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# Wpływ leczenia autologicznymi komórkami macierzystymi na wybrane aspekty kliniczne i psychospołeczne u pacjentek z łysieniem androgenowym

ROZPRAWA DOKTORSKA

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za możliwość rozwoju naukowego w tematyce, która jest moja wielką pasją
i za bezcenną pomoc na wszystkich etapach tworzenia pracy.

*Mojej rodzinie i przyjaciołom*

*za nieustanne wsparcie i wiarę we mnie.*

# Spis treści

# 1.CYKL PRAC STANOWIĄCYCH ROZPRAWĘ DOKTORSKĄ

1. **Krefft-Trzciniecka Katarzyna,** Piętowska Zuzanna, Nowicka Danuta, Szepietowski Jacek C.: Human stem cell use in androgenetic alopecia: a systematic review, Cells, 2023, vol. 12, nr 6, art.951 [12 s.], DOI:10.3390/cells12060951.

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2. **Krefft-Trzciniecka Katarzyna,** Piętowska Zuzanna, Pakiet Alicja, Nowicka Danuta, Szepietowski Jacek C.: Short-term clinical assessment of treating female androgenetic alopecia with autologous stem cells derived from human hair follicles, Biomedicines, 2024, vol. 12, nr 1, art.153 [12 s.], DOI:10.3390/biomedicines12010153.

   IF: 4,7

   *Punktacja Ministerialna:* 100

3. **Krefft-Trzciniecka Katarzyna,** Cisoń Hanna, Pakiet Alicja, Nowicka Danuta, Szepietowski Jacek C.: Enhancing quality of life and sexual functioning in female androgenetic alopecia: therapeutic potential of hair follicle-derived stem cells, Healthcare, 2024, vol. 12, nr 6, art.608 [11 s.], DOI:10.3390/healthcare12060608.

   IF: 2,8

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# 2. WYKAZ SKRÓTÓW

| | |
|---|---|
| ACM | Mikroprzeszczep komórek autologicznych (ang. autologous cell micrografts) |
| ADSCs | Komórki macierzyste z tkanki tłuszczowej (ang. adipose tissue-derived stem cells) |
| AGA | Łysienie androgenowe (ang. androgenic alopecia) |
| ANA | Przeciwciała przeciwjądrowe (ang. antinuclear antibody) |
| ASC | Stromalne komórki macierzyste (ang. stromal stem cells) |
| BM-MSC | Komórki mezenchymalne ze szpiku kostnego (ang. mesenchymal cells from bone marrow) |
| DHT | Dihydrotestosteron (ang. dihydrotestosterone) |
| DPCs | Komórki brodawek skórnych (ang. dermal papilla cells) |
| FDA | Agencja Żywności i Leków (ang. Food and Drug Administration) |
| FDSCs | Komórki macierzyste z powięzi (ang. fascia-derived stem cells) |
| FSFI | Indeks Funkcji Seksualnych Kobiety (ang. Female Sexual Function Index) |
| HFSCs | Komórki macierzyste z mieszków włosowych (ang. hair follicle-derived stem cells) |
| MSCSs | Komórki mezenchymalne (ang. mesenchymal stem cells) |
| ORS | Zewnętrzna osłonka korzenia (ang. outer root sheath) |
| SHGB | Globulina wiążąca hormony płciowe (ang. sex hormone-binding globulin) |
| SVF | Frakcja stromalna (ang. stromal vascular fraction) |
| VAS | Wizualna skala analogowa (ang. visual analogue scale) |
| WHOQOL-BREF | Skrócona wersja ankiety oceniającej jakość życia (ang. The World Health Organization Quality of Life Brief Version) |

# 3. OMÓWIENIE ROZPRAWY DOKTORSKIEJ

## 3.1. Wstęp

Łysienie androgenowe (ang. androgenetic alopecia, AGA) jest najczęściej występującą formą łysienia niebliznowaciejącego zarówno u mężczyzn jak i kobiet, która objawia się postępującą utratą włosów o bardzo charakterystycznym i przewidywalnym wzorcu. Choroba ta może rozpocząć się na każdym etapie życia, jednak częstość jej występowania wzrasta wraz z wiekiem. Około 70 roku życia 42% kobiet i 80% mężczyzn wykazuje charakterystyczne cechy AGA. Łysienie androgenowe jest zaburzeniem wypadania włosów, w którym pośredniczy dihydrotestosteron (ang. dihydrotestosterone, DHT) poprzez indukowanie miniaturyzacji mieszków włosowych i przekształcanie końcowych włosów we włosy welusowe**.** W etiopatogenezie tego stanu dużą rolę przypisuje się także stresowi oksydacyjnemu i mikrozapaleniu wokół mieszków włosowych skóry objętej procesem chorobowym.

Włosy stanowią ważną rolę społeczno-kulturową, a ich długość i uczesanie są istotnymi elementami tożsamości jednostki. Dlatego też utrata włosów często prowadzi, zwłaszcza wśród kobiet, do niezadowolenia z wyglądu, co może mieć negatywny wpływ na samoocenę oraz skutkować trudnościami psychologicznymi i społecznymi.

Aktualnie w leczeniu łysienia androgenowego substancjami zatwierdzonymi przez amerykańską Agencję Żywności i Leków (ang. Food and Drug Administration, FDA) są minoksydyl stosowany miejscowo (u mężczyzn i u kobiet) oraz finasteryd stosowany doustnie (tylko u mężczyzn). Dostępne terapie AGA często nie przynoszą zadowalających efektów klinicznych dlatego istnieje zapotrzebowanie na nowe strategie leczenia. Terapie oparte na komórkach macierzystych w ostatnim czasie spotkały się ze znacznym zainteresowaniem jako potencjalne nowe metody leczenia polegające na reaktywacji komórek macierzystych mieszków włosowych, a tym samym poprawiające wzrost, regenerację i rozwój mieszków włosowych i włosów. Przedmiotem największej uwagi autorki stały są dwa rodzaje komórek macierzystych w mieszku włosowym. Pierwsze z nich to komórki macierzyste mieszków włosowych (ang. hair follicle-derived stem cells, HFSC), znajdujące się w okolicy przyczepu mięśnia przywłośnego oraz zewnętrznej osłonki korzenia (ang. outer root sheath, ORS), w obszarze określanym jako wybrzuszenie. Drugi typ to komórki brodawki skórnej (dermal papilla cells, DPC), które odpowiedzialne są za kontrolowanie

indukcji i wzrostu włosów, a także uczestniczą w tworzeniu nowych mieszków włosowych. W przeciwieństwie do łysienia bliznowaciejącego, w AGA nie dochodzi do uszkodzenia puli HFSC, co sprawia, że łysienie androgenowe jest potencjalnie odwracalne.

AGA jest chorobą dynamiczną i postępującą, dlatego po wstępnej diagnozie ważne jest, aby szybko zastosować nie tylko leczenie hamujące postęp choroby, ale również odwracające zmiany, które już wystąpiły.

Podjęty temat badania jest nowatorski i istotny w kontekście możliwego wykorzystania tej metody leczenia w praktyce klinicznej biorąc pod uwagę fakt, że dostępne piśmiennictwo obejmuje w większości zastosowanie komórek macierzystych głównie w leczeniu łysienia męskiego.

## 3.2. Cel badań i problemy badawcze

Celem badań wchodzących w skład rozprawy doktorskiej był przegląd aktualnie dostępnych badań oceniających skuteczność terapii opartych na ludzkich komórkach macierzystych w leczeniu łysienia androgenowego, przeprowadzenie badania z autologicznymi komórkami macierzystymi pochodzącymi z mieszków włosowych w grupie kobiet chorujących na AGA jak i ocena skuteczności zastosowanej terapii. Dodatkowo autorka oceniała i scharakteryzowała obciążenie psychospołeczne związane z tą chorobą, a także wpływ leczenia komórkami macierzystymi na jakość życia oraz funkcjonowanie seksualne wśród zakwalifikowanych do badania pacjentek.

Cele szczegółowe:

3.2.1 Dokonanie przeglądu systematycznego piśmiennictwa dotyczącego efektywności oraz bezpieczeństwa stosowania ludzkich komórek macierzystych różnego pochodzenia w leczeniu łysienia androgenowego.

3.2.2 Ocena skuteczności leczenia komórkami macierzystymi pochodzącymi z mieszków włosowych (HFSCs) w grupie pacjentek z łysieniem androgenowym.

3.2.3 Ocena obecności i stopnia nasilenia obciążenia psychospołecznego w grupie badanych pacjentek z łysieniem androgenowym przez leczeniem.

3.2.4 Ocena wpływu terapii autologicznymi komórkami macierzystymi na jakość życia i funkcjonowanie seksualne w grupie badanych pacjentek z łysieniem androgenowym.

3.2.5 Analiza korelacji pomiędzy wskaźnikami laboratoryjnymi i skutecznością terapii z wykorzystaniem komórek macierzystych w grupie badanych pacjentek z łysieniem androgenowym.

## 3.3. Materiały i metody

Pierwszą pracą spośród cyklu jest przegląd systematyczny piśmiennictwa dotyczący wykorzystania ludzkich komórek macierzystych różnego pochodzenia w leczeniu łysienia androgenowego. Przeglądu dokonano zgodnie z wytycznymi protokołu PRISMA w marcu 2023 r. Bazy danych Medline, Web of Science oraz Scopus zostały przeszukane pod kątem odpowiednich artykułów przy użyciu kombinacji słów kluczowych: „łysienie androgenowe" (ang. androgenic alopecia) lub „łysienie wzorcowe" (ang. pattern hair loss) oraz „komórki macierzyste" (ang. stem cells) lub „ADSC" (ang. adipose tissue-derived stem cells) lub „ASC" (ang. adipose-derived stromal stem cells) lub „FDSC" (ang. fascia-derived stem cells) lub „HFCS" (ang. hair follicle-derived stem cells) lub „MSC" (ang.mesenchymal stem cells). Kryteria wykluczenia obejmowały modele przedkliniczne (badania na zwierzętach), badania in vitro, przeglądy narracyjne, przypadki hipotetyczne i badania obserwacyjne, a także artykuły w języku innym niż angielski. W przypadku badań z tych samych ośrodków zgłaszających prawdopodobnie nakładające się kohorty uwzględniono najnowsze badanie. Do dalszej analizy włączono oryginalne artykuły pełnotekstowe dotyczące zastosowania komórek macierzystych w leczeniu łysienia androgenowego.

W badaniach będących podstawą drugiej i trzeciej publikacji cyklu badano wpływ leczenia za pomocą autologicznych mikroprzeszczepów komórek macierzystych (autologous cellular micrografts, ACM) pochodzących z mieszków włosowych u pacjentek z rozpoznanym łysieniem androgenowym. Badania prowadzono w latach 2022-2023. Zakwalifikowano do niego pacjentki powyżej 18 roku życia, które podpisały świadomą zgodę na udział w badaniu. Podstawowe kryteria wyłączenia obejmowały: immunosupresję, choroby nowotworowe, ciężkie choroby przewlekłe, ciążę, karmienie piersią, wiek poniżej 18 lat,

stosowanie antykoncepcji hormonalnej, hiperprolaktynemię, niedoczynność tarczycy, dodatnie przeciwciała przeciwjądrowe 3 (ang. antinuclear antibodies, ANA3), aktywne zapalenie skóry głowy, zaburzenia krzepnięcia, alergię na lignokainę i niestabilny stan emocjonalny. Wykluczono także pacjentki, które w ciągu sześciu miesięcy przed rozpoczęciem projektu otrzymywały leczenie AGA w postaci doustnej (finasteryd, dutasteryd, minoksydyl, antyandrogeny) lub miejscowej (minoksydyl, analogi prostaglandyn, kortykosteroidy). Ostatecznie do badania zakwalifikowano 23 pacjentki z łysieniem androgenowym, których średni wiek wynosił 40,1±12 lat. Od wszystkich pacjentek zostały pobrane próbki krwi celem wykonania badań laboratoryjnych. Parametry biochemiczne analizowano w następujący sposób: testy elektrochemiluminescencji na obecność hormonu tyreotropowego (TSH), przeciwciał przeciwko peroksydazie tarczycowej (anty-TPO), przeciwciał przeciwko tyreoglobulinie (anty-TG), testosteronu, globuliny wiążącej hormony płciowe (SHGB), prolaktyny i kortyzolu; testy kolorymetryczne na obecność żelaza analizowano za pomocą cobas® e 411 (Roche Diagnostics GmbH, Mannheim, Niemcy). Testy chemiluminescencji dla androstendionu, witaminy D3, kwasu foliowego, ferrytyny i witaminy B12 przeprowadzono na LIAISON® XL (DiaSorin, Saluggia, Włochy). Diagnostyczne zestawy laboratoryjne firmy EUROIMMUN (Wrocław, Polska) zostały użyte do enzymatycznych testów immunosorbcyjnych na siarczan dehydroepiandrosteronu (DHEA-S), dihydrotestosteron (DHT), 17α-hydroksyprogesteronu, adrenokortykotropiny (ACTH) oraz do immunoblottingu przeciwciał przeciwjądrowych (ANA), które analizowano na EUROBlot One (EUROIMMUN, Wrocław, Polska). Badania hematologiczne wykonano na aparacie Sysmex XN-1000 (Sysmex, Norderstedt, Niemcy). W przypadku każdego testu zestawy i odczynniki zostały zakupione od producenta urządzenia i były obsługiwane zgodnie z dostarczonymi instrukcjami.

Pacjentkom zakwalifikowanym do badania, z okolicy zausznej owłosionej skóry głowy, pobrano pięć wycinków skórnych przy pomocy sztancy o średnicy 2,5 mm. Z pobranych mikroprzeszczepów za pomocą Rigeneracons® otrzymano zawiesinę komórek, którą metodą mezoterapii zaaplikowano w skórę głowy objętą procesem chorobowym. Regenera Activa® (Human Brain Wave SRL, Turyn, Włochy) to technologia wykorzystująca urządzenie Regenera Activa®, które jest systemem do mechanicznej dezintegracji i filtrowania tkanek stałych w celu ekstrakcji komórek macierzystych. Procedura jest przeprowadzana przy użyciu metody Rigenera HBW (Regenera® Protocol, Rigenera® Activa, Human Brain Wave SRL, Turyn, Włochy), opracowanej we Włoszech w 2013 roku i

dostępnej w ponad 50 krajach. Protokół obejmuje użycie kilku urządzeń: Regenera Activa® do pobierania biopsji punkcyjnych, Rigeneracons (Human Brain Wave SRL, Turyn, Włochy) do wytwarzania zawiesiny komórek stosowanej jako ACM oraz standardowej strzykawki do wstrzykiwania ACM w obszary docelowe.

W celu oceny efektów leczenia, wykonano zdjęcia głowy pacjentek przed leczeniem i sześć miesięcy po jego zakończeniu. Fotografie przed i po zabiegu zostały wykonane w tym samym pomieszczeniu, w podobnych warunkach oświetleniowych i w tej samej pozycji głowy. Czterech specjalistów dermatologii niezależnie oceniło zdjęcia przed i po leczeniu przy użyciu wizualnej skali analogowej (ang. visual analog scale, VAS). Dodatkowo za pomocą skali Ludwiga autorka przedłożonej rozprawy, oceniła stopień zaawansowania choroby w badanej grupie przed i po zakończeniu leczenia.

Wszystkie zakwalifikowane do badania pacjentki zostały poproszone o wypełnienie dwóch kwestionariuszy przed i sześć miesięcy po wykonanej procedurze z komórkami macierzystymi. Wykorzystano kwestionariusz jakości życia w wersji skróconej Światowej Organizacji Zdrowia (ang. The World Health Organization Quality of Life Brief Version, WHOQOL-BREF) do oceny jakości życia w czterech domenach: zdrowie fizyczne, zdrowie psychiczne, relacje społeczne i środowisko. Każda domena była oceniana w skali Likerta od 1 do 5. Po zebraniu wypełnionych kwestionariuszy wyniki domen zostały przekształcone w skalę od 0 do 100, gdzie wyższe wyniki wskazywały na wyższą jakość życia. Drugim wykorzystanym kwestionariuszem był Indeks Funkcjonowania Seksualnego Kobiet (ang. Female Sexual Function Index, FSFI) czyli 19-elementowa skala badająca sześć różnych obszarów kobiecych funkcji seksualnych, a mianowicie: pożądanie, podniecenie, nawilżenie, orgazm, satysfakcje i ból. W FSFI możliwe jest do uzyskania od minimalnie 2 punktów do maksymalnie 36 punktów. Skala ta jest szeroko stosowana zarówno jako narzędzie przesiewowe do wykrywania zaburzeń seksualnych jak i narzędzie do pomiaru wyników w zakresie funkcji seksualnych kobiet. FSFI ma kliniczny wynik odcięcia wynoszący 26,55 punktów i służy obecnie jako standard kliniczny do różnicowania pacjentów z dysfunkcjami seksualnymi. W poszczególnych domenach wyniki poniżej mediany uznano za wskazujące na dysfunkcję dla danej domeny, tj. dla pożądania $\leq 3,6$, dla podniecenia $\leq 4,8$, dla nawilżenia $\leq 5,1$, dla orgazmu $\leq 4,4$, dla satysfakcji $\leq 4,4$ i dla bólu $\leq 5,6$.

