab. Andrzej Szuba (choroby wewnętrzne, angiologia

ks. prof. Andrzej Tomko (duchowny)

prof. dr hab. Mieszko Więckiewicz (stomatologia)

dr hab. Andrzej Wojnar, prof. nadzw. (histopatologia, dermatologia) przedstawiciel Dolnośląskiej Izby Lekarskiej)

dr hab. Jacek Zieliński (filozofia)

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

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

„Aspekty kliniczne i immunologiczne chorych z hidradenitis suppurativa"

zgłoszonym przez **lek. Beatę Jastrząb,** doktoranta Uniwersytetu Medycznego we Wrocławiu oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła **wyrazić zgodę** na przeprowadzenie badania w Katedrze i Klinice Dermatologii, Wenerologii i

Alergologii UM we Wrocławiu i Katedrze i Zakładzie Periodontologii UM we Wrocławiu, pod nadzorem prof. dr hab. Łukasza Matusiaka, **pod warunkiem zachowania anonimowości uzyskanych danych**.

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

Opinia powyższa dotyczy projektu badawczego będącego podstawą rozprawy doktorskiej.

Przewodniczący Komisji Bioetycznej
przy Uniwersytecie Medycznym

prof. dr hab. Jerzy Rudnicki

Wrocław, dnia 26 listopada 2021 r.

10. CURRICULUM VITAE

CURRICULUM VITAE

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Szkoła Doktorska 10.2020 – obecnie

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Lekarz (stażysta) 10/2018 – 10/2019

Dolnośląskie Centrum Onkologii we Wrocławiu

Naukowe:

Publikacje:

• 9 pełnotekstowych artykułów opublikowanych w polskich oraz międzynarodowych czasopismach, z czego 5 jako pierwszy autor

• Całkowity współczynnik wpływu (Impact Factor) opublikowanych prac: 20,348

• Punktacja ministerialna: 661,0

Granty i Nagrody:

• Grant Polskiego Towarzystwa Dermatologicznego na kliniczny staż zagraniczny, 2023 rok

• Subwencja Uniwersytetu medycznego we Wrocławiu na realizację projektu Badanie surowiczego i tkankowego stężenia IL-35 u chorych z hidradenitis suppurativa", 2023 rok

• Subwencja Uniwersytetu medycznego we Wrocławiu na realizację projektu "Prewalencja chorób przyzębia u pacjentów z hidradenitis suppurativa", 2022 rok

• Grant edukacyjny "Dolnośląscy Liderzy Medycyny" finansowany z Rady Inicjatywy Doskonałości, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu, Polska, 2021 rok

• Wielokrotne stypendia rektora dla najlepszych studentów

• Kierunek lekarski ukończony z wyróżnieniem rektora

Członkostwo w towarzystwach naukowych:

• Polskie Towarzystwo Dermatologiczne

• International Society of Dermatology

• European Academy of Dermatology and Venerology

11. DOROBEK NAUKOWY

11.1. Publikacje w czasopiśmie naukowym z IF

1. Chlebicka Iwona, **Jastrząb Beata**, Stefaniak Aleksandra, Hryncewicz-Gwóźdź Anita, Szepietowski Jacek C.: Giant superficial basal cell carcinoma diagnosed and treated as psoriasis: report of two cases and a literature review, Acta Dermato-Venereologica, 2020, vol. 100, art.adv00194 [2 s.], DOI:10.2340/00015555-3559

2. **Jastrząb Beata A**., Stefaniak Aleksandra A., Hryncewicz-Gwóźdź Anita, Nockowski Piotr, Szepietowski Jacek C.: Pityriasis lichenoides et varioliformis acuta triggered by human papillomavirus vaccine: a case report and literaturę review, Acta Dermato-Venereologica, 2021, vol. 101, art.adv00552 [2 s.],DOI:10.2340/00015555-3921

3. Chlebicka Iwona, **Jastrząb Beata**, Stefaniak Aleksandra, Szepietowski Jacek: Basal cell carcinoma secondary to trauma: a 3-year experience of the single center, Advances in Clinical and Experimental Medicine, 2021, vol. 30, nr 1, s.83-86, DOI:10.17219/acem/130593

4. **Jastrząb Beata**, Paśnik-Chwalik Barbara, Konopka Tomasz, Krajewski Piotr K., Szepietowski Jacek C., Matusiak Łukasz: The prevalence of periodontitis and assessment of oral micro-biota in patients with hidradenitis suppurativa: a descriptive cross-sectional study, Journal of Clinical Medicine, 2022, vol. 11, nr 23, art.7065 [10 s.], DOI:10.3390/jcm11237065

5. **Jastrząb Beata**, Szepietowski Jacek C., Matusiak Łukasz: Hidradenitis suppurativa and follicular occlusion syndrome: where is the pathogenetic link? Clinics in Dermatology, 2023, vol. 41, nr 5, s. 576-583,DOI:10.1016/j.clindermatol.2023.08.021

6. **Jastrząb Beata**, Paśnik-Chwalik Barbara, Dębska-Łasut Katarzyna, Konopka Tomasz, Krajewski Piotr K., Szepietowski Jacek C., Matusiak Łukasz: The composition of subgingival microbiome in hidradenitis suppurativa and periodontitis patients, Pathogens, 2023, vol. 12, nr 3, art.377 [13 s.], DOI:10.3390/pathogens12030377

