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Angiografia OCT w ocenie gęstości mikrokrążenia siatkówki u pacjentów z układowym toczniem rumieniowatym

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2. STRESZCZENIE W JĘZYKU POLSKIM

Toczeń rumieniowaty układowy (Systemic Lupus Erythematosus – SLE) to przewlekła choroba zapalna tkanki łącznej, w której najczęściej zajęta jest skóra, stawy oraz nerki, ale proces chorobowy może dotyczyć każdego narządu organizmu, w tym narządu wzroku. Objawy oczne w przebiegu SLE występują u około 1/3 chorych i mogą poprzedzać zajęcie innych narządów. Retinopatia, czyli zajęcie siatkówki, jest drugą co do częstości manifestacją okulistyczną w SLE oraz najczęstszym powikłaniem okulistycznym obniżającym ostrość widzenia. Retinopatia dotyka od 7 do 26% pacjentów ze SLE, a jej wystąpienie jest negatywnym czynnikiem prognostycznym dotyczącym przeżycia w porównaniu do pacjentów bez retinopatii. Ponadto retinopatia jest częściej wykrywana u pacjentów z niewydolnością nerek i/lub zajęciem ośrodkowego układu nerwowego.

Optyczna koherentna tomografia (OCT) siatkówki jest stosowana do diagnozowania i monitorowania retinopatii w przebiegu SLE oraz jako badanie przesiewowe toksyczności hydroksychlorochiny (HCQ). Angiografia oparta na OCT (Angio-OCT) to połączenie urządzenia OCT oraz angiografii. To nowa, nieinwazyjna metoda obrazowania struktury siatkówki oraz naczyń krwionośnych za pomocą oceny ruchu czerwonych krwinek. Jest bezpieczniejsza, szybsza i łatwiejsza do wykonania niż stosowana w tych samych wskazaniach medycznych, angiografia fluoresceinowa. Ponadto Angio-OCT nie wymaga podania dożylnie kontrastu oraz ułatwia ocenę siatkówki mierząc ilościowo nasilenie zmniejszonej perfuzji w naczyniach.

Celem głównym pracy doktorskiej była ocena przydatności Angiografii OCT do diagnostyki zaburzeń unaczynienia siatkówki u pacjentów ze SLE bez objawów retinopatii w badaniu dna oka oraz bez obniżenia ostrości wzroku.

Badania oryginalne poprzedzono artykułem przeglądowym w celu uporządkowania dostępnej w temacie wiedzy oraz zaplanowania metodologii kolejnych badań. Do badań oryginalnych włączono 64 pacjentów (113 oczu), w tym 33 pacjentów (57 oczu) z rozpoznanym SLE będących pod opieką Katedry i Kliniki Reumatologii i Chorób Wewnętrznych Uniwersyteckiego Szpitala Klinicznego we Wrocławiu oraz 31 zdrowych ochotników (56 oczu).

W pracy przeglądowej przeanalizowano siedem artykułów, których przedmiotem badania była subkliniczna retinopatia w przebiegu SLE mierzona za pomocą urządzenia Angio-OCT. We wszystkich pracach wykazano zmniejszenie gęstości naczyń włosowatych splotu powierzchownego u bezobjawowych pacjentów z rozpoznaniem SLE w porównaniu ze zdrową

grupą kontrolną. Pierwsze badanie oryginalne wykazało mniejszą gęstość naczyń mikrokrążenia siatkówki w dolnym i nosowym kwadrancie splotu powierzchownego oraz w jej strefie okołodołkowej u pacjentów ze SLE w porównaniu do grupy kontrolnej. W grupie badanej zajęcie nerek związane było z dalszą redukcją mikrokrążenia w porównaniu do pacjentów ze SLE bez zajęcia nerek. Ostrość wzroku była istotnie statystycznie niższa u pacjentów ze SLE, co może być wtórne do stopnia utraty naczyń włosowatych. Gęstość naczyń w górnym kwadrancie splotu powierzchownego była zwiększona u pacjentów ze SLE leczonych HCQ przez ponad 5 lat w porównaniu z pacjentami leczonymi HCQ mniej niż 5 lat. Badanie wykazało również dodatnią korelację między skumulowaną dawką HCQ oraz gęstością naczyń w splocie powierzchownym i głębokim. W pracy nie wykazano korelacji pomiędzy skalami SLICC/ACR i SLEDAI-2K a gęstością naczyń, jednakże stwierdzono związek między gęstością naczyń a zajęciem innych narządów. Pacjenci ze SLE i zajęciem nerek mieli mniejszą gęstość naczyń w kwadrantach nosowych i skroniowych, a także całkowitą i okołodołkową splotu powierzchownego w porównaniu z pacjentami ze SLE bez zajęcia nerek. W drugim badaniu oryginalnym nie wykazano różnic morfologicznych w badaniu OCT między grupą chorującą na SLE bez objawów retinopatii w badaniu dna oka oraz bez obniżenia ostrości wzroku a zdrową grupą kontrolną.