Następnie zbadano korelację pomiędzy zmianą wyniku VAS po leczeniu a wyjściową charakterystyką kliniczną pacjentów i korelacje między funkcjonowaniem seksualnym a jakością życia kobiet z AGA po leczeniu.

Do analizy statystycznej wykorzystano oprogramowanie SigmaPlot 14.5 (Systat, Software Inc., San Jose, CA, USA). Dane o rozkładzie normalnym przedstawiono jako średnia ± odchylenie standardowe (SD), dane niespełniające założenia o normalności przedstawiono jako medianę (rozstęp międzykwartylowy). W testach statystycznych $p < 0,05$ uznano za istotne statystycznie.

## 3.4. Podsumowanie wyników

Wyniki badań laboratoryjnych zakwalifikowanych pacjentek wykazały, że poziomy ferrytyny i żelaza były bliższe dolnej granicy normy, a poziom TSH był zgodny z normami w populacji ogólnej oraz tymi dotyczącymi kobiet w wieku rozrodczym u wszystkich pacjentek. Analiza hormonów płciowych wykazała, że pacjentki nie miały nieprawidłowo podwyższonego poziomu DHT, DHEA-S, androstendionu i testosteronu, podczas gdy stężenie SHGB było na górnej granicy normy.

Zdjęcia skóry głowy pacjentek przed i sześć miesięcy po terapii HFSC zostały ocenione przez czterech niezależnych specjalistów dermatologii. Ocena ta wykazała znaczną poprawę kliniczną w oparciu o skalę VAS ze średnim wzrostem o 1,5 punktu ($p < 0.05$) i o 1 stopień w skali Ludwiga ($p < 0.05$).

Związek między początkowymi parametrami krwi a wynikami klinicznymi oceniono na podstawie współczynników korelacji Spearmana. Ocena efektów klinicznych w skali VAS przez 4 niezależnych specjalistów dermatologii wykazała umiarkowaną ujemną korelację z wyjściowym stężeniem ferrytyny i dodatnią korelację ze stężeniem żelaza**,** jednak korelacja ta nie była istotna w kontekście wyniku delta VAS (średni wynik w skali VAS po leczeniu - średni wynik w skali VAS przed leczeniem)**.** Wśród hormonów płciowych średnie lepsze wyniki terapii były związane z wyższymi początkowymi poziomami SHGB ($r = 0,47$; $p < 0.05$) i 17α-hydroksyprogesteronu ($r = 0,44$; $p < 0.05$). Ani stężenia testosteronu, ani DHT nie wykazywały istotnej korelacji z wynikami oceny VAS.

W kolejnym etapie pracy badawczej wykazano, że przed leczeniem w skali FSFI 11 pacjentek uzyskało wyniki poniżej 26,55, co wskazuje na obecność dysfunkcji seksualnych w tej grupie pacjentek. Liczba ta zmniejszyła się do 6 pacjentek z dysfunkcjami seksualnymi po 6 miesiącach od sesji ACM. Na początku badania większość (65%) pacjentek zgłosiło wyniki poniżej mediany w zakresie pożądania i podniecenia, 61% poniżej mediany w zakresie

nawilżenia i bólu, a 57% poniżej mediany w odniesieniu do orgazmu i satysfakcji. Po leczeniu ACM pacjentki zgłaszały znacznie wyższe pobudzenie z medianą 4,8 (1,5) przed i 5,10 (0,9) po leczeniu (p = 0,035, wielkość efektu r = -0,31, co wskazuje na średni efekt), a także satysfakcję z medianą 4,4 (1,4) przed i 4,8 (1,8) po leczeniu (p = 0,025, wielkość efektu r = -0,324). Całkowity wynik FSFI, a także wskaźniki pożądania, nawilżenia, orgazmu i bólu nie różniły się istotnie między punktami badania.

Spośród domen WHOQOL-BREF pacjentki z AGA zgłaszali najniższą jakość życia w domenie zdrowia fizycznego. Ocena za pomocą WHOQOL-BREF wykazała, że 6 miesięcy po zabiegu ACM pacjentki odczuwały wyższą jakość życia w zakresie zdrowia psychicznego (średnia przed 57,96 ± 19,0 vs. średnia po 69,35 ± 14,0; p = 0,031, wielkość efektu mierzona za pomocą d Cohena wyniosła d = 0,68, co wskazuje na średni efekt) i środowiska (średnia przed 72,96 ± 13,4 vs. średnia po 81,09 ± 12,6; p = 0,007, d Cohena wyniosło 0,63). Nie odnotowano znaczących zmian w zgłaszanym zdrowiu fizycznym i relacjach społecznych.

Analiza korelacji między wynikami WHOQOL-BREF a wynikami FSFI wykazała, że we wszystkich domenach ogólna jakość życia i zdrowie seksualne były umiarkowanie lub silnie dodatnio skorelowane. Najsilniejsze związki (powyżej 0,7 rho Spearmana) stwierdzono między pobudzeniem FSFI a relacjami społecznymi (p<0.001) oraz satysfakcją FSFI a relacjami społecznymi (p < 0,001). Nie wykryliśmy żadnego związku między domenami WHOQOL-BREF lub FSFI a wiekiem lub nasileniem AGA.

Analizowane w przeglądzie systematycznym badania kliniczne wykazały, że stosowanie ludzkich komórek macierzystych w leczeniu AGA u kobiet i mężczyzn jest rokującą nadzieję opcją terapeutyczną. Również wyniki uzyskane w badaniach będących podstawą publikacji drugiej i trzeciej wskazują na obiecujące efekty terapii ACM. Przyszłe wysiłki powinny skupić się na poprawie projektowania badań klinicznych, przeprowadzeniu większej liczby badań z komórkami macierzystymi u kobiet z AGA oraz ustaleniu najlepszych praktyk w zakresie miejsc wstrzyknięć, typów komórek, sesji i częstotliwości. Ważne jest stworzenie ustandaryzowanej metody pobierania, przygotowywania i wstrzykiwania komórek macierzystych. Istnieją liczne doniesienia na temat ADSC i HFSC w leczeniu AGA, jednak dalsze badania z komórkami macierzystymi szpiku kostnego (*ang. bone marrow stem cells, BMSC*) i rozpoczęcie badań z komórkami macierzystymi z galarety Whartona są niezbędne, aby zacząć rozważać je jako opcję terapeutyczną. Pomocne byłoby przeprowadzenie badania porównującego skuteczność różnych rodzajów komórek

macierzystych w leczeniu AGA, ponieważ możliwość ich uzyskania jest bardzo zróżnicowana.

## 3.5. Etyka

Projekt pracy doktorskiej opartej na poniższych publikacjach został zatwierdzony przez Komisję Bioetyczną Uniwersytetu Medycznego we Wrocławiu na podstawie zgody Nr KB-1074/2021. 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.

## 3.6. Wnioski

3.6.1. Zastosowanie ludzkich komórek macierzystych w łysieniu androgenowym wydaje się być obiecującą opcją terapeutyczną wobec standardowego leczenia lub może odgrywać rolę terapii uzupełniającej w celu poprawy efektu leczenia podstawowego.

3.6.2. Leczenie ludzkimi komórkami macierzystymi niezależnie od ich pochodzenia ma pozytywny wpływ na gęstość włosów u pacjentów chorujących na łysienie androgenowe.

3.6.3. Terapia wykorzystująca autologiczne komórki macierzyste z mieszków włosowych przynosi satysfakcjonujące efekty sześć miesięcy po pojedynczej sesji leczenia u kobiet z łysieniem androgenowym.

3.6.4. Pacjentki, u których stwierdzono w pobranych próbkach krwi wyższe wyjściowe stężenie globuliny wiążącej hormony płciowe (SHGB) i 17α-hydroksyprogesteronu osiągały lepsze wyniki kliniczne oceniane za pomocą skali VAS.

3.6.5. Łysienie androgenowe żeńskie wpływa negatywnie na jakość życia i funkcjonowanie sekusalne kobiet, a wykorzystanie terapii z komórkami macierzystymi w leczeniu kobiet z AGA działa pozytywnie na oba aspekty.

3.6.6. Konieczne są dalsze badania w celu oceny długoterminowej skuteczności stosowania autologicznych komórek macierzystych pochodzących z mieszków włosowych pacjentów chorujących na łysienie androgenowe.

## 4. ARTYKUŁ PIERWSZY

# HUMAN STEM CELL USE IN ANDROGENETIC ALOPECIA:

# A SYSTEMATIC REVIEW

cells

MDPI

*Review*

# Human Stem Cell Use in Androgenetic Alopecia: A Systematic Review

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**Abstract:** Androgenetic alopecia is a condition that results in hair loss in both men and women. This can have a significant impact on a person's psychological well-being, which can lead to a decreased quality of life. We conducted a systematic review to evaluate the efficacy of using stem cells in androgenic alopecia. The search was conducted in MEDLINE via PubMed, Web of Science, and Scopus databases. The review was performed on data pertaining to the efficacy of using different types of stem cells in androgenic alopecia: quantitative results of stem cell usage were compared to the control treatment or, different types of treatment for female and male androgenetic alopecia. Of the outcomes, the density of hair was analyzed. Fourteen articles were selected for this review. During and after treatment with stem cells, no major side effects were reported by patients with alopecia. The use of stem cells in androgenic alopecia seems to be a promising alternative to the standard treatment or it could play the role of complementary therapy to improve the effect of primary treatment. However, these results should be interpreted with caution until they can be reproduced in larger and more representative samples.

**Keywords:** stem cells; androgenic alopecia; female pattern hair loss; mesenchymal stem cell; follicle-derived stem cells; alopecia; male pattern hair loss; tissue regeneration; clinical application



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## 1. Introduction

The common cause of non-scarring alopecia among both men and women is androgenic alopecia (AGA). The disease manifests by progressive hair loss, usually in a pattern distribution. It can begin at any age after puberty, but the incidence increases with age. At the age of 70 and above, up to 42% of women and 80% of men present characteristic features of AGA [1]. The miniaturization of hair follicles and decreased hair density occur in the affected scalp area of patients with AGA. Terminal hair growth length is gradually reduced in this disease entity. Both women and men show an increase in short telogen hairs (<30 mm) over the course of the disease. This indicates that hair completes its life cycle in less than 6 months in PHL (pattern hair loss) patients [2]. Although the causes of miniaturization are unknown, genetic tendencies and androgen effects are thought to be associated with other factors that have not yet been clarified [3].

The hair of the human scalp plays an important symbolic role in determining one's appearance and is an important sociocultural role. Hairstyles and lengths are distinctive features of an individual's identity, and hair loss can lead to dissatisfaction with appearance, especially among women, and can have a negative impact on self-esteem. Hair loss is also associated with psychological and social difficulties in men [4,5].

At present, minoxidil and finasteride are the relevant only approved drugs by the US Food and Drug Administration (FDA). Dutasteride, despite not being an FDA-approved drug for androgenic alopecia, showed greater long-term effectiveness and safety versus finasteride in patients with male androgenic alopecia [6]. Low level laser light therapy (LLLLT) is the only approved device by the FDA to treat androgenetic alopecia [7]. Gupta et al. [8], in a systematic review with meta-analysis from 2022, came to the conclusion that

the only treatment option with strong evidence, for both males and females with AGA is 5% minoxidil. AGA is a dynamic and progressive disease, therefore after initial diagnosis it is important to quickly apply not only a treatment that inhibits the progression of the disease but also one that can reverse the changes that have already occurred.

Stem cell-based therapies have recently gained considerable attention as potential novel treatments, focusing on the reactivation of hair follicle stem cells and thus improving the growth, regeneration, and development of hair follicles [9]. The sources of multi-potent stem cells with regenerative potential for hair follicles are adipose tissue, hair follicles from unaffected regions, blood, bone marrow, and Wharton's jelly. There are two main types of stem cell transplants: autologous and allogeneic. The stem cells in autologous transplants come from the same person who will get the transplant, so the patient is their own donor. The stem cells in allogeneic transplants are from a person other than the patient, either a matched related or unrelated donor. Anudeep et al. proposed the classification of stem cells into adult stem cells and perinatal stem cells. Adult stem cells were divided into adipose tissue-derived stem cells (ADSCs), hair follicle-derived stem cells (HFSCs), and bone marrow-derived stem cells (BMSCs). In addition, ADSCs were divided into nanofat and stromal vascular fraction (SVF). HFSCs on autologous micrografts and cultured HFSCs. Perinatal stem cells included umbilical cord blood derivatives, MSCs from Wharton's jelly, MSCs from amniotic fluid, and MSCs from the placenta [10]. Cell transplantation is one of the strategies to achieve the functional regeneration of hair follicles. Studies show that the injection of a mixture containing skin epithelial stem cells and mesenchymal stem cells can induce new hair follicles. Importantly, hair follicular stem cells (HFSCs) periodically switch between the active and inactive phases which enables keeping stem cell populations in the hair follicles stable; however, this ability is diminished with aging [11].

Hair follicles contain a variety of cell resources, such as melanocytic cells, epithelial cells, and stem cells from different developmental origins, which are capable of constantly renewing, distinguishing, and regulating hair growth and skin homeostasis [12,13]. The subjects of the greatest interest are two types of stem cells in the hair follicle. The first are HFSCs, which are in the region of the attachment of the arrector pili muscle and within the outer root sheath (ORS), in the region of the proximal end of the isthmus. Both regions are referred to as the "bulge." The second type is dermal papilla cells (DPCs), which are responsible for controlling hair induction and growth as well as participating in the formation of new hair follicles [14]. Unlike scarring alopecia, in AGA, which belongs to non-scarring alopecia, there is no damage to HFSCs while progenitor cells are damaged [15]. That fact makes androgenetic alopecia potentially reversible. DPCs in the skin affected by androgenetic alopecia have reduced replicative potential and were also found to have changes in their shape, size, and loss of characteristic markers. The influence of dihydrotestosterone on DPCSs is considered a potential cause of senescence. Abnormally functioning DPCs produce inhibitory factors that suppress HFSCs. In turn, they lose the function of their stimulation [16].

Adipose tissue, in addition to its role in energy storage, is a well-known source of precursors and stem cells. The adipose tissue is a storage area for regenerative molecules. Indeed, a variety of regenerative products can be generated from adipose tissue, including nano fat, vascular stem cell fraction (SVF), MSCs, adipose-derived stem cell conditioning medium (ADSC-CM), and extracellular veins (EV) [10]. The stromal vascular fraction (SVF) refers to all the cellular elements of the adipose tissue and is formed from heterogeneous cell population components of this tissue: adipocytes, blood cells, endothelial cells, extracellular matrix, and the most essential elements which are adipose-derived stromal/stem cells (ASC) [17,18]. Multipotent stem cells derived from adipose tissues, stromal vascular cells derived from adipose (ADSVC), or regenerative cells derived from adipose (ADRC) refer to the newly used primary multipotent stem cells derived from the stromal vascular fraction. When these cells are cultured, they acquire additional characteristics and become a set of mesenchymal stem cells (MSCs) which are known as adipose-derived stem cells (ADSCs) [9,19,20].

Bone marrow is the main source of MSC. Many animal models showed the progression from the telogen phase to the anagen phase after the intradermal injection of mesenchymal cells from bone marrow (BM-MSC) and induced genes involved in hair regeneration [10,21]. Yoo et al. [22] studied the influence of MSCs from the umbilical cord and bone marrow on human hair proliferation in vitro. The researchers have attempted to cultivate hair follicle cells in vitro and implant them in the treatment area. The study showed that created DPLTs (dermal papilla-like tissues) have the same hair bulb structure inductive ability as natural DPSCs and that the transplantation of DPLTs can induce new hair follicles in athymic mice.

Studies using Wharton's jelly stem cells on AGA patients have not been conducted. Their uniqueness and advantage over other mesenchymal cells are due to several of their features: non-invasive and non-painful derivation, large number of donors, no ethical concerns, high cell proliferation, and broad differentiation potential. In addition, they have negligible immunogens [23].

In recent years, there has been an intensive development of simple, outpatient stem cell isolation methods. At the same time, due to high availability and media publicity, they have become popular among both physicians and patients suffering from androgenetic alopecia. These are usually one-day procedures that do not require convalescence.

Along with the development of these techniques, a multitude of studies was published on the efficacy of stem cell-based treatments in AGA. However, no systematic review was performed. Therefore, this study aims to conduct a systematic review of studies assessing the efficacy of stem cell-based therapies in the treatment of AGA.

## 2. Materials and Methods

This systematic review was conducted to identify evidence on the efficacy of using stem cells in the treatment of AGA. To conduct this study, the MEDLINE, Web of Science, and Scopus databases were used. In addition, the reference list of included studies was also manually analyzed by the reviewers. This review was designed and conducted according to the PRISMA guidelines.

To retrieve articles, the following search query was used: (androgenic alopecia OR pattern hair loss) AND (stem cells OR ADSC OR ASC OR FDSC OR HFSC OR MSC). The search was conducted on 11 January 2023.