11.2. Publikacje w czasopiśmie naukowym bez IF

1. Idzior Marta, Laskowska Marta, **Jastrząb Beata**, Neubauer Katarzyna, Reich Adam: Analiza problemów skórnych u chorych z nieswoistymi zapaleniami jelit, Dermatologia Estetyczna, 2017, vol. 19, nr 5, s. 234-239

2. Zdrojewicz Zygmunt, **Jastrząb Beata**, Rewera Małgorzata: Hortikuloterapia - moc ukryta w ogrodach, Medycyna Rodzinna, 2017, vol. 20, nr 2, s. 130-135

3. **Jastrząb Beata Anna**: Side-effects of topical glucocorticosteroids - can they be avoided? Medycyna Ogólna i Nauki o Zdrowiu, 2020, vol. 26, nr 2, s. 97-101, DOI:10.26444/monz/122138

Sumaryczny Impact Factor: 20,348

Punktacja ministerialna: 661,0

11.3. Doniesienia zjazdowe

1. **Beata Jastrząb**, Barbara Paśnik-Chwalik, Tomasz Konopka, Jacek C. Szepietowski, Łukasz Matusiak. The potential role of periodontal pathogens in hidradenitis suppurativa. 31st Congress of European Academy of Dermatology and Venereology, Milan, Italy, 7-10.09.2022.
2. **Beata Jastrząb,** Barbara Paśnik-Chwalik, Tomasz Konopka, Piotr K. Krajewski, Jacek C. Szepietowski, Łukasz Matusiak. Periodontal status in patients with hidradenitis suppurativa. 2022 SHSA Symposium on hidradenitis suppurativa advances, Miami, USA, 7-9.10.2022.
3. **Beata Jastrząb**. Jama ustna w HS: czy to problem kliniczny? Hidradenitis Suppurativa i Przewlekłe Dermatozy Zapalne, Białystok, Polska, 14-15.04.2023.
4. **Beata Jastrząb**, Barbara Paśnik-Chwalik, Tomasz Konopka, Piotr Krajewski, Jacek Szepietowski, Łukasz Matusiak. Ocena mikrobiomu przyzębia u chorych z hidradenitis

suppurativa. 32 Zjazd Polskiego Towarzystwa Dermatologicznego, Lublin, Polska, 31.05.- 3.06.2023.

5. **Beata Jastrząb**, Barbara Paśnik-Chwalik, Tomasz Konopka, Piotr Krajewski, Jacek C Szepietowski, Łukasz Matusiak. The prevalence of periodontits and periodontal pathogens in patients with hidradenitis suppurativa. 25th World Congress of Dermatology, Singapore, 3-8.07.2023.
6. **Jastrząb-Miśkiewicz Beata**, Studniarek Agnieszka, Maj Joanna, Matusiak Łukasz. Necrolytic acral erythema - opis przypadku. V Bieszczadzkie Spotkania z Dermatologią, Arłamów, Polska, 06.09-08.09.2023.
7. **Beata Jastrząb,** Barbara Paśnik-Chwalik, Tomasz Konopka, Piotr Krajewski, Jacek C Szepietowski, Łukasz Matusiak. The evaluation of periodontal health status in patients with hidradenitis suppurativa. 32nd Congress of European Academy of Dermatology and Venereology, Berlin, Germany, 11-14.10.2023.

12. OŚWIADCZENIA WSPÓŁAUTORÓW

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Jastrząb B, Paśnik-Chwalik B, Konopka T, Krajewski PK, Szepietowski JC, Matusiak Ł. The Prevalence of Periodontitis and Assessment of Oral Micro-Biota in Patients with Hidradenitis Suppurativa: A Descriptive Cross-Sectional Study. J Clin Med. 2022 Nov 29;11(23):7065.

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

.....
Data i podpis

UNIWERSYTET MEDYCZNY
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Jastrząb B, Paśnik-Chwalik B, Dębska-Łasut K, Konopka T, Krajewski PK, Szepietowski JC, Matusiak Ł. The Composition of Subgingival Microbiome in Hidradenitis Suppurativa and Periodontitis Patients. Pathogens. 2023 Feb 25;12(3):377.

mój udział polegał na zbieraniu materiału do badań opisanych w tej pracy.

12.04.24

Data i podpis

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Jastrząb B, Paśnik-Chwalik B, Dębska-Łasut K, Konopka T, Krajewski PK, Szepietowski JC, Matusiak Ł. The Composition of Subgingival Microbiome in Hidradenitis Suppurativa and Periodontitis Patients. Pathogens. 2023 Feb 25;12(3):377.

mój udział polegał na wykonaniu analizy statystycznej zgromadzonych wyników.

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Data i podpis

UNIWERSYTET MEDYCZNY
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Wrocław, 08.04.2024

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w pracy:

Jastrząb B, Paśnik-Chwalik B, Konopka T, Krajewski PK, Szepietowski JC, Matusiak Ł. The Prevalence of Periodontitis and Assessment of Oral Micro-Biota in Patients with Hidradenitis Suppurativa: A Descriptive Cross-Sectional Study. J Clin Med. 2022 Nov 29;11(23):7065.

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Data i podpis

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

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Wrocław, 08.04.2024

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w pracy:

Jastrząb B, Paśnik-Chwalik B, Dębska-Łasut K, Konopka T, Krajewski PK, Szepietowski JC, Matusiak Ł. The Composition of Subgingival Microbiome in Hidradenitis Suppurativa and Periodontitis Patients. Pathogens. 2023 Feb 25;12(3):377.

mój udział polegał na zbieraniu materiału do badań opisanych w tej pracy.

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