OCT wyposażone w funkcję angiografii jest obiecującą metodą diagnostyczną do bezinwazyjnej oceny zaburzeń unaczynienia siatkówki u pacjentów ze SLE. Zmniejszenie gęstości naczyń siatkówki może być uważane za wczesny marker retinopatii w przebiegu SLE, a wyniki uzyskane za pomocą Angio-OCT mogą być dobrym wskaźnikiem rokowania SLE. Wykazano także, że hydroksychlorochina może pełnić funkcję ochronną dla mikrokrążenia siatkówki. Angio-OCT może przyczynić się do wcześniejszej diagnozy i monitorowania progresji retinopatii w przebiegu SLE. Wykazano również, że u pacjentów ze SLE i bez retinopatii zmiany w mikrostrukturze siatkówki nie są widoczne w OCT. OCT bez funkcji angiografii jest mniej czułe u tej grupy pacjentów niż Angio-OCT w wykrywaniu subklinicznych uszkodzeń siatkówki.

3. STRESZCZENIE W JĘZYKU ANGIELSKIM

Systemic Lupus Erythematosus (SLE) is a chronic, inflammatory connective tissue disease that most commonly affects the skin, joints and kidneys, but the disease can affect any organ of the body, including the eye. Ocular symptoms in the course of SLE occur in 1/3 of patients and may precede the involvement of other organs. Retinopathy is the second most common ophthalmic manifestation in SLE and the most common ophthalmic complication that reduces visual acuity. Retinopathy affects 7 to 26% of patients with SLE, its occurrence is a negative prognostic factor for survival, and it is more frequently detected in patients with renal insufficiency and/or central nervous system involvement.

Optical coherence tomography (OCT) of the retina is used to diagnose and monitor lupus retinopathy and as a screening test for hydroxychloroquine (HCQ) toxicity. Optical coherence tomography angiography (Angio-OCT) is a combination of an OCT and angiography. It is a new, non-invasive method of imaging the structure of the retina and blood vessels by assessing the movement of red blood cells. It is safer, faster, and easier to perform than fluorescein angiography. Additionally, Angio-OCT does not require intravenous contrast and facilitates the assessment of the retina by quantifying the severity of reduced perfusion in the vessels.

The main aim of the dissertation was to assess the usefulness of Angio-OCT for the diagnosis of retinal vascular disorders in SLE patients without retinopathy in the fundus examination and without visual acuity reduction.

The original research was preceded by a review article to summarize the available knowledge on the subject. Sixty-four patients (113 eyes) were included in the original study, including 33 patients (57 eyes) with SLE undergoing treatment in the Department of Rheumatology and Internal Medicine of the University Clinical Hospital in Wrocław and 31 healthy volunteers (56 eyes).

In the review, seven articles were analyzed regarding the subclinical retinopathy measured by the Angio-OCT in the course of SLE. All studies showed a decrease in the vessel density of the superficial retinal capillary plexus in asymptomatic patients diagnosed with SLE compared to the healthy control group. The first original study revealed lower vessel density in parafovea, inferior and nasal quadrants of the superficial retinal capillary plexus in patients with SLE compared to the control group. In the study group, renal involvement was associated with a further reduction of microcirculation compared to patients with SLE without renal involvement. Visual acuity was statistically significantly lower in SLE patients, which may be secondary to the degree of capillary loss. Vessel density in the superior quadrant of the

superficial capillary plexus was increased in SLE patients treated with HCQ for more than 5 years compared to patients treated with HCQ for less than 5 years. The study also showed a positive correlation between the cumulative dose of HCQ and the density of vessels in the superficial and deep capillary plexus. The study showed no correlation between the SLICC/ACR and SLEDAI-2K scales and vessel density, however, a relationship was found between vessel density and involvement of other organs. Patients with SLE and nephritis had lower whole en face superficial vessel density, superficial parafoveal density and superficial density in nasal and temporal quadrants compared to patients with SLE without kidney involvement. The second original study showed no morphological differences in the OCT between the healthy control group and patients suffering from SLE without signs of retinopathy in the examination of the fundus and without visual acuity reduction.

Angio-OCT is a promising diagnostic method for non-invasive assessment of retinal vascular disorders in patients with SLE. Decreased retinal vascular density may be considered an early marker of lupus retinopathy and results obtained with the use of Angio-OCT may be a good indicator of SLE prognosis. It has also been shown that hydroxychloroquine may have a protective function on the retinal microcirculation. Angio-OCT may contribute to earlier diagnosis and monitoring of lupus retinopathy progression. It has also been shown that in SLE patients without retinopathy, changes in the retinal microstructure are not visible in OCT thus it is less sensitive than Angio-OCT in detecting subclinical retinal lesions.