Inclusion criteria were randomized controlled trials (RCT), non-RCTs, case studies/series, and studies assessing treatments with stem cells in people with AGA. Pre-clinical models (animal studies), in vitro studies, narrative reviews, hypothetical cases, and observational studies were excluded. The exclusion criteria were as follows: full text not available, full text not available in English, studies with duplicate information published elsewhere, nonoriginal data such as reviews, commentaries, and editorials. In the case of studies from the same centers reporting possibly overlapping cohorts, the newest study was included. The inclusion criteria are reported as per the PICOS criteria and presented in Table 1.

**Table 1.** PICO criteria.

| | |
|---|---|
| **P**atients = women and men with androgenic alopecia | Descriptions: female pattern hair loss, male pattern hair loss, female androgenic alopecia, male androgenic alopecia, alopecia in women, alopecia in men. |
| **I**nterventions = treatment with stem cells | Descriptions: ADSC, HFSC, BMSC. |
| **C**omparison | Descriptions: placebo, different treatments. |
| **O**utcomes | Objective measurement of hair density. |

ADSC, adipose-derived stem cell; BMSC, bone marrow stromal cell; HFSC, hair follicular stem cells; PICO, patient/population, intervention, comparison, and outcomes.

Study identification and screening were made by two independent reviewers and discrepancies were resolved by consensus. One reviewer extracted data, while a second reviewer validated the extracted data. The following data were retrieved: study design, year of publication, percentage of female subjects, number of participants, age of participants, type of stem cells, evaluation method, and results.

## 3. Results

In the search, we identified 1889 records (685 in MEDLINE/PubMed; 289 in Web of Science; 915 in Scopus). Out of these, 210 duplicate records were removed. All titles and abstracts were reviewed, and 22 articles were assessed in full and reviewed for eligibility. Fifteen articles met the inclusion criteria and are summarized in this review. The selection process in presented in the PRISMA flowchart (Figure 1). The studies included in this review were conducted between 2015 and 2021. Studies were conducted in Italy (3), Egypt (2), Saudi Arabia (1), Japan (3), Spain (2), and South Korea (4). These studies included a total of 653 participants diagnosed with AGA. In total, 5 out of the 15 studies were reported as randomized controlled trials. Three were non-randomized controlled trials. Four were single-arm trials without a control group. Three were retrospective reports of a series of patients. The characteristics of included studies are shown in Table 2.

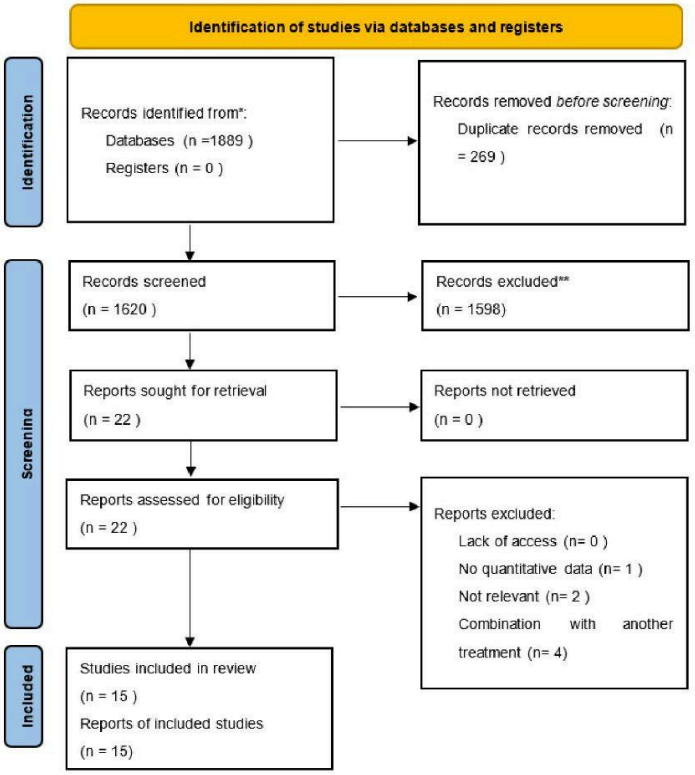


**Figure 1.** PRISMA flowchart of selected studies.

**Table 2.** Characteristics of included studies.

| Author, Year | Design Country | N, Age (Year) F (%) | Duration and Type of Treatment | Progression of the Disease (Scale) | Assessment | Hair Density |
|---|---|---|---|---|---|---|
| Tsuboi et al. [24], 2020 | RCT Japan | 65 33–64 23 | HFSCs 1 session n/r injections | N-H 3-6 S 3-6 | P, hair density, hair diameter, trichogram | IMPROVEMENT: total hair density increased vs. placebo ($p < 0.025$), an increase was greater in people ≥51 years of age |
| Gentile et al. [24], 2017 | NRCT Italy | 11 38–61 0 | HFSCs 1 session subcutaneous injections | N-H 3-5 | P | IMPROVEMENT: hair density increased by 29% ± 5% for a treated area and by less than 1% for the placebo area |
| Elmadaavi et al. [25], 2018 | RCT Egypt | 20 10–50 (26 ± 8) 60 | BMSCs and HFSCs 1 session intradermal injections | n/r | P, dermosopic examination, digital dermoscopic, and histological examination | IMPROVEMENT: increase in hair density of 52 ± 28 in subjects receiving BMMC and 42 ± 27 in subjects receiving FSC with a non-statistically significant difference |
| Zari et al. [26], 2021 | single arm, non-controlled Saudi Arabia | 140 18–65 (mean age 32.1) 80,7 | HFSCs 1 session subcutaneous injections | S 2–4, N-H 2–4 | P, trichoscopy (TrichoScan®) | IMPROVEMENT: hair density increases by +4.5 to 7.12 hair/cm |
| Narita et al. [27], 2020 | NRCT Japan | 40 23–74 47,5 | ADSCs-CM 6 sessions intradermal injections | L 1-2, N-H 2–6 | P, trichoscopy (TrichoScan®) | IMPROVEMENT: increased hair density from T0 to T6 ($p < 0.001$) |
| Ruiz et al. [28], 2019 | single arm, non-controlled Spain | 100 n/r n/r | HFSCs 1 session n/r injections | n/r | P, trichoscopy (TrichoScan®) | IMPROVEMENT: increased hair density of 30% ± 3.0% |
| Gentile et al. [29], 2019 | ROCA Italy | 21 25–72 28,2 | HFSCs 2 sessions subcutaneous injections | L 1-2, N-H 2-5 | P | IMPROVEMENT: increased hair density of 30 ± 5.0% for the treatment group and less than a 1% increase for the placebo |
| Kim et al. [29], 2021 | single arm, non-controlled Republic of Korea | 9 43–64 (53 ± 1.22) men: 51.5 ± 3.43; women 55,5 | ADSCs 1 session subcutaneous injections | L 1-3, N–H 4-5 | P | IMPROVEMENT: hair density increased compared to the non-treated side ($p = 0.01$ and $p = 0.009$ per each); density increased in the treated site by 48.11% as compared to the non-treated site density of 35.48% |
| Fukuoka et al. [30], 2015 | NRCT Japan | 32 20–70 40,2 | ADSCs-CM 6 sessions intradermal injections | n/r | P, trichoscopy (TrichoScope) | IMPROVEMENT: the mean increase in hair density was 29 ± 4.1 in male patients and 15.6 ± 4.2 in female patients |
| El-Khalawany et al. [26], 2022 | single arm, non-controlled Egypt | 30 21–45 (30.1 ± 6.3) 53,3 | ADSCs 1 session intradermal injections | L 1-3, N-H 1–6 | P, trichoscopy | IMPROVEMENT: hair count/cm$^2$ showed a high statistically significant increase from 130.87± 14/cm$^2$ before the study to 151.93 ± 22.36/cm$^2$ at the 6-month follow-up visit with a 16.09% improvement |
| Shin et al. [28], 2015 | ROCS Republic of Korea | 27 22–69 (41.9 ± 13.4) 100 | ADSCs-CM 12 sessions topical wit micro-niddle roller | L 1 | medical records and phototrichographic images were analyzed | IMPROVEMENT: hair density increased from 105.4 to 122.7 hairs/cm$^2$ over the 12 weeks of treatment ($p < 0.001$), representing an increase of 16.4%. |
| Gentile et al. [31], 2020 | RCT Italy | 27 n/r 37 | HFSCs 3 sessions subcutaneous injections | L 1-2, N-H 2-5 | P, phototrichograms | IMPROVEMENT: an increase of hair count and hair density, respectively, of 18.0 hairs per 0.65 cm$^2$ and 23.3 hairs per cm$^2$ compared with the baseline, while the control area displayed a mean decrease of 1.1 hairs per 0.65 cm$^2$ and 0.7 hairs per cm$^2$ (control vs. treatment: $p < 0.0001$) |

**Table 2.** *Cont.*

| Author, Year | Design Country | N, Age (Year) F (%) | Duration and Type of Treatment | Progression of the Disease (Scale) | Assessment | Hair Density |
|---|---|---|---|---|---|---|
| Perez Meza et al. [19], 2017 | ROCS Spain | 6 18–55 11,1 | ADSCs 1 session subcutaneous injections | L 1-3, N–H 2-6 | P, trichoscopy (FotooFinder®) | IMPROVEMENT: the mean increase of hair density was 31 hairs/cm$^2$ of (represents a 23% relative percentage increase) |
| Lee et al. [32], 2020 | RCT Republic of Korea | 30 20–61 (46.6) 50 | ADSCs-CM topical 12 weeks, 1 session weekly | n/r | P, phototrichogram | IMPROVEMENT: the hair density of the placebo group was 89.3 ± 3.79/cm$^2$ and that of the ADSC-CM group was 102.1 ± 4.09/cm$^2$, showing a significant difference ($p < 0.05$) |
| Tak et al. [33], 2020 | RCT Republic of Korea | 38 45.3 23,7 | ADSCs-CM topical 16 weeks twice daily | n/r | P, phototrichogram | IMPROVEMENT: in the treatment group the mean hair density and thickness increased by 28.1% and 14.2% by 16 weeks, which were 3.95 and 2.25 times those in control group using the vehicle placebo |

F, female; L, Ludwig scale; N-H, Norwood-Hamilton scale; S, Shiseido scale; N, number of participants; NRCT, non-randomized clinical trial; P, photography with baseline evaluation; RCT, randomized controlled trial; ROCS, retrospective observational case series study; S, Sinclair scale; n/r, non-reported.

### *3.1. Studies Comparing the Use of Stem Cells with a Placebo*

Of the 15 studies, 6 compared the use of stem cells with a placebo. Four of them compared HFSCs and two of them ADSCs.

Tak et al. [33] conducted a double-blind, randomized, placebo-controlled clinical trial. This study took place in the Republic of Korea and involved 38 patients (23.7% were females) diagnosed with AGA. Two groups were distinguished: the intervention group (IG; n = 19), in which participants received ADSC-CE (adipose-derived stem cell constituent extract) and the control group (CG; n = 19), in which participants received the vehicle placebo. Participants used ADSC-CE topical twice a day for 16 weeks. After 16 weeks, an evaluation based on phototrichogram showed that the total hair count was significantly lower in CG than in IG (13.95 ± 4.01 vs. 17.58 ± 4.13 counts per cm$^2$ $p = 0.009$), although there was no significant difference in the hair thickness between the groups. During the course of the study, seven mild side effects were reported in five patients, which resolved without any medical intervention.

Another double-blind randomized controlled study was performed by Lee et al. [32] with 30 females and males aged 20–61 years, with MPHL (male pattern hair loss) or FPHL (female pattern hair loss). The treatment course consisted of the repeated application of ADSC-CM topically or normal saline (placebo) once per week for 12 consecutive weeks. At the endpoint, the hair density of the placebo group was 89.3 ± 3.79/cm$^2$ and that of the ADSC-CM group was 102.1±4.09/cm$^2$, showing a statistically significant difference ($p < 0.05$). No adverse events occurred during the duration of this study.

Gentile et al. [25] used human follicle stem cells (HFSCs) in 11 patients (38 to 61 years old) affected by AGA in stages 3–5, as determined by the Norwood-Hamilton classification scale. He used the system Rigenera® which obtains stem cells from patients' scalp biopsies without culturing. In patients with hair loss in the frontal and parietal areas, the HFSC injections were administered exclusively to the front scalp, and placebo injections (i.e., normal saline) were administered to the parietal areas. Similarly, in patients with hair loss limited to the parietal and vertex regions, HFSCs were injected into the parietal region and placebos were injected into the scalp vertex. The hair density after 23 weeks increased by 29% ± 5% for a treated area and by less than 1% for the placebo area. They hypothesized that stem cells can improve the formation of new follicles. No major side effects were reported.

Another study conducted by Gentile et al. [27] in 2019 with 21 participants demonstrated that the average hair density among patients from the treatment group with HFSCs

increased by more than 30 ± 5.0% and from the placebo group it increased by less than 1% 12 weeks after the treatment. There was no mention of the occurrence of any side effects.

Furthermore, in 2020 Gentile et al. [31] used autologous micrograft injections with HFSCs 3 times 45 days apart on a group of 27 participants and reported an improvement in the mean hair count after 58 weeks (58 weeks vs. 0 weeks). The mean increase (vs. baseline) was 18.0 hairs in the treated area while the control area displayed a mean decrease of 1.1 hairs. There was no mention of the occurrence of any side effects.

Tsuboi et al. [24] studied the effectiveness of autologous cell therapy with dermal sheath cup cells (DSCs) to treat MPHL and FPHL. Subjects received injections with three concentrations of DSC cell suspensions (7.5 × 106, 1.5 × 106 and 3.0 × 105,134 cells) and a placebo (each in a volume of 1 mL) into 4 randomly allocated injection sites. The effectiveness was assessed by imaging of the phototrichogram before injection and 3, 6, 9, and 12 months later, and the hair density and hair diameter were measured using an image analysis system. The total hair density and cumulative hair diameter increased significantly for 6 months and 9 months at the DSC cell injection site with a low dose compared to placebo. In 14 cases, mild adverse reactions such as erythema, purpura, and small hemorrhages were observed at the injection sites.

### *3.2. Studies Analyzing the Efficacy of Stem Cell Treatment Alone*

Of the 15 studies, 4 analyzed the use of stem cells treatment alone. Two of them assessed HFSCs and two of them ADSCs.

The study carried out by Zari et al. [34] in a group of 140 consecutive adults with confirmed AGA sought to examine the efficacy of autologous cellular micrografts which contain HFSCs. Efficacy was evaluated 1–6 months after treatment by analyzing the change of trichometry parameters, which showed that depending on the scalp region there was an increase in the mean hair density by 4.5–7.12 hair/cm$^2$. No side effects were reported.

Ruiz et al. [35] performed a study in a group of 100 participants with HFSCs from autologous micrografts obtained through Rigenera® micrografting technology. The outcomes were confirmed by the TrichoScan® and showed that the mean increase in the total hair density was already 30% ± 3.0% after 2 months of treatment compared with baseline values for the treated area. In addition, scalp dermoscopic analysis also showed an improvement in hair density after both 4 and 6 months following treatment. No side effects have been reported.

Kim et al. [29] reported nine patients who were suffering from AGA with single transplantation of autologous SVF in the upper scalp. Hair density of the ADSCs-treated side was significantly increased after 3 and 6 months of transplantation compared to the non-treated side ($p$ = 0.01 and $p$ = 0.009 per each). There was no mention of the occurrence of any side effects.

El-Khwalawany et al. [26] analyzed the efficacy of the non-enzymatic vascular fraction (SVF) in 30 patients with AGA. Patients received one SVF injection and a single 6-month follow-up session. The number of hairs increased from 130.87 ± 14/cm$^2$ to 151.93 ± 22.36/cm$^2$. Patients were asked about experienced pain during and after the procedure and 21 reported mild pain and 9 reported moderate pain. No one reported severe pain. Other than that, no other side effects were reported.

David Perez Meza et al. [19], in their retrospective observational case-series study, analyzed the results of using SVF-enhanced adipose tissue among 6 men and women aged 18–55 years with MPHL and FPHL. In this pilot case series, a mean increase of 31 hairs/cm$^2$ of the scalp (represents a 23% relative percentage increase) was documented in patients undergoing treatment of fat plus. One side effect was described, and it was a hematoma in the hairline area after fat injection. The patient did not require medical intervention.

A retrospective, observational study of outcomes in 27 patients with FPHL treated with ADSC-CM was also performed by Shin et al. [28] The application of ADSC-CM with a micro-needle roller once per week showed efficacy in treating FPHL after 12 weeks of therapy. The hair density increased from 105.4 to 122.7 hairs/cm$^2$ ($p < 0.001$). The hair

thickness increased from 57.5 lm to 64.0 lm ($p < 0.001$). No serious side effects were observed in any patient.

### 3.3. Studies Comparing Stem Cells and/or Other Treatments

Of the 15 studies, 3 compared the use of stem cells to another treatment.

Elmaadavi et al. [36] studied the safety and efficacy of autologous bone marrow-derived mononuclear cells (BMMCs) including stem cells and follicular stem cells (FSCs) in 40 patients with alopecia areata (AA) and AGA. From 20 patients with AGA, 10 received BMMCs and 10 received HFSCs injections intradermally. The evaluation by immunostaining and digital dermatoscopy showed an increase in hair thickness as well as hair density after six months of single injection therapy in all groups of patients with no significant difference between both methods in either type of alopecia ($p = 0.426$). The average improvement percentage in AGA patients was $52 \pm 28$ in subjects receiving autologous BMMC and $42 \pm 27$ in subjects receiving autologous FSC, with no statistically significant difference. Elmaadavi et al. reported fatigue and chills in several patients after the administration of a granulocyte colony-stimulating factor. Moreover, 80 percent of the subjects developed bone pain and hematomas.

Narita et al. [37] evaluated the effectiveness of ADSC-CM in 21 male and 19 female patients. The ADSC-CM treatment was evaluated in subpopulations depending on whether or not finasteride was administered. Patients received ADSC-CM intradermal injections each month for 6 months, followed by follow-up assessments before and after 2 and 6 months. In this study, the density of hair in all the groups increased considerably. The density of hair increased from T0 (time of the intervention) to T (status after 6 months after treatment) ($p < 0.001$). However, specific results were reported only for 2 patients. There was no mention of the occurrence of any side effects.

In a study published in 2015, Fukuoka and Suga [30] compared the effectiveness of ADSC-CM in male patients with AGA who took finasteride and those who did not, and among female patients without finasteride. Patients received 6 sessions of ADSC-CM injections every 3–5 weeks. The number of hairs based on a trichogram increased significantly after treatment in both male (n = 11) and female (n = 11) patients. The mean increase in the number of hairs was $29 \pm 4.1$ in male patients and $15.6 \pm 4.2$ in female patients. No significant difference was observed between men and women. In male patients, groups with (n = 6) and without (n = 5) finasteride administration were compared. Fukouka and Suga reported that the most common complication during the procedure was pain during and after injections with ADSC-CM.

## 4. Discussion

This is the first systematic review on the use of different types of stem cells in the treatment of female and male AGA. In total, 15 studies, in which 653 patients were involved, provided a comprehensive view of the effects of autologous stem cells in the treatment of AGA. This review shows the impact of stem cells from different origins on the density of hair. The main conclusion of the analyses of the studies we selected is that stem cell treatments have positive effects on the density of hair regardless of its origin.

We analyzed databases of privately and publicly funded clinical trials conducted around the world (clinicaltrials.gov, accessed on 15 March 2023) and are awaiting the results of many of them.

Stem cells used in the treatment of androgenetic alopecia are mainly derived from two sources: hair follicles and adipose tissue. Hence, almost all studies relate specifically to these cells. Only Elmaadavi et al. [36] studied the efficacy of BMSCs in a group of 10 people with AGA, while the available research on stem cells from Wharton's jelly refers only to alopecia areata. We made the decision to compare hair density even though the more defining feature of AGA is hair thickness because only a few studies measured this parameter, while everyone studied hair density. In androgenetic alopecia, the diameter variation of more than 20% of hair in the androgen-dependent region is considered to be a

major diagnostic standard of androgenetic alopecia [38]. Of note, 2 studies included over 100 patients and reported increased mean hair density. Zari et al. involved 140 participants in their study and in 66, 4% reported a significant improvement in hair density in the frontal region of the head.

In the papers we reviewed, the main side effects were reported by Elmaadavi et al., who declared that some patients after granulocyte-colony stimulating factor reported fatigue and chills. Eighty percent of subjects also suffered from bone pain and hematoma. All symptoms were managed with painkillers and anti-inflammatory drugs. In the same study, for 20% of patients treated with FSC, the only side effect was scalp irritation, which was treated with emollients. For the reasons mentioned above, the effectiveness of different stem cells needs to be compared, as treatment with them is associated with different recovery. Treatment with BMSCs is more absorbent for doctors and patients.

It seems interesting that several researchers have confirmed differences between the effectiveness of stem cells according to gender. Elmaadavi et al. reported a larger improvement in females compared to males after both BMMC and FSC therapies ($p = 0.016$ and 0.008, respectively), but no significant difference was found between both types of therapy. Zari et al. showed, in a trichoscopy examination, that the most notable effect was increased hair density in men, whereas in women it was improved hair thickness and reduced yellow dots. On the other hand, Tsuboi et al. [24] reported that men and women achieved similar results in their study. They concluded that since cell therapy has similar results in both sexes, it will be an excellent treatment alternative for women, who have more limited treatment options compared to men.

An interesting result presented by Tsuboi et al. [24] is that treatment with HFSCs was more effective in patients older than 51 years and in those with moderate disease severity (Hamilton grade III, IV and Shiseido grade 3, 4). It was suggested that this may be due to the fact that older patients may have a higher number of inactive resting hair follicles (telogen hair), so the injection of DSC cells showed a more notable improvement in the induction of hair growth.

The involvement of inflammatory cells (neutrophils and macrophages) in inducing hair follicle anagen and the relationship between hair follicle stem cell activation and inflammation remain further topics of discussion. [39] It is possible that the stem cell products being tested cause subtle inflammation that could contribute to transient hair growth.

We identified several limitations in the current research. Owing to the heterogeneity of the studies in terms of the demographic characteristics, treatment methods, and final evaluations of the subject, performing a meta-analysis was not feasible. The results we present should be interpreted with an awareness of their limitations.

Important limitations of the evidence are that the studies present different treatment protocols, with different types of stem cells and different amounts of sessions, duration of follow-up, etc. The researchers used different devices to evaluate the effects at different intervals. The criteria for the exclusion and inclusion of patients in the studies were also varied. It is also worth noting that patients at various stages of the disease, including those at very advanced stages, were enrolled in the studies. Moreover, it is widely known that many factors affect the quality of the stem cells administered, and not all studies reported information on how they were collected and prepared. Notably, only 9 of the 15 papers presented had a control group, and only 3 of those 9 studies compared the use of stem cells with another treatment. Six studies compared stem cells with a placebo. All controls should include products from other cellular sources, such as primary fibroblasts/keratinocytes, to confirm the necessity of stem cell use and exclude the contribution of buffers, media, and other components to treatment efficacy. This is an important limitation of those papers. Since many commonly used treatments for hair loss have no proven statistically significant effect, it is important to compare new therapies with other available effective treatments. In the case of the scientific papers described above, four of them evaluate the effect of stem cells only, which calls into question the usefulness of these studies.

## 5. Conclusions

According to the results of this review, the use of stem cell injections in female and male AGA appears to be a promising treatment option. Future research should focus on improving clinical research design, conducting more studies with stem cells in women, and establishing best practices in injection sites, cell types, sessions, and frequency. It is important to create a standardized method for collecting, preparing, and injecting stem cells. While there are numerous reports on ADSCs and HFSCs for the treatment of AGA, further studies with BMSCs and the initiation of studies with stem cells from Wharton's Jelly are necessary to begin considering them as a therapeutic option. It would be helpful to conduct a study comparing the effectiveness of different types of stem cells for the treatment of AGA, as the ease of obtaining them varies widely. We highlight the need for studies investigating this because currently available therapies for AGA are unsatisfactory, and there is a demand for new treatment strategies.

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## 5. ARTYKUŁ DRUGI

# SHORT-TERM CLINICAL ASSESSMENT OF TREATING FEMALE ANDROGENETIC ALOPECIA WITH AUTOLOGOUS STEM CELLS DERIVED FROM HUMAN HAIR FOLLICLES

biomedicines

MDPI

*Article*

# Short-Term Clinical Assessment of Treating Female Androgenetic Alopecia with Autologous Stem Cells Derived from Human Hair Follicles

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**Abstract:** Background: Androgenetic alopecia (AGA) is the most common form of alopecia, but treatment options are limited. This study evaluated clinical improvement in hair condition in women with AGA six months after a single injection of autologous cell micrografts (ACMs) containing hair follicle stem cells and dermal papilla cells. Methods: Twenty-three women with clinically and dermoscopy-confirmed AGA were included. Five 2.5 mm punch biopsies were taken from the skin of each patient with the Regenera device. The cell suspension was prepared with the Rigeneracons device and then injected into the hormone-dependent hairy zone of the scalp. Results: A significant improvement was observed on the visual analog scale (VAS) when comparing pre- and post-procedure photos ($p < 0.001$). The change in VAS scores was moderately negatively correlated with baseline ferritin concentration and positively with iron concentration. Improved outcomes were associated with higher baseline levels of sex hormone-binding globulin and 17α-hydroxyprogesterone. Neither testosterone nor DHT showed a significant correlation with VAS scores. Conclusions: The ACM procedure was shown to be both safe and effective, yielding satisfying results six months after a single treatment session. Future investigations should aim to gather evidence that enables the development of a cost-effective approach while minimizing treatment burden and costs.

**Keywords:** androgenetic alopecia; stem cell therapy; hair follicle stem cells; autologous cell micrografts; regenerative medicine



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## 1. Introduction

Androgenetic alopecia (AGA) stands as the most common form of alopecia globally [1]. Both male and female types of hair loss are characterized by a gradual conversion of terminal hair into miniaturized hair. AGA affects at least 80% of men and 50% of women by the age of 70, with a higher incidence among Caucasians [2]. The inheritance patterns of AGA are polygenic, involving complex inheritance from either or both sides of the family [3]. In individuals genetically predisposed, androgens play a causal role in AGA. In individuals with AGA, there is an increase in 5-reductase activity and elevated dihydrotestosterone (DHT) levels in hair follicles for both women and men. Testosterone undergoes conversion by 5-alpha-reductase to DHT, which is considered the underlying cause of hair follicle miniaturization [4–7].

During hair follicle morphogenesis and regular hair growth, hair follicle stem cells (HFSC) and dermal papilla cells (DPCs) play a leading role [8]. In AGA, the differentiation of HFSCs is hampered by factors secreted by dermal cells [9]. It is assumed that HFSCs are located in the bulge region of the outer root sheath of the hair follicle [10]. DPCs, originating from the hair follicle, form a superficial papilla located at the base of the hair follicle, surrounded by a large number of androgenic receptors [11]. HFSCs and DPCs ensure conducive conditions for hair regeneration. In scarring alopecia, occurring, for example, in planus lichen and lupus erythematous, provocative cell invasions around the

bulge lead to irreversible loss of HFSCs. Despite damage to the progenitor cells, HFSCs remain preserved in AGA, making this type of hair loss reversible [12].

Society continually seeks effective interventions to reduce the incidence and economic burden of mental and physical illnesses associated with alopecia. Consequently, therapies and treatment products for alopecia have been widely studied for decades [13]. Currently, only two drugs for AGA, topical minoxidil and oral finasteride, have received approval from the US Food and Drug Administration (FDA). Finasteride competitively inhibits types II and III 5-alpha-reductase isoenzymes, preventing the conversion of testosterone to dihydrotestosterone. While it slows hair loss in the treatment of AGA, it does not halt the process completely. Given potential adverse effects such as decreased libido, erectile dysfunction, reduced ejaculatory volume, and gynecomastia, alternative methods are often favored by men experiencing AGA [14]. The formulation of topical minoxidil to treat AGA was developed in 1987. It is used both for men and women to stimulate hair growth; however, the mechanism of action remains poorly understood. Clinically, minoxidil shortens telogen and stimulates hair follicles to enter anagen, the duration of which it also extends. The effect of this substance is to increase hair thickness and length. The sulfotransferase enzyme in the human scalp transforms minoxidil into its active form, minoxidil sulfate, but variations in sulfotransferase activity between individuals impact the efficacy of minoxidil [15]. In addition to approved therapies, many non-FDA-approved treatments have demonstrated effectiveness in treating AGA [16]. Regenerative medical therapies, such as stem cells and platelet-rich plasma therapies, are currently reported as promising interventions for alopecia [17,18]. The molecular mechanisms that underlie the effects of these regenerative therapies remain elusive. Stem cells possess essential properties, including self-renewal, migration, anti-inflammatory, and immune modulation properties, which are crucial for tissue and organ repair. Initially, it was believed that the therapeutic effects of SCs were based on their ability to migrate to damaged tissue and then differentiate to replace damaged tissue or organs. However, Gnecchi et al. found that the therapeutic effects of stem cells on diseased tissues were, at least partially, caused by the release of trophic factors (paracrine) [19,20]. In our recent systematic review, we analyzed the use of different stem cells for the treatment of AGA, encompassing 15 studies with 653 female and male patients. This study illustrates the effects of different stem cells on hair density. The main conclusion drawn from the analysis was that stem cell therapy has a positive effect on hair density regardless of the hair origin [21].

Autologous cell micrograft (ACM) is a method used to extract autologous mature stem cells from the patient's scalp biopsy through preparatory systems for mechanical disintegration and solid tissue filtering. Gentile et al. [22] examined 27 samples of the micrografts to identify HFSCs. Their calculations showed that each micrograft contained about 4000 cells, of which DPCs constituted about 4.6%, while HFSCs comprised 2.4%. The proposed mechanism of action of ACMs in AGA is to enhance the regeneration of hair cells by transplanting mature multipotent stem cells and to restore hair growth signals by injecting growth factors. However, the exact mechanism has not yet been established [23]. In this article, we describe the short-term clinical efficacy of a single application of ACM, obtained with the Regenera Activa® device to treat female AGA. The aim of this work was to evaluate clinical improvement in hair condition, specifically hair pigmentation and density, obtained through a single injection of ACMs containing HFSCs and DPCs.

## 2. Materials and Methods

### *2.1. Study Overview*

The primary objective of the study was to compare clinical effects observed in images taken before and six months after a single session of ACM. Regenera Activa® (Human Brain Wave SRL, Turin, Italy) is a technology that uses the Regenera Activa® device, which is a preparative system for mechanical disintegration and filtering of solid tissues to extract stem cells [24]. The procedure is conducted using the Rigenera HBW method (Regenera® Protocol, Rigenera® Activa, Human Brain Wave SRL, Turin, Italy), developed in Italy in

2013 and available in over 50 countries. In this method, ACM is prepared in a 3-step protocol. Initially, the treatment involves mechanically disintegrating a tissue sample obtained through a skin punch. Subsequently, the sample is filtered (50 microns) and administered intradermally to the affected area following technical specifications. This technique has been found to be beneficial in dermatology, esthetic medicine, wound care, orthopedics, and rehabilitation, as well as oral surgery and dentistry for regenerating various tissues. The protocol involves using several devices: Regenera Activa® to collect punch biopsies, Rigeneracons (Human Brain Wave SRL, Turin, Italy) to produce a cell suspension used as an ACM, and a standard syringe to inject an ACM into target areas. All devices are CE-certified as Class I medical devices [25]. The protocol for regenerating tissues is described in various publications [26–29].

Four dermatology specialists used the visual analog scale (VAS) [30] for the assessment and presentation of treatment effects. The diagnosis of AGA was established through a comprehensive evaluation, including detailed treatment history, clinical tests, blood tests, and trichoscopy. The severity of AGA was assessed based on the Ludwig scale [31].

### 2.2. Patients

The study included 23 patients who were clinically and dermoscopy-confirmed to have been diagnosed with AGA in grades 1–3 according to the Ludwig scale. The main dermatoscopic features of AGA were hair shaft thickness heterogeneity, yellow dots, and perifollicular hyperpigmentation [32]. Primary exclusion criteria included immunosuppression, cancer, severe chronic diseases, pregnancy, breastfeeding, age under 18 years, hormonal contraception, hyperprolactinemia, hypothyroidism, positive ANA3 antibodies, active inflammation of the scalp, coagulation disorders, lignocaine allergy, and unstable emotional state. Patients with positive ANA3 were also excluded. ANA is an antibody class that binds to cell components of a cell nucleus. These proteins are usually divided into two groups: antibodies against DNA and histones and antibodies against nuclear material. Of the entire population, 20–30% have ANA antibodies. The presence of ANAs and their subtypes increases the likelihood of systemic autoimmune diseases but does not necessarily confirm the onset of autoimmune diseases [33–35]. Patients who had received oral treatments (finasteride, dutasteride, minoxidil, antiandrogens) and topical treatments (minoxidil, prostaglandin analogs, corticosteroids) for AGA in the past six months were excluded. Additionally, patients who used medical devices such as low-level laser therapy or underwent procedures such as platelet-rich plasma or micro-needling were not included in the study. Prior to the enrollment, all patients gave written, informed consent for participation in the study. This study was conducted in compliance with the Declaration of Helsinki of the World Medical Association. The study protocol was approved by the local ethics committee (approval no. 1074/2021).