4. WSTĘP

Toczeń rumieniowaty układowy (Systemic Lupus Erythematosus – SLE) to przewlekła, wieloczynnikowa choroba zapalna tkanki łącznej, w której najczęściej zajęta jest skóra, stawy oraz nerki, ale proces chorobowy może dotyczyć każdego narządu organizmu, w tym narządu wzroku (1). Predyspozycja genetyczna wraz z czynnikami środowiskowymi oraz hormonalnymi są uważane za główne czynniki etiologiczne, lecz dokładna etiopatogeneza jest nieznana (2).

Objawy oczne w przebiegu SLE występują u około 1/3 chorych i mogą poprzedzać zajęcie innych narządów (3). Retinopatia, czyli zajęcie siatkówki, jest drugą co do częstości manifestacją okulistyczną w SLE, po suchym zapaleniu rogówki i spojówki, oraz najczęstszym powikłaniem okulistycznym obniżającym ostrość widzenia (4). W zależności od aktywności choroby podstawowej retinopatia dotyka od 7 do 26% pacjentów ze SLE, a jej wystąpienie jest negatywnym czynnikiem prognostycznym dotyczącym przeżycia w porównaniu do pacjentów bez retinopatii (5). Retinopatia częściej występuje u pacjentów z ciężką postacią SLE lub jest wynikiem nieadekwatnej kontroli choroby podstawowej. Ponadto retinopatia jest częściej wykrywana u pacjentów z niewydolnością nerek i/lub zajęciem ośrodkowego układu nerwowego (OUN) (6).

Retinopatia w przebiegu tocznia rumieniowatego układowego może mieć różny obraz kliniczny. Może przybierać formę mikroangiopatii, niedrożności naczyń, zapalenia naczyń, pseudoretinopatii Purtschera czy retinopatii nadciśnieniowej związanej z toczniowym zapaleniem nerek (7-13). Klasyczna retinopatia pod postacią mikroangiopatii jest spowodowana odkładaniem się kompleksów immunologicznych w śródbłonku naczyń, aktywacją dopełniacza i zwiększoną fagocytozą prowadząc do stanu zapalnego i zapalenia naczyń (2,14,15). Jest najczęstszą postacią retinopatii w przebiegu SLE, cechuje się łagodnym przebiegiem i w przypadku braku zmian w obrębie plamki żółtej, dobrą ostrością wzroku. W badaniu dna oka charakteryzuje się ogniskami waty, małymi wylewami śródsiatkówkowymi, mikrotętniakami, ogniskowym obrzękiem siatkówki (7). Zmiany naczyniowo-okluzyjne mogą dotyczyć naczyń siatkówki o różnej średnicy i występują częściej u pacjentów z zespołem antyfosfolipidowym (16). Zaburzenia w krążeniu spowodowane przez zakrzepicę żylną lub zatory tętnicze w odpowiedzi na niedotlenienie siatkówki mogą prowadzić do neowaskularyzacji. W konsekwencji mogą powodować odwarstwienie siatkówki, krwotok w komorze ciała szklistego, a także jaskrę neowaskularną. Niedrożność tętnicy środkowej siatkówki i niedrożność żyły środkowej siatkówki obserwuje się u mniej niż 1% pacjentów, ale

wiążą się ze znaczną utratą wzroku (15). U około 40% pacjentów z rozpoznanym SLE występują dodatnie przeciwciała antykardiolipinowe. Jednakże u pacjentów z rozpoznaną retinopatią odsetek ten sięga nawet 86% co sugeruje, że komponenta okluzyjna odgrywa znacząca rolę w etiopatogenezie zajęcia naczyń siatkówki. Bardziej okluzyjny charakter tej retinopatii, w porównaniu z retinopatią cukrzycową i retinopatią nadciśnieniową, zazwyczaj prowadzi do głębszego niedokrwienia siatkówki (6,15,17,18).

W toczniu rumieniowatym układowym, zajęcie naczyń tylnego odcinka oka odzwierciedla zajęcie naczyń krwionośnych innych narządów, a zmiany mikronaczyniowe są związane ze wzrostem ilości powikłań ogólnoustrojowych (6,19,20). Chociaż kryteria diagnostyczne SLE nie uwzględniają zmian w obrębie narządu wzroku, wystąpienie retinopatii świadczy o aktywności tocznia rumieniowatego układowego. Retinopatia może pozostać bezobjawowa lub nieznacznie objawowa przez wiele lat, a jej wykrycie w najwcześniejszym stadium jest kluczowe do szybkiego wdrożenia leczenia, a także uniknięcia zmian ogólnoustrojowych.