Biochemical parameters were analyzed as follows: electrochemiluminescence assays for thyroid-stimulating hormone (TSH), anti-thyroid peroxidase antibodies (anty-TPO), antithyroglobulin antibodies (anti-TG), testosterone, sex hormone-binding globulin (SHGB), prolactin, and cortisol; and colorimetric assays for iron were analyzed with cobas® e 411 (Roche Diagnostics GmbH, Mannheim, Germany). Chemiluminescence assays for androstenedione, vitamin D3, folic acid, ferritin, and vitamin B12 were performed on LIAISON® XL (DiaSorin, Saluggia, Italy). Diagnostic laboratory kits from EUROIMMUN, Wroclaw, Poland) kits were used for enzyme-linked immunosorbent assays for dehydroepiandrosterone sulfate (DHEA-S), dihydrotestosterone (DHT), 17α-hydroxyprogesterone, adrenocorticotropin (ACTH), and for immunoblotting of antinuclear antibodies (ANA), which were analyzed on EUROBlot One (EUROIMMUN, Wroclaw, Poland). Hematology was performed on Sysmex XN-1000 (Sysmex, Norderstedt, Germany). For every test, the kits and reagents were purchased from the instrument manufacturer and operated according to the instructions provided.

### 2.3. ACM Procedure

Under local anesthesia, five punch biopsies with a diameter of 2.5 mm each were taken from the skin behind the patient's ear. The collected micrografts and the necessary equipment are shown in Figure 1. Subsequently, the collected samples were placed in the Rigeneracons and covered with 2 mL of sterile physiological solution. The cell suspension was then generated by rotating Rigeneracons at 80 RPM for 2 min. Following this, the obtained suspension was diluted with an additional 2 mL of sterile physiological solution. The resulting solution was injected subdermally into the scalp hair area using a 1 mL syringe and a 30 mm needle. Each injection point received 0.1 mL of the solution, spaced at about 1 cm between needle punctures. Importantly, only the hormone-dependent hairy zone of the scalp was subjected to the therapy.

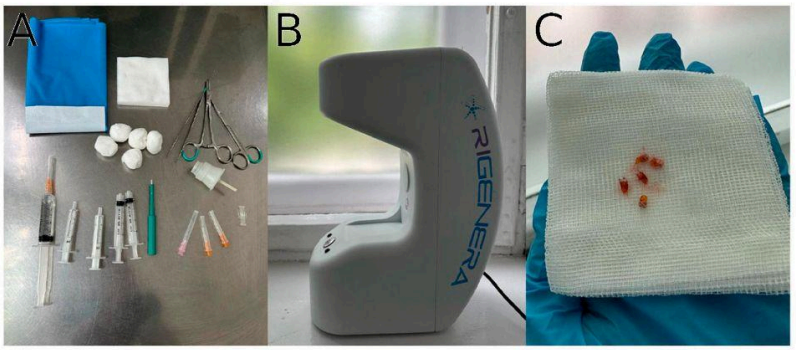


**Figure 1.** Autologous cell micrograft treatment protocol elements. Necessary tool kit (**A**); Rigenera® class I medical device (**B**); five micrograft biopsies from the skin behind the ear (**C**).

### 2.4. Clinical Evaluation of Hair Growth

To evaluate the effects of the treatment, pictures of the patient's scalps were taken before and six months after the treatment session. The pre- and post-treatment images were taken in the same room, under similar lighting conditions, and with patients in the same head position. Four dermatology specialists independently evaluated the pre- and post-treatment images using the VAS scale. Additionally, following the treatment, the principal researcher recorded the patients on the Ludwig scale.

### 2.5. Statistical Analysis

The data analyses were performed using SigmaPlot version 14.5 (Systat, Software Inc., San Jose, CA, USA). The distribution of data was verified using the Shapiro–Wilk test. Variables with normal distributions were presented as mean ± standard deviation (SD) and those without normal distribution were presented as medians with interquartile range (IQR). To investigate differences before and after treatment, paired *t*-tests or Wilcoxon signed-rank tests were utilized according to the distribution of the variables. Associations between baseline clinical characteristics and clinical outcomes were further evaluated by calculating Spearman correlation coefficients.

## 3. Results

### 3.1. Baseline Characteristics of Study Patients

A total of 23 patients were female, with a mean (SD) age of 40.1 (12) years. The distribution according to Ludwig classification showed type I at 60.9%, type II at 30.4%, and type III at 8.8%. At the beginning of the study, we conducted laboratory tests in patients diagnosed with AGA. The baseline characteristics of study patients are presented in Table 1. Test results of eligible patients showed that ferritin and iron levels were closer to the lower

limit of normal. Thyroid-stimulating hormone (TSH) levels were consistent with endocrine gynecological standards in all patients. Analysis of sex hormones showed that the patients did not have abnormally elevated levels of DHT, dehydroepiandrosterone sulfate (DHEA-S), androstenedione, and testosterone, while the sex hormone-binding globulin (SHGB) concentration was at the upper limit of normal.

**Table 1.** Baseline characteristics of study patients.

| Variable | Format | Value | Min–Max Value |
|---|---|---|---|
| Age | Mean (SD) | 40.1 (12) | 25.0–68.0 |
| Vitamin D3 (ng/mL) | Mean (SD) | 38.4 (19) | 8.00–81.0 |
| Vitamin B12 (pg/mL) | Median (IQR) | 260 (181) | 123–763 |
| Ferritin (µg/L) | Median (IQR) | 43.0 (47) | 8.00–261 |
| Iron (µg/dL) | Median (IQR) | 20.4 (39) | 7.00–113 |
| Folic acid (ng/mL) | Median (IQR) | 5.40 (4.5) | 3.00–68.0 |
| TSH (µIU/mL) | Median (IQR) | 1.41 (1.0) | 0.00–3.00 |
| Anti-TPO (IU/mL) | No. over/under norm † | 1/22 | N/A |
| Anti-TG (IU/mL) | No. over/under norm ‡ | 1/22 | N/A |
| SHBG (nmol/L) | Median (IQR) | 85.4 (112) | 22.0–322 |
| ACTH (pg/mL) | Median (IQR) | 9.64 (6.9) | 1.00–35.0 |
| Cortisol (µg/L) | Median (IQR) | 11.4 (10) | 3.00–35.0 |
| DHEA-S (µg/dL) | Mean (SD) | 131 (91) | 1.00–346 |
| Prolactin (ng/mL) | Median (IQR) | 5.84 (8.5) | 2.00–26.0 |
| Androstenedione (ng/mL) | Mean (SD) | 1.43 (1) | 0.00–4.00 |
| Testosterone (ng/mL) | Median (IQR) | 0.30 (3.36) | 0.00–56.0 |
| Hb (g/dL) | Mean (SD) | 13.3 (0.9) | 11.0–14.0 |
| 17α-hydroxyprogesterone (ng/mL) | Median (IQR) | 0.59 (0.4) | 0.00–2.00 |
| DHT (pg/mL) | Median (IQR) | 134 (118) | 22.0–409 |
| ANA | No. positive/negative | 7/16 | N/A |
| Ludwig scale score | 1/2/3 | 7/14/2 | N/A |

† norm is up to 35 IU/mL; ‡ norm is up to 40 IU/mL. ACTH, adrenocorticotropin; ANA; anti-nuclear antibodies, Anti-TG, antithyroglobulin antibodies; Anti-TPO, anti-thyroid peroxidase antibodies; DHEA-S, dehydroepiandrosterone sulfate; DHT, dihydrotestosterone; Hb, hemoglobin; N/A, not applicable; SHGB, sex hormone-binding globulin; TSH, thyroid-stimulating hormone.

### *3.2. Evaluation of ACM Treatment Effectiveness*

Patients' scalp photos (Figure 2) before and six months after therapy with HFSCs were evaluated by four independent specialists. This assessment showed significant improvement based on the VAS scale (Table 2), with an average increase of 1.5 points. After ACM, there was an average improvement of 1 degree on the Ludwig scale. Both Ludwig scale scores and mean VAS scores showed significant differences after treatment as depicted in Figure 3.

**Table 2.** VAS scoring results.

| Variable | Format | After | *p* Value † | Value |
|---|---|---|---|---|
| Specialist 1 | 5 (2) | 7 (2) | <0.001 | 40.1 (12) |
| Specialist 2 | 6 (2.5) | 8 (2.5) | <0.001 | 38.4 (19) |
| Specialist 3 | 5 (2.5) | 7 (2) | <0.001 | 260 (181) |
| Specialist 4 | 5 (2) | 7 (2) | <0.001 | 43.0 (47) |

† paired *t*-test; values are medians (IQR).

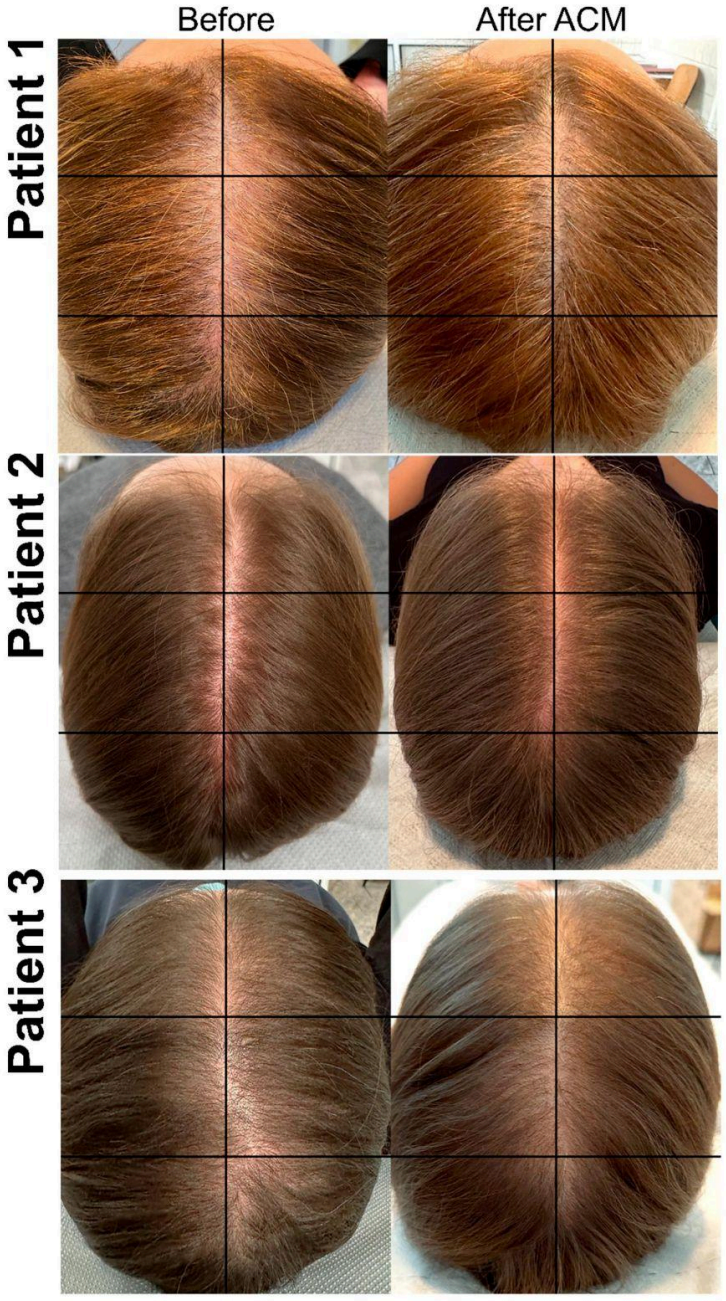


**Figure 2.** Photographs of sample patients with AGA pre- and post-ACM treatment. **Patient 1.** A 47-year-old female with AGA classified as having stage-2 vertex balding according to the Ludwig scale. Photo before therapy with widening of the central parting. Photo six months after ACM showing

improvement in the quantity as well as quality of hair in the central part of scalp. **Patient 2.** A 26-year-old female with AGA classified as having stage-1 vertex balding according to the Ludwig scale. Photo before therapy with noticeable thinning of hair on the top of the head with the normal frontal hairline maintained. Photo after six months after ACM shows an improvement in hair density over the top of the scalp. **Patient 3.** A 39-year-old female with AGA classified as having stage-2 in the Ludwig scale. Photo before therapy with widening of the central parting. Photo six months after ACM showing improvement in the quantity as well as quality of hair in the central part of the scalp.

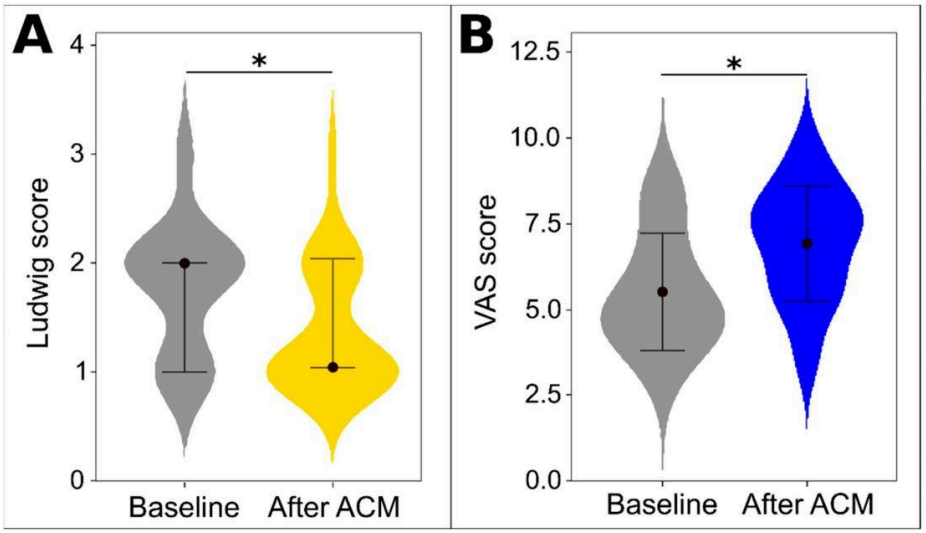


**Figure 3.** Clinical evaluation of treatment with ACM. Mean Ludwig score (**A**) and mean VAS score from all four specialists (**B**). In plot (**A**), the bars are 1st and 3rd quartile, the dot represents median, and the asterisk (*) indicates a *p*-value of <0.05 from the Wilcoxon signed-rank test. In plot (**B**), the dot represents mean, bars represent standard deviation, and the asterisk (*) indicates a *p*-value of <0.05 from the paired *t*-test.

### *3.3. Associations between Outcomes and Baseline Characteristics*

The association between the initial blood parameters and clinical outcomes was evaluated based on a calculation of the Spearman correlation coefficients (Figure 4). Upon assessment by half of the specialists, delta VAS scores showed a moderate negative correlation with baseline ferritin concentration and a positive correlation with iron concentration; however, this correlation was not significant when considering the mean delta VAS score. Among sex hormones, the mean better outcomes were associated with higher initial levels of SHGB and 17α-hydroxyprogesterone. Neither testosterone nor DHT showed a significant correlation with VAS scores.

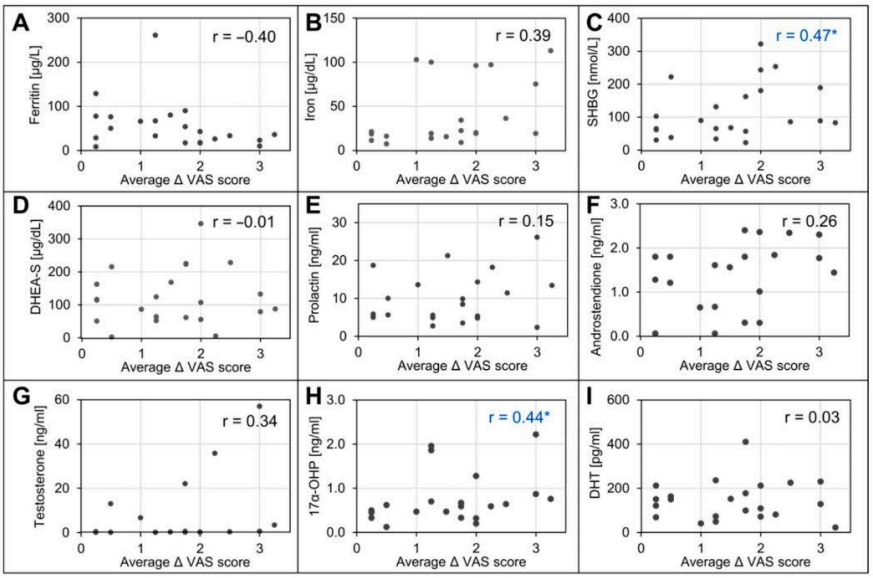


**Figure 4.** Correlations between changes in VAS score after treatment and baseline clinical characteristics of patients (**A–I**). In blue, * $p < 0.05$ is highlighted. Spearman correlation coefficient r for average delta VAS scores (average VAS score after–average VAS score before treatment) for individual independent specialists and mean delta from all specialists. Abbreviations: 17α-OHP, 17α-hydroxyprogesterone DHEA-S, dehydroepiandrosterone sulfate; DHT, dihydrotestosterone; SHGB, sex hormone-binding globulin; TSH, thyroid-stimulating hormone.

## 4. Discussion

The existing literature on the treatment of female AGA with HFSCs is sparse. In a recent systematic review we conducted, we gathered all available studies pertaining to the use of autologous stem cells of various origins in the treatment of AGA [21]. The use of stem cells in alopecia treatment is a topic of significant interest, yet it remains relatively novel and requires further research. The effectiveness of the ACM treatment with the Regenera® medical device is supported by available evidence, including studies conducted by Gentile et al. [22,36]. In one study, 11 patients showed a 29% ± 5% increase in hair density in the treated area at the 23-week follow-up, compared to less than 1% in the placebo area [36]. In another study, the treated area experienced an average increase of 18.0 hairs compared to baseline after the ACMs were used three times at 45-day intervals [22]. The study by Zari et al., involving 140 patients (113 of whom were female) showed that a single session with Regenera Activa® resulted in an increase in hair density ranging from 4.5 to 7.12 hairs/cm$^2$ after six months [23]. The treatment of AGA with HFCSs obtained from autologous micrografts through Regenera® micrografting technology was further evidenced by Ruiz et al. [37]. The study involved 100 patients (both male and female) with measurements of hair density with TrichoScan® two months after the procedure and scalp dermoscopic analysis after four and six months.

Our study further confirmed the effectiveness of the ACM therapy for female patients with AGA. To evaluate the treatment effectiveness, we relied on the VAS scale scores of pre- and post-therapy photos. This approach considers the real cosmetic effect, which is the most significant change as perceived by the patient. Using patient scalp photos as a method for assessing treatment effects might not appear accurate. However, in our opinion, this approach is the most indicative of clinical condition, and it translates directly into the

well-being and self-esteem of our patients. The value of photography-based assessment as a measure of visibly significant results was also highlighted in a systematic review and meta-analysis of the effectiveness of AGA treatments [38].

Our secondary aim was to explore the association between the serological characteristics of patients and treatment outcomes. We observed that a higher initial SHGB concentration correlated with a more significant improvement in AGA, as assessed by dermatology specialists. SHGB is a circulating glycoprotein important for transporting sex hormones and regulating their bioavailability [39]. In humans, the role of SHGB is to protect against excess endogenous and exogenic steroids by combining with them [40]. Among female patients, Chen et al. found that low-serum SHGB correlated negatively with AGA severity [41]. Taken together with our observation, this seems to confirm SHGB's crucial involvement in the presentation of AGA in women.

We did not find any significant deviation in DHT concentrations in our study group, suggesting that AGA may not be dependent on DHT levels. Conflicting evidence exists regarding DHT levels in AGA patients, while Urysiak-Czubatka et al. [42] found no statistically significant difference in DHT levels in patients with AGA compared to healthy controls in a mixed-gender study, suggesting that genetically determined, individualized sensitivity to androgens plays a crucial role in AGA presentation. Zhang et al. reported an increased concentration of DHT in males and a correlation between DHT levels and the curative effect of finasteride [43]. After ACM treatment, we found no association between baseline DHT concentrations and treatment outcomes. This suggests potential sex-based differences that could underlie the degree of therapy effectiveness.

Our study exclusively included women, which did not allow us to stratify the analysis by gender. There are differences between male and female patterns of AGA. The condition is more prevalent in men than in women as it affects about 80% of men and about 50% of women. It typically manifests at an earlier age in men, often beginning in the late teens to early twenties and progressing gradually. Female AGA may onset later, usually after menopause, and its progression can be more variable. In men, the frontal hairline often significantly recedes, forming an "M" shape, while women typically maintain their frontal hairline, and the thinning is more evenly distributed [44,45]. Some hormonal factors can contribute to the picture and pathogenesis of male and female patterns of AGA. In men, AGA is primarily associated with dihydrotestosterone, a byproduct of testosterone, while in women, hormonal fluctuations, including changes in androgens, may contribute to AGA. Nevertheless, the study by Urysiak-Czubatka et al. [42] on the differences in dihydrotestosterone concentration between men and women with AGA yielded inconclusive results, emphasizing the genetically determined sensitivity of the follicles to dihydrotestosterone. This variable sensitivity may be responsible for the diverse reactions to androgens.

Treatment options vary between men and women. Specifically, oral testosterone and its derivatives are not recommended for women, especially those of reproductive age, who may be pregnant or planning to conceive [14,45]. Stem cell therapy and ACM are novel techniques. While some studies have shown promising results, offering substantial benefits to patients, the long-term efficacy is still awaiting confirmation. The study conducted by Zari et al. [23] employed ACMs to treat AGA in both men and women, with a total of 113 female and 27 male participants. Statistically significant improvements were observed in women, particularly in terms of hair density and hair shaft thickness. Specifically, women experienced significant enhancement in hair density in the temporal and occipital scalp regions, while men noted significant improvement in the frontal scalp region. These findings align with the natural course of the disease, demonstrating improvement in the areas most affected in both men and women [44,45]. Considering the pattern of hair loss, Álvarez et al. [29] administered ACM injections in various areas of the scalp in men and women. Their study included 17 participants, of whom eight were women aged between 21 and 58 years. Since this was a descriptive study, the authors concluded that all participants were satisfied with the treatment, noting improvements primarily in thickness and hair loss.

Moreover, ACM was well-tolerated with no reported side effects. On the contrary, Gentile et al. [36] exclusively studied a male population. They observed a notable increase in hair density by 29% ± 5% in the treated areas compared to less than 1% in the untreated areas. These findings could suggest that there may be no difference in effectiveness between male and female patterns of AGA.

Over-secretion of adrenal androgens can result from enzyme deficiencies in the biosynthesis of cortisol. Approximately 2% of hyperandrogenic patients present with late adrenal hyperplasia (LOAH) characterized by a lack of 21-hydroxylase [46]. All patients included in our study had levels of 17α-hydroxyprogesterone within the normal range, ruling out hyperandrogenism as the cause of AGA. We noted a positive correlation between 17α-hydroxyprogesterone concentrations and clinical outcomes as assessed by specialists; however, further studies are needed to elucidate the causes of this association.

SC therapies present a novel and promising approach to treating hair loss. Current treatments of AGA often fail to meet the expectations of patients and medical professionals, so there is a substantial demand for new therapies, particularly for individuals with contraindications to standard methods. Our study demonstrated the curative effect of ACM therapy, utilizing the Regenera® procedure.

There were some limitations that should be considered when interpreting the results of our study, one of which was a limited sample size. Furthermore, we did not have access to the technology needed to perform hair evaluation using trichoscopy equipment and hair mapping programs. In the future, we would like to expand our study to include a comparison with one of the FDA-approved treatments. Presently, the FDA endorses the use of two drugs, minoxidil and finasteride, as well as treatment with low-level light/laser therapy devices. The effectiveness of these treatments, compared to placebo, was supported in a recent meta-analysis [38]. Despite the growing interest in alternative therapies, such as the use of growth factors or SCs, there is a scarcity of data on the performance of these strategies relative to the more prevalent forms of treatment. Undoubtedly, the SC-based treatment has some advantages, such as convenience for the patients. The ACM treatment does not face challenges in achieving high compliance, as is the case with oral or topical drugs [47]. Over the course of our study, no adverse effects were reported by the patients. However, there are also some drawbacks. The ACM procedure incurs a significant one-time cost to the patients, and, moreover, the method has not yet been standardized. Nonetheless, the use of the Regenera Activa® device appears to be a promising AGA therapy to explore further, both as a standalone procedure and in conjunction with classical treatments.

## 5. Conclusions

Given the limited treatment options for AGA, there is an increasing demand for alternative therapies that demonstrate acceptable performance levels. This study provides valuable insights into the potential of ACM therapy for AGA and underscores the importance of continued exploration and refinement of the ACM procedure. Our study on the ACM procedure revealed it to be both safe and effective, yielding satisfying results six months after a single treatment session. However, the absence of a standardized procedure highlights the need for further research. Future investigations should aim to gather evidence that enables the development of a cost-effective approach while minimizing treatment burden and costs for patients. Additionally, long-term studies are required to evaluate the sustained effectiveness of the ACM procedure over time.

**Author Contributions:** Conceptualization, K.K.-T., Z.P., A.P., D.N. and J.C.S.; Data curation, K.K.-T., Z.P. and A.P.; Formal analysis, K.K.-T. and Z.P.; Investigation, K.K.-T., Z.P. and A.P.; Methodology, K.K.-T., D.N. and J.C.S.; Resources, K.K.-T., D.N. and J.C.S.; Writing—original draft, K.K.-T., Z.P. and A.P.; Writing—review and editing, K.K.-T., Z.P., D.N. and J.C.S. All authors have read and agreed to the published version of the manuscript.

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**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki, and approved by the Bioethics Committee at Wroclaw Medical University (approval no. 1074/2021).

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

**Data Availability Statement:** The data that support the findings of this study are available on request from the corresponding author.

**Conflicts of Interest:** The authors declare no conflicts of interest.

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## 6. ARTYKUŁ TRZECI

# ENHANCING QUALITY OF LIFE AND SEXUAL FUNCTIONING IN FEMALE ANDROGENETIC ALOPECIA: THERAPEUTIC POTENTIAL OF HAIR FOLLICLE-DERIVED STEM CELLS

healthcare

MDPI

*Article*

# Enhancing Quality of Life and Sexual Functioning in Female Androgenetic Alopecia: Therapeutic Potential of Hair Follicle-Derived Stem Cells

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**Abstract:** Background: The study aimed to examine the impact of stem cell treatment on quality of life (QoL) and sexual functioning in women with androgenetic alopecia (AGA). Methods: Twenty-three women underwent a single session of autologous cellular micrografts (ACMs). The World Health Organization Quality of Life Brief Version (WHOQOL-BREF) and Female Sexual Function Index (FSFI) were used before and after 6 months. Results: The AGA severity decreased by an average of 1 point on the Ludwig scale ($p = 0.004$) after treatment. FSFI scores indicated sexual dysfunction in over half of the women at baseline, but they improved significantly post-treatment for arousal [median (IQR): 4.8 (1.5) vs. 5.10 (0.9); $p = 0.035$] and satisfaction [4.4 (1.4) vs. 4.8 (1.8); $p = 0.025$]. QoL scores improved after treatment in psychological health (57.96 ± 19.0 vs. 69.35 ± 14.0; $p = 0.031$) and environment (72.96 ± 13.4 vs. 81.09 ± 12.6; $p = 0.007$), but not in physical health and social relationships. No associations were found between the WHOQOL-BREF or FSFI domains versus age and AGA severity. Conclusions: AGA reduces QoL and impacts sexual functioning in women with AGA. The high treatment burden arises from the chronic and progressive nature of AGA, coupled with limited treatment effectiveness. Effective treatments for AGA, like ACM, are urgently needed to enhance patient-reported outcomes along with clinical results.

**Keywords:** stem cell therapy; regenerative therapy; androgenetic alopecia; quality of life; female sexual function



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## 1. Introduction

Androgenetic alopecia (AGA) is a condition characterized by gradual and ongoing hair loss with an unpredictable pattern of progression [1]. A female pattern of hair loss can cause various psychological problems that reduce quality of life. The loss of self-confidence and decreases in self-esteem are common reactions to hair loss, especially in women [2]. The World Health Organization (WHO) explains that quality of life is a subjective assessment of the perception of reality through the lens of culture and the value system observed by its targets [3,4]. In European culture, physical appearance is highly valued, which is why AGA is such a significant problem [5].

In several studies, alopecia has been shown to have a psychosocial impact on both men and women, but the effects can be more severe and devastating on women [6]. Concerning the male population, the disease affects social functioning and emotional well-being, with pronounced detrimental effects observed among young men [7]. Camacho et al. [8] deduced that depression in the course of AGA was more common in women than in men and was most often described as a "minor". Moreover, Russo et al. [9] concluded that women with AGA are characterized by greater social anxiety and social phobia compared to men with this disease. AGA is usually considered a benign process, mainly cosmetic, but numerous studies confirm that AGA can be a complication and manifestation of underlying systemic diseases, which further increases the patient's anxiety [10]. Gonul et al. [2] examined and

compared the quality of life in patients with AGA and alopecia areata using the Hairdex, an instrument developed to assess the quality of life in patients with hair loss. The results are very interesting and surprising, because, among people with AGA, hair loss had a more adverse impact on their emotions, functioning, and symptoms, compared to those with alopecia areata. A similar study was conducted by Jun et al. [11], who used the Hair Specific Skindex-29 to examine quality of life in patients with AGA and alopecia areata, identifying risk factors associated with its deterioration. Patients with AGA were more likely to report a symptomatic decline in quality of life ($p = 0.033$), while patients with alopecia areata showed significantly worse functional quality of life than AGA patients ($p = 0.013$).

Hair has been a significant aspect of identity and image for decades, holding sociological and psychological importance for a person's appearance and personality [12,13]. Sexual health encompasses the physical, emotional, and mental well-being associated with sexuality, while impaired sexual health may have a significant impact on quality of life [14]. Sexual functions are closely linked to other aspects of behavior and cannot be considered independent phenomena. Sexuality has attracted considerable attention throughout human civilization and exerts a significant impact on people's quality of life [13,15]. Quality of life and sexual health are multidimensional and share a bidirectional relationship.

AGA is a hair loss disorder mediated by dihydrotestosterone, which induces the miniaturization of hair follicles and transforms the final hair into vellus hair [16]. The pathogenesis of this condition also involves oxidative stress and microinflammation occurring around the hair follicles [17]. In women with AGA, hair loss can manifest clinically in a variety of ways. The two most common patterns are diffuse hair loss in the central front and posterior regions (Ludwig type—severity is evaluated on the Ludwig scale in three steps) or hair loss in the central part of the front scalp (Olson type), also known as front accentuation or "Christmas tree type" patterns [18–20]. Yu et al. [21] showed that the way people with AGA perceive their disease has a significant impact on health outcomes of other diseases. They also found that all patients considered alopecia to be a major concern with a considerable emotional impact. Patients reported relatively poor control over the disorder and its treatment, as well as a limited understanding of its course.

Minoxidil (topical administration) for female and male pattern hair loss and finasteride (oral administration) only for male pattern hair loss are the two drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of AGA [22]. Iamsumang et al. [23] reviewed studies involving oral and topical finasteride used in women. Although there are few studies available, their analysis concluded that finasteride was effective and safe for the treatment of female pattern hair loss. However, larger studies are needed to further validate these findings. The literature reports on the efficacy and safety of numerous other therapies, including platelet-rich plasma, dutasteride (systemic administration) (not approved by the FDA for alopecia), hair transplants, oral minoxidil, and low-level laser therapy [22].

Recently, regenerative medicine therapies have been gaining popularity. The goal of regenerative medicine is to restore the normal function of cells and organs by replacing and regenerating damaged cells or organs. Stem cells, cytokines, growth factors from either stem cells or hematopoietic tissues, and gene therapies are used for this purpose. Stem cells possess unique abilities such as self-renewal and the ability to exhibit anti-inflammatory and immunomodulatory effects. These characteristics make them applicable in the treatment of alopecia [24]. For the treatment of AGA, most reports focus on adipose-derived stem cells and hair follicle stem cells, while only a few studies are available on the use of bone marrow stem cells and Wharton's jelly stem cells [25].

In this study, we aimed to investigate whether the stem cell treatment of AGA affects quality of life and sex life. Additionally, we sought to examine the correlation between sexual functioning and the quality of life among women with AGA after treatment.

## 2. Materials and Methods

### 2.1. Participants

This study was conducted through face-to-face surveys at the Clinic of Dermatology, Venerology and Allergology of Wroclaw Medical University, during which, participants completed questionnaires. Twenty-three female patients aged between 18 and 65 (mean 40 ± 12) years and diagnosed with AGA were included in the study.

Inclusion criteria were determined through clinical examination by dermatologists and assessed using the Ludwig scale. The distribution of the patients according to Ludwig's female pattern hair loss classification showed that patients were classified as follows: Grade I—60.9%; Grade II—30.4%; and Grade III—8.8%. The primary exclusion criteria for this study included immunosuppression, cancer, severe chronic disease, pregnancy, breastfeeding, age under 18 years, hormonal contraception, hyperprolactinemia, hypothyroidism, active inflammation of the scalp, coagulation disorders, lignocaine allergy, and unstable emotional state. Patients with a positive antinuclear antibody (ANA) 3 test were also excluded. Additionally, patients who had received oral (finasteride, dutasteride, minoxidil, antiandrogens) or topical (minoxidil, prostaglandin analogs, corticosteroids) AGA-targeted treatment in the past 6 months were excluded. The study did not include patients who had used medical devices such as low-level laser therapy or undergone procedures such as platelet-rich plasma injections or micro-needling.

The patients received a single session of autologous cellular micrografting (ACM) obtained with the Regenera Activa® device (Human Brain Wave SRL, Turin, Italy). Before and 6 months after the therapy, all participants completed two questionnaires: the World Health Organization Quality of Life Brief Version (WHOQOL-BREF) and the Female Sexual Function Index (FSFI). We used validated Polish versions of the FSFI and WHOQOL-BREF questionnaires. Both the FSFI and WHOQOL-BREF have a 4-week recall period. All participants provided written, informed consent prior to the enrollment and received instructions on how to complete the study questionnaires. The study was approved by the Bioethics Committee of Wroclaw Medical University (KB-1074/2021, approval date: 3 January 2022).

### 2.2. ACM Procedure

Under local anesthesia, five 2.5 mm diameter punch biopsies were collected from the scalp skin behind the patient's ear. The collected samples were placed in medical devices (Class I, Rigneracons CE certified; Human Brain Wave SRL, Turin, Italy) and coated with 2 mL of sterile physiological solution. Then, the cell suspension was produced by turning the Rigeneracons at 80 RPM for 2 min. The suspension was then diluted with an additional 2 mL of sterile physiological solution. The resulting solution was injected into the scalp hair area using a 1 mL syringe and 30 mm needles. A volume of 0.1 mL was injected per point, with about 1 cm intervals between the needles.

### 2.3. Instruments

#### 2.3.1. World Health Organization Quality of Life Brief Version (WHOQOL-BREF)

The WHOQOL-BREF [26,27] is a self-report questionnaire that assesses quality of life in four domains: physical health (7 elements), psychological health (6 elements), social relationships (3 elements), and environment (8 elements). Each item is scored on a 1–5 Likert scale. After collecting filled questionnaires, the domain scores were transformed to a scale of 0 to 100, where higher scores indicate a higher quality of life. The recall period for this questionnaire is 4 weeks.

#### 2.3.2. Female Sexual Function Index (FSFI)

The FSFI is a 19-element measure, composed of six different areas of female sexual function, namely: desire (2 items), arousal (4 items), lubrication (4 items), orgasm (3 items), satisfaction (3 items), and pain (3 items). Total FSFI scores range from 2 (lowest possible score) to 36 (highest score) [28]. This scale is widely used as both a screening and outcome

measurement tool for female sexual function, with a 4-week recall period [29]. The FSFI has a clinical cutoff score of 26.55 points total, as proposed by Wiegel et al. [30]. This score currently serves as the clinical standard for differentiating between patients with and without sexual dysfunction. In individual domains, scores below the median were considered indicative of dysfunction for that particular domain, i.e., for desire $\leq$ 3.6, for arousal $\leq$ 4.8, for lubrication $\leq$ 5.1, for orgasm $\leq$ 4.4, for satisfaction $\leq$ 4.4, and for pain $\leq$ 5.6.

### 2.4. Data Analysis

Variables with normal distributions were presented as mean ± standard deviation (SD), and those without normal distribution were presented as medians with the interquartile range (IQR) in parentheses. Box plots were used to illustrate the distribution of different domains of the WHOQOL-BREF and FSFI among patients. To investigate the differences in patients before and after treatment, paired *t*-tests (for WHOQOL-BREF domains) or Wilcoxon signed rank tests (for FSFI domains) were performed depending on the distribution of the variables, which was checked with the Shapiro–Wilk test. The correlation between WHOQOL-BREF and FSFI was assessed with Spearman's correlation coefficients. The effect size was calculated as described by Cohen [31]. For variables that underwent a paired *t*-test with Cohen's d statistic, $d = (M_1 - M_2)/SD_{pooled}$, where $M_1$ and $M_2$ are the means of the compared groups and $SD_{pooled}$ is a pooled standard deviation of the two groups ($SD_{pooled} = \sqrt{[(SD_1^2 + SD_2^2)/2]}$. For variables that underwent Wilcoxon signed rank tests, effect size was calculated with r, defined as $r = z/\sqrt{n}$, where z is a z-score and n is a sum of the grouped sizes. All calculations were performed using SigmaPlot 14.5 (Systat, Software Inc., San Jose, CA, USA).

## 3. Results

The results included data from all 23 patients with AGA. Table 1 presents the characteristics of the study patients. Following the ACM treatment, the severity of AGA significantly decreased by an average of 1 point on the Ludwig scale ($p = 0.004$). We did not detect any association between the WHOQOL-BREF or FSFI domains and age or AGA severity.

**Table 1.** Age and androgenetic alopecia severity in patients.

| Age | N | Mean (SD) |
|---|---|---|
| <30 years | 9 | 28 (2) |
| >30 years | 14 | 47 (10) |
| **Androgenetic alopecia severity** | **N Before** | **N After** |
| Ludwig score 1 | 7 | 15 |
| Ludwig score 2 | 14 | 7 |
| Ludwig score 3 | 2 | 1 |

Before treatment, 11 patients had scores below 26.55, indicating sexual dysfunction, and this number decreased to 6 patients with sexual dysfunction after 6 months following the ACM session. At baseline, the majority of the patients experienced sexual dysfunction in specific domains, with 65% of patients reporting below the median for desire and arousal, 61% below the median in lubrication and pain, and 57% below the median with regard to orgasm and satisfaction. The FSFI results are summarized in Figure 1. After ACM treatment, patients reported significantly higher arousal with a median of 4.8 (1.5) before and 5.10 (0.9) after treatment ($p = 0.035$, effect size $r = -0.31$, indicating medium effect), as well as satisfaction with a median of 4.4 (1.4) before and 4.8 (1.8) after treatment ($p = 0.025$, effect size $r = -0.324$) as measured by the FSFI. The total FSFI score, as well as the desire, lubrication, orgasm, and pain indexes, did not differ significantly between study points.

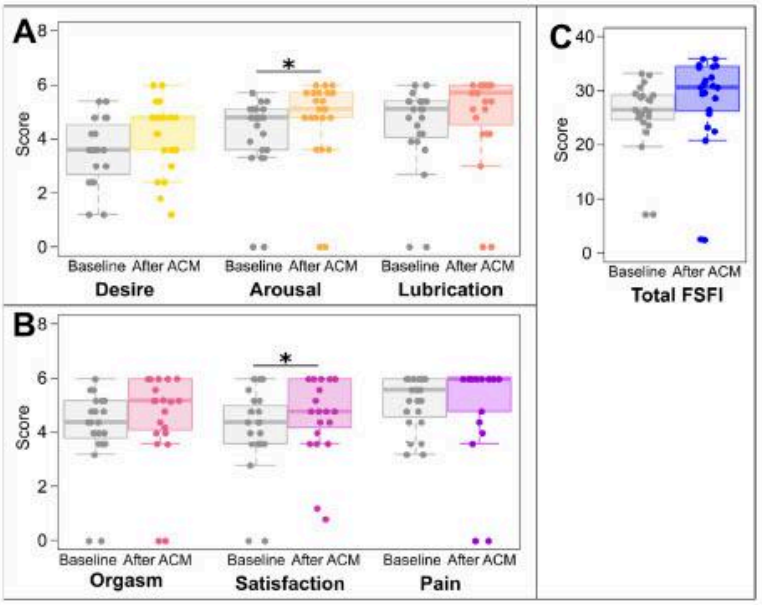


**Figure 1.** Female Sexual Satisfaction Index scores. Domains (**A**,**B**) and total score (**C**). * $p < 0.05$; values from Wilcoxon Signed Rank test; ACM, autologous cellular micrograft procedure.

Among the WHOQOL-BREF domains (summarized in Figure 2), the AGA patients reported the lowest quality of life in the physical health domain. The assessment with WHOQOL-BREF showed that 6 months after the ACM procedure, the patients experienced higher quality of life in psychological health (mean before 57.96 ± 19.0 vs. mean after 69.35 ± 14.0; $p = 0.031$, the effect size measured by Cohen's d was d = 0.68, indicating a medium effect) and environment (mean before 72.96 ± 13.4 vs. mean after 81.09 ± 12.6; $p = 0.007$, Cohen's d was 0.63). There were no significant changes in reported physical health and social relationships.

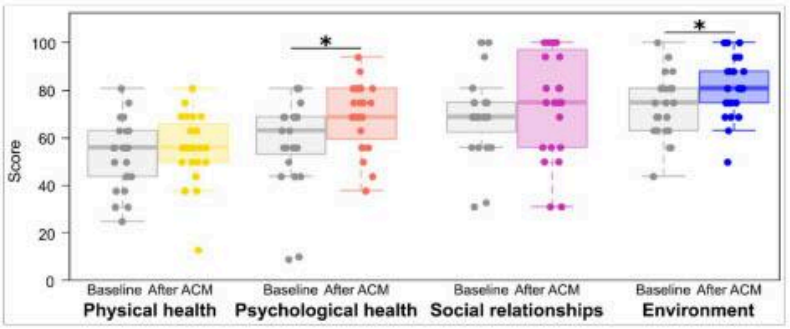


**Figure 2.** WHOQOL-BREF scores. * $p < 0.05$ from two-tailed $t$ test; ACM, autologous cellular micrograft procedure.

The analysis of correlations between WHOQOL-BREF scores and FSFI results revealed that, across all domains, overall quality of life and sexual health were moderately to strongly positively correlated (Table 2). The strongest associations (above 0.7 Spearman's

rho) were found between FSFI arousal and social relationships and FSFI satisfaction and social relationships.

**Table 2.** Correlations between sexual health and quality and life domains.

| | Physical Health | Psychological Health | Social Relationships | Environment |
|---|---|---|---|---|
| Desire | 0.26 | 0.46 * | 0.56 ** | 0.28 |
| Arousal | 0.53 ** | 0.48 ** | 0.71 ** | 0.52 ** |
| Lubrication | 0.34 * | 0.55 ** | 0.69 ** | 0.47 ** |
| Orgasm | 0.48 ** | 0.47 * | 0.63 ** | 0.40 * |
| Satisfaction | 0.54 ** | 0.46 * | 0.76 ** | 0.35 * |
| Pain | 0.33 * | 0.52 ** | 0.59 ** | 0.44 * |

Shown are Spearman's correlation coefficients. * $p < 0.05$, ** $p < 0.001$.

## 4. Discussion

Our analyses indicated that female patients with AGA had a reduced quality of life in the physical health domain, which, however, was not dependent on ACM treatment. The applied therapy significantly improved patients' quality of life in the mental health and environmental domains.

Researchers emphasize that women with AGA experience reduced quality of life, a finding consistent with our study. Moorthy et al. [32] also employed the WHO-BREF scale to assess quality of life, using a similar approach employed in our study. Additionally, they used the Hairdex questionnaire, a hair- and scalp-specific measurement tool designed to assess the specific effects of hair loss on the quality of life of patients. This questionnaire consists of 48 items categorized into five domains: symptoms, functions, emotions, self-confidence, and stigma. Their study included 170 patients with AGA of both sexes. The study found that in women under 30, the physical health and mental health domains were most impaired. Among singles, the symptom and emotion domains were affected, while those with less education exhibited impairment in all domains except physical health. Another study conducted by Reid et al. [33] discovered that patients often view their hair loss as more distressing in terms of quality of life than dermatologists perceive it to be. While physician and patient ratings of clinical severity align, the study found that clinical severity alone does not predict the impact of the disease on a patient's quality of life, hence the importance of employing additional validated tools to assess quality of life and using advanced devices to monitor disease progression. In a recent systematic review, Aukerman and Jafferany [5] investigated the psychosocial consequences of AGA and concluded that female patients experience severe dissatisfaction with their hair, leading to a decline in overall body image. Furthermore, dissatisfaction with one's body image significantly contributes to reduced desire and arousal [34]. In the present study, desire was the most affected area of sexual function at baseline, and it did not improve after therapy. However, we observed significant improvements in the domains of arousal and satisfaction, suggesting that ACM treatment has a positive effect on the sexual health of female AGA patients. These two FSFI domains exhibited the strongest association with the social relationships domain of WHOQOL-BREF. The latter did show some improvement after ACM treatment, although it was not statistically significant. Van der Donk et al. [35], based on their study on a group of 58 women, concluded that women with AGA often feel less attractive. Positive perceptions of one's attractiveness are associated with higher sexual satisfaction, higher sexual frequency, and more sexual partners [36]. Improving AGA through treatment and enhancing patients' appearance can boost their self-esteem, thereby influencing their sex lives. Our analysis of the associations between sexual health scores and quality of life indices also suggests that improvements in physical, and psychological health, as well as social relationships and environmental factors, are all linked with better sexual function. Biondo et al. [37], similarly to Reid et al. [33], hypothesized that women with AGA often rate their condition as more severe than their physicians do. However,

their study, which examined disparities in perceptions of hair loss severity between patients and clinicians, revealed that women seeking treatment for AGA often underestimate the severity of their disease. Therefore, the findings of Biondo et al. suggest that it can be worthwhile to raise awareness among patients about alopecia and initiate effective treatment, as untreated AGA can progress and negatively affect both quality of life and sexual function. Tas et al. [38] used the ASEX scale, a tool designed to assess the sexual functioning of patients with AGA according to the severity of the disease. This scale assesses five domains: drive, arousal, penile erection/vaginal lubrication, ability to reach orgasm, and orgasmic satisfaction. Their analysis showed that the likelihood of patients developing psychosexual disorders increases with disease progression. Consequently, patients with AGA, especially those in advanced stages, should be referred to psychological or sexology counseling. While mental status becomes improved, the pain domain of the FSFI does not change in response to AGA treatment. Dyspareunia, defined as pain during sexual intercourse, has a complex etiology [39]. Leeners et al. [40] showed that dyspareunia often occurs alongside other psychiatric disorders, with depression being the most common. Depression is an illness frequently associated with AGA, implying a possible overlap of these conditions within our study group.

The availability of studies examining the effect of a specific therapeutic method in relation to the quality of life in women with AGA is limited. While most studies have focused on quality of life in the AGA population, it seems interesting to explore the impact of specific treatments on both quality of life and sexual functioning. Due to limited FDA-approved treatments, experimental and off-label treatments are commonly explored for this condition.

Pharmacotherapy is often used for treating AGA in women; however, many of the agents have not been approved by the FDA for this specific indication. Zhuang et al. [41] conducted a study involving 31 patients diagnosed with AGA to assess the impact on quality of life and clinical improvement after 12 months of using 2% topical minoxidil. They used the Visual Analog Scale (VAS) and the Dermatologic Quality of Life Index (DLQI). The results indicated that hair loss is significantly associated with a reduced quality of life, and the use of topical minoxidil was observed to improve this condition. In another study, Yamazaki et al. [42] investigated how 1 mg of oral finasteride taken for 6 months affected the quality of life of 27 men with AGA aged between 19 and 76 years. They used WHOQOL-BREF, the DLQI, the State–Trait Anxiety Inventory (STAI), and VAS scales. The comparison of WHOQOL-BREF scores before and after the administration of 1 mg of finasteride showed an overall improvement in the quality of life in the study group, although the improvement in individual domains was not statistically significant. It is worth noting that while finasteride treatment is well established in men, only a small number of studies focus on the use of 5 α-reductase inhibitors in female pattern hair loss, which is considered as an off-label treatment. Seale et al. [43] emphasized the potential side effects that 5 α-reductase inhibitors may cause in women when used as an oral treatment for female pattern hair loss and frontal fibrosing alopecia. However, the frequency of sexual function impairment after the administration of dutasteride or finasteride in the identified studies varied. Two studies reported that the daily administration of 5 mg of finasteride contributed to treatment discontinuation due to decreased libido. The occurrence of post-finasteride syndrome in women was not determined in that review. However, post-finasteride syndrome, which includes, among other adverse side effects, sexual dysfunction secondary to 5 α-reductase inhibitors, is well described among male patients and includes the loss of libido and erectile dysfunction [44]. Although finasteride is not yet FDA-approved for female patients, its potential as an alternative treatment is being considered [23]. To date, the limited data available seem to indicate very few side effects of 5 α-reductase inhibitors on sexual function in women [43]. To our knowledge, there are no published studies evaluating the effect of AGA treatment on women's sexual functioning, and the available data on the association of AGA and impaired sexual function are contradictory. Sancak et al. [14] evaluated the correlations between female sexual dysfunction and AGA in premenopausal

women, finding that the presence of AGA significantly impaired their sexual function. Conversely, Eyada et al. [45] found no correlation between the incidence of sexual function impairment and AGA.

Topical preparations for AGA are characterized by a lower frequency of side effects, but their high treatment burden limits patient adherence and, consequently, effectiveness. In a study by Zac and da Costa [46], quality of life, treatment satisfaction, and dermatoscopic criteria were evaluated among female patients with AGA undergoing treatment with topical 5% minoxidil. The study concluded that treatment with 5% minoxidil had positive psychological benefits. Interestingly, patient satisfaction and quality of life were not found to be related to age, alopecia severity, or hair shaft reduction per follicle unit. Another study conducted by Moorthy et al. [32] on 170 women with AGA showed that female AGA was associated with significantly reduced quality of life, particularly among young, less educated, and single women. This suggests that the potential benefits of treatment could be age-dependent. In our analysis, we considered the association between age and found no correlation between improvements in quality of life after treatment with hair follicle stem cells and the age of the patients. Vastarella et al. [47] retrospectively studied the effect of oral minoxidil at a dose of 0.5 mg to 2 mg daily in women diagnosed with AGA. The study group consisted of 12 women with AGA (Ludwig scale I-3-III) with a mean age of 36.7 ± 18.8 years. The Women with Androgenetic Alopecia Quality of Life Questionnaire (WAA-QoL) was used to assess quality of life, showing a statistically significant improvement after 24 weeks compared to baseline. The median WAA-QoL score was 70.33 at baseline and decreased to 25.58 at 24 weeks ($p < 0.01$).

There are only a few studies that have investigated quality of life among women with AGA treated with platelet-rich plasma. Meyers et al. [48] conducted a study examining the effect of platelet-rich plasma treatments on the quality of life of 92 female and male patients with pattern hair loss. Using the Hairdex 48 scale, they found that this type of treatment is effective in improving the overall quality of life. The study also revealed a decrease in the domains of symptoms, emotions, and functioning, with improvements demonstrated in the domains of stigma and self-confidence. A study conducted by Bruce et al. [49] was a randomized, controlled pilot trial investigating the efficacy of platelet-rich plasma in comparison to topical minoxidil foam for the treatment of AGA among women. The secondary outcome of this study included the measurement of quality of life using a 16-item questionnaire administered at baseline and after the 12-week treatment period. Notably, no improvements were observed after minoxidil treatment, whereas the platelet-rich plasma group demonstrated significant improvement in aspects such as self-consciousness about people looking at their hair, feelings of jealousy, ability to socialize with people, and satisfaction with overall hair appearance.

Hair transplants involve the surgical transplantation of hair follicles from a donor area, typically the back or sides of the scalp, to areas with hair loss. This procedure is invasive and expensive but effective, providing natural-looking results. Nilforoushzadeh et al. [50] conducted a survey involving 35 men to assess quality of life and self-esteem before and after hair transplant surgery. They used the Rosenberg Self-Esteem Scale (RSES) and the DLQI and demonstrated a statistically significant difference in self-esteem and quality of life before and after the restoration surgery. Additionally, the study revealed a statistically significant relationship between educational achievement and quality of life. This study suggests that as self-esteem improves, patients' quality of life also improves, emphasizing the close connection between self-esteem and a satisfying physical appearance. Xiao et al. [51] investigated health utility measures among patients with AGA after a hair transplant. They compared 31 patients with alopecia with 237 otherwise healthy people. After the hair transplant, the improvement in time trade-off—a technique used to measure the experienced quality of life for economic analyses—was significantly greater for patients with AGA (+0.08 ± 0.12 vs. +0.02 ± 0.09; $p = 0.0070$) and significantly more often exceeded the minimal clinically important difference (45.2% vs. 16.9%; $p = 0.0006$).

A limitation of our study is undoubtedly the small sample size and the lack of a placebo group. A major challenge is to find women with AGA who are willing to abstain from other types of treatment for 6 months. In the future, we aim to investigate how stem cell therapy affects quality of life and sexual functioning in men affected by the disease. It also seems interesting to compare this therapy with others, especially with FDA-approved drugs, in terms of their impact on quality of life. Another important limitation of our study is that the quality of life of our female patients may be affected by factors other than AGA, which were not controlled for. We lacked sufficient information to account for factors that could influence quality of life, such as socialized frequency and marital status. Certainly, collaboration with psychiatrists and psychotherapists, who would be able to professionally assess the mental state of the patients, could have ruled out other potential causes of lowered mood or dissatisfaction with sexual life. Another limitation of our work is the inability to interpret the interesting and surprising result of improved quality of life in the environmental domain. Unfortunately, due to the lack of information about the demographics of the patients, we were not able to interpret its reliably. This area requires further research.

## 5. Conclusions

Dermatologists need to recognize the tremendous impact that AGA has on the quality of life and sexual functioning of women affected by the condition. The assessment of quality of life and sexual functioning in women with AGA is increasingly important for assessing the effects of the disease on patients and the required treatment. The chronic and progressive nature of AGA, coupled with limited treatment effectiveness, contributes to substantial suffering for those affected. Therefore, there is a pressing need for novel and effective treatments for AGA. Highlighting the potential advantages of a multidisciplinary approach that includes dermatologists, endocrinologists, and psychologists, this study offers optimism regarding the ability of new stem cell treatments to diminish the severity of AGA. This, in turn, holds the promise of enhancing the overall quality of life for individuals affected by the condition.

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

**Data Availability Statement:** The data that support the findings of this study are available on request from the corresponding author.

**Conflicts of Interest:** The authors declare no conflicts of interest.

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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) 13,5 oraz punktacji MEiN 280 punktów. We wszystkich artykułach doktorantka jest pierwszym i wiodącym autorem.

Pierwszą pracą spośród cyklu jest przegląd systematyczny piśmiennictwa dotyczący wykorzystania ludzkich komórek macierzystych w leczeniu łysienia androgenowego. Stanowi ona podsumowanie aktualnej wiedzy na temat klinicznej skuteczności oraz bezpieczeństwa terapii z wykorzystaniem komórek macierzystych. Przeglądu dokonano zgodnie z wytycznymi protokołu PRISMA w 2023 r. Jest to pierwszy systematyczny przegląd dotyczący stosowania różnych rodzajów komórek macierzystych w leczeniu AGA u kobiet i mężczyzn, w ramach którego analizowano 15 badań, w których wzięło udział 653 pacjentów.

Następnie, w badaniach będących podstawą drugiej i trzeciej publikacji cyklu oceniono wpływ leczenia autologicznymi komórkami macierzystymi pochodzącymi z mieszków włosowych pacjentek z łysieniem androgenowym na przebieg tej choroby. Ponadto zbadano wpływ tej terapii na jakość życia i funkcjonowanie seksualne w badanej grupie kobiet. Badania prowadzono w latach 2022-2023. Do badań włączono grupę liczącą 23 pacjentek chorujących na łysienie androgenowe, u których zaawansowanie choroby oceniono w klasyfikacji Ludwiga (typ I u 60,9%, typ II u 30,4% i typ III u 8,8%). Od wszystkich pacjentek zostały pobrane próbki krwi celem wykonania badań laboratoryjnych: morfologia, TSH, anty-TPO, anty-TG, testosteron, SHGB, prolaktyna, kortyzol, żelazo, androstendion, witamina D3, kwas foliowy, ferrytyna, witamina B12, DHEA-S, DHT, 17α-hydroksyprogesteronu, ACTH oraz ANA1 i ANA3. Przed rozpoczęciem terapii i 6 miesięcy po jej zakończeniu pacjentki były proszone o wypełnienie dwóch kwestionariuszy: kwestionariusz jakości życia w wersji skróconej Światowej Organizacji Zdrowia (WHOQOL-BREF) oraz oceny funkcjonowania seksualnego kobiet (FSFI). Użyto zwalidowanych polskich wersji kwestionariuszy FSFI i WHOQOL-BREF. Ocena kliniczna pacjentek została przeprowadzona przed terapią i 6 miesięcy po jej zastosowaniu, przez

czterech niezależnych specjalistów dermatologii za pomocą wizualnej skali analogowej (VAS). Następnie zbadano korelację stężenia badanych substancji z wynikiem w skali VAS.

W badaniu przeprowadzonym wśród pacjentek z AGA ocena po leczeniu za pomocą HFSCs wykazała znaczną poprawę w oparciu o skalę VAS ze średnim wzrostem o 1,5 punktu i średnia poprawę o 1 stopień w skali Ludwiga. Zarówno wyniki w skali Ludwiga, jak i średnie wyniki w skali VAS wykazały znaczące różnice po leczeniu. Pacjentki, u których stwierdzono początkowo wyższe poziomy SHGB i 17α-hydroksyprogesteronu uzyskały lepsze efekty kliniczne. Zarówno stężenie testosteronu i DHT nie wpłynęły na końcowy efekt kliniczny w badanej grupie pacjentek.

Badanie wykazało także, że po 6 miesiącach od sesji ACM liczba pacjentek z dysfunkcjami seksualnymi mierzonymi za pomocą skali FSFI spadła z 11 do 6 osób. Domenami, w których odnotowanoy istotną różnice były podniecenie i satysfakcja. Całkowity wynik FSFI, a także wskaźniki pożądania, nawilżenia, orgazmu i bólu nie różniły się istotnie między punktami badania. Jakość życia została oceniona za pomocą kwestionariusza WHOQOL-BREF, która wykazała, że 6 miesięcy po zabiegu ACM pacjenci odczuwali wyższą jakość życia w zakresie zdrowia psychicznego i środowiska, jednakże nie odnotowano znaczących zmian w zgłaszanym zdrowiu fizycznym i relacjach społecznych. Analiza korelacji między wynikami WHOQOL-BREF a wynikami FSFI wykazała, że we wszystkich domenach ogólna jakość życia i zdrowie seksualne były umiarkowanie lub silnie dodatnio skorelowane

Podsumowując, wyniki prac zawartych w rozprawie doktorskiej potwierdzają skuteczność autologicznych komórek macierzystych pochodzących z mieszków włosowych pacjentek chorujących na łysienie androgenowe w jego leczeniu, a także dowodzą, że terapia ACM ma pozytywny wpływ na jakość życia i funkcjowanie seksulane kobiet cierpiących na tę chorobę.

# 8. STRESZCZENIE W JĘZYKU ANGIELSKIM

The doctoral dissertation is based on a series of three monothematic articles published in international scientific journals indexed in the PubMed database and included in the Journal Citation Reports list, as well as in the list of scientific journals of the Ministry of Education and Science (MEiN). The articles included in the doctoral dissertation have been accepted for publication in international journals with a total Impact Factor (IF) of 13,5 and a MEiN score of 300 points. In all articles, the doctoral student is the first and lead author.

The first work in the series is a systematic review of the literature on the use of human stem cells in androgenetic alopecia (AGA). It summarizes the current knowledge on the clinical effectiveness and safety of therapies with human stem cells. The review was carried out in accordance with the PRISMA protocol guidelines in March 2023. This is the first systematic review on the use of different types of stem cells for the treatment of AGA in men and women, which included 15 studies involving 653 patients.

The studies being the basis for the second and third publications in the series evaluated the effectiveness of stem cells derived from the hair follicles of patients with AGA in the course of this disease. In addition, the impact of this therapy on quality of life and sexual functioning in the study group was examined. The study was conducted between 2022 and 2023. A group of 24 female patients suffering from AGA, whose progression was assessed by the Ludwig classification ( type I in 60.9%, type II in 30.4% and type III in 8.8%) was included in the study, Blood samples were taken from all patients for numerous laboratory tests: CBC, TSH, anti-TPO, anti-TG, testosterone, SHGB, prolactin, cortisol, iron, androstendione, vitamin D3, folic acid, ferritin, vitamin B12, DHEA-S, DHT, 17α-hydroxyprogesterone, ACTH, and ANA1 and ANA3. At baseline and 6 months after therapy, patients completed two questionnaires: the World Health Organization Quality of Life Questionnaire-Brief Version (WHOQOL-BREF) and the Female Sexual Function Questionnaire (FSFI). Validated Polish versions of the FSFI and WHOQOL-BREF questionnaires were used. Clinical evaluation of the patients was carried out, at baseline and 6 months after the applied therapy, by four independent dermatology specialists using a visual analog scale (VAS). The correlation of the concentration of the tested substances with the VAS scale score was then examined.

In the study of AGA patients, post-treatment evaluation with HFSCs showed significant improvement based on the VAS scale with an average increase of 1.5 points and an average improvement of 1 degree on the Ludwig scale. Both Ludwig scale scores and mean

VAS scale scores showed significant differences after treatment. Patients who initially had higher levels of SHGB and 17α-hydroxyprogesterone had better clinical outcomes. Both testosterone and DHT levels did not affect the final clinical outcome in the group of patients we studied.

The study also showed that 6 months after the autologous cell micrografts (ACM) sessions, the number of patients with sexual dysfunctions as measured by the FSFI scale dropped from 11 to 6. The domains in which we noted significant differences were arousal and satisfaction. The total FSFI score, as well as indices of desire, lubrication, orgasm and pain, did not differ significantly between study sites. Quality of life was assessed using the WHOQOL-BREF questionnaire. Results showed that 6 months after ACM, patients experienced a higher quality of life in terms of mental health and environment, but there were no significant changes in reported physical health and social relationships. Correlation analysis between WHOQOL-BREF and FSFI scores showed that in all domains, overall quality of life and sexual health were moderately to strongly positively correlated.

In conclusion, the results of the work presented in the dissertation confirm the effectiveness of autologous stem cells derived from the hair follicles of patients suffering from AGA in the treatment of this disease. Furthermore, ACM has been proven to positively impact quality of life and sexual function of women experiencing hair loss in the course of AGA.

# 9. OPINIA KOMISJI BIOETYCZNEJ



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

OPINIA KOMISJI BIOETYCZNEJ Nr KB – 1074/2021

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.:

„Ocena wpływu autologicznego przeszczepu komórek macierzystych na przebieg łysienia androgenowego u kobiet "

zgłoszonym przez **lek. Katarzynę Krefft-Trzciniecką** pracownika Kliniki Dermatologii, Wenerologii i Alergologii Uniwersyteckiego Szpitala Klinicznego we Wrocławiu oraz

złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła **wyrazić zgodę** na przeprowadzenie badania w Katedrze i Klinice Dermatologii, Wenerologii i Alergologii Uniwersytetu Medycznego we Wrocławiu, pod nadzorem dr hab. Danuty Nowickiej, **pod warunkiem zachowania anonimowości uzyskanych danych.**

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

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

Opinia powyższa dotyczy projektu badawczego będącego podstawą rozprawy doktorskiej.

Przewodniczący Komisji Bioetycznej
przy Uniwersytecie Medycznym

prof. dr hab. Jerzy Rudnicki

Wrocław, dnia 3 stycznia 2022 r.

## 10.CURRICULUM VITAE

*CURRICULUM VITAE*

# *KATARZYNA KREFFT-TRZCINIECKA*

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10/2011 – 06/2017

*Kierunek Lekarski, Wydział lekarski*

**Doświadczenie:**

***Zawodowe:***

Lekarz rezydent (w trakcie specjalizacji) 01/04/2020 – obecnie
*Klinika Dermatologii, Wenerologii i Alergologii, Uniwersytecki Szpital Kliniczny im. Mikulicza Radeckiego we Wrocławiu*

Lekarz (stażysta) Wojewódzki Szpital Specjalistyczny we Wrocławiu 01/10/2017 – 29/10/2018

***Naukowe:***

*Publikacje:*

•3 pełnotekstowe artykuły opublikowane w krajowych i międzynarodowych czasopismach, w tym indeksowanych w bazie PubMed, z czego 3 jako pierwszy autor

• Całkowity współczynnik wpływu (Impact Factor) opublikowanych prac = 13,5

• Punktacja ministerialna: 300

*Członkostwo w towarzystwach naukowych:*

• Polskie Towarzystwo Dermatologiczne

• International Society of Dermatology

• European Academy of Dermatology and Venereology

• International Dermoscopy Society

• Polska Grupa Dermatoskopowa

• Polskie Towarzystwo Dermatologii Włosów

# 11. DOROBEK NAUKOWY

## I. Publikacje w czasopiśmie naukowym z IF

1. **Krefft-Trzciniecka Katarzyna**, Piętowska Zuzanna, Nowicka Danuta, Szepietowski Jacek C.: Human stem cell use in androgenetic alopecia: a systematic review, Cells, 2023, vol. 12, nr 6, art.951 [12 s.], DOI:10.3390/cells12060951.
2. **Krefft-Trzciniecka Katarzyna**, Piętowska Zuzanna, Pakiet Alicja, Nowicka Danuta, Szepietowski Jacek C.: Short-term clinical assessment of treating female androgenetic alopecia with autologous stem cells derived from human hair follicles, Biomedicines, 2024, vol. 12, nr 1, art.153 [12 s.], DOI:10.3390/biomedicines12010153.
3. **Krefft-Trzciniecka Katarzyna**, Cisoń Hanna, Pakiet Alicja, Nowicka Danuta, Szepietowski Jacek C.: Enhancing quality of life and sexual functioning in female androgenetic alopecia: therapeutic potential of hair follicle-derived stem cells, Healthcare, 2024, vol. 12, nr 6, art.608 [11 s.], DOI:10.3390/healthcare12060608.

## II. Publikacje w czasopiśmie naukowym bez IF

1. Białynicki-Birula Rafał, Cisoń Wiktor, **Krefft-Trzciniecka Katarzyna**, Cisoń Hanna: Acute generalized exanthematous pustulosis caused by sulfasalazine, Nasza Dermatologia Online, 2024, vol. 15, nr 1, s. 71-74, DOI:10.7241/ourd.20241.17
2. **Katarzyna Krefft**, Marzena Maciejewska, Patrycja Rojewska, Adam Czyżyk, Błażej Męczekalski. Complete androgen insensitivity syndrome (CAIS) in the 44-year-old patient with XY karyotype - a case report. Arch. Perinat. Med. 2016 : Vol. 22, nr 2, s. 51.

**Sumaryczny Impact Factor: 13,5**

**Punktacja MNiSW: 300**

# 12. OŚWIADCZENIA WSPÓŁAUTORÓW

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

Wrocław, 2024-05-15

Oświadczam, że w pracy:

Krefft-Trzciniecka K, Piętowska Z, Nowicka D, Szepietowski JC. Human Stem Cell Use in Androgenetic Alopecia: A Systematic Review, Cells 2023, 12(6), 951.

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

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mój udział polegał na wykonaniu analizy statystycznej wyników badań.

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

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