Optyczna koherentna tomografia (OCT) siatkówki jest stosowana do diagnozowania i monitorowania retinopatii w przebiegu SLE oraz jako badanie przesiewowe toksyczności hydroksychlorochiny. Jest to nieinwazyjne urządzenie, które wykorzystuje koherentną wiązkę światła podczerwonego do skanowania in vivo tylnego bieguna oka. Skany OCT są szybkie i łatwe do wykonania oraz powtarzalne. OCT jest szeroko stosowane w okulistyce m.in. w diagnostyce i obserwacji jaskry, zwyrodnienia plamki żółtej, a także przydatne w niektórych chorobach neurodegeneracyjnych, np. stwardnieniu rozsianym. Diagnostyka retinopatii w przebiegu tocznia rumieniowatego układowego, który jest chorobą o podłożu naczyniowym, opiera się na badaniu dna oka oraz angiografii. Ponad 50 lat złotym standardem w ocenie krążenia siatkówki była angiografia fluoresceinowa. Angiografia OCT – OCTA, Angio-OCT, to połączenie urządzenia OCT oraz angiografii, której wprowadzenie uważane jest za kamień milowy w okulistyce (21). Angio-OCT to najnowsza metoda obrazowania mikrokrążenia siatkówki i naczyniówki, która wykorzystuje odbicie światła laserowego od powierzchni czerwonych krwinek, eliminując potrzebę stosowania dożylnie kontrastu (22). Jest bezpieczniejsza, szybsza i łatwiejsza do wykonania niż angiografia fluoresceinowa. Angio-OCT jest całkowicie nieinwazyjna oraz ułatwia ocenę siatkówki mierząc ilościowo nasilenie zmniejszonej perfuzji w naczyniach. Ponadto Angio-OCT umożliwia ocenę splotu powierzchownego i splotu głębokiego siatkówki wewnętrznej, a także siatkówki zewnętrznej i choriokapilar. Najnowsze badania pokazują, że Angio-OCT pozwala wykryć zmiany w siatkówce i jej mikrokrążeniu w wielu chorobach ogólnoustrojowych jak SLE, stwardnienie rozsiane czy choroba Behçeta (7,23-25).

5. CEL PRACY

5.1. Cel główny pracy

Celem głównym badania była ocena przydatności Angiografii OCT, przy użyciu parametrów: gęstości naczyń (vessel density – VD) oraz strefy awaskularnej dołka (foveal avascular zone – FAZ), do diagnostyki zaburzeń unaczynienia siatkówki u pacjentów z toczniem rumieniowatym układowym bez objawów retinopatii w badaniu dna oka oraz bez obniżenia ostrości wzroku.

5.2. Cele szczegółowe pracy

5.2.1. Podsumowanie dostępnej wiedzy oraz identyfikacja luk w dotychczas opublikowanych pracach naukowych na temat zastosowania Angio-OCT u asymptomatycznych okulistycznie pacjentów z toczniem rumieniowatym układowym.

5.2.2. Określenie gęstości mikrokrążenia siatkówki w Angio-OCT z podziałem na strefy u pacjentów bez objawów retinopatii.

5.2.3. Ocena związku między unaczynieniem siatkówki a aktywnością SLE (za pomocą skali SLEDAI), wskaźnikiem uszkodzenia (za pomocą skali SLICC/ACR DI), zajęciem nerek oraz OUN, skumulowaną dawką hydroksychlorochiny (HCQ) i chlorochiny (CQ).

5.2.4. Określenie grubości poszczególnych warstw siatkówki w OCT u pacjentów bez objawów retinopatii.

5.2.5. Ocena związku między grubością warstw siatkówki a aktywnością SLE (za pomocą skali SLEDAI), wskaźnikiem uszkodzenia (za pomocą skali SLICC/ACR DI), zajęciem nerek oraz OUN, skumulowaną dawką hydroksychlorochiny (HCQ) i chlorochiny (CQ).

5.2.6. Ocena przydatności OCT bez funkcji angiografii u pacjentów ze SLE bez objawów retinopatii w badaniu dna oka w lampie szczelinowej oraz bez obniżenia ostrości wzroku.

6. MATERIAŁ I METODY

Badania oryginalne poprzedzono systematycznym przeglądem literatury w celu uporządkowania dostępnej w temacie wiedzy. Zidentyfikowane luki i ograniczenia w dostępnych badaniach były kluczowe do określenia metodologii badań oryginalnych. Przegląd systematyczny, będącym pierwszą pracą z cyklu publikacji, przygotowano na podstawie bazy PubMed oraz zgodnie z wytycznymi PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Do pracy włączono artykuły, wymienione w powyższej bazie do 15 marca 2021 roku. Bibliografia analizowanych artykułów została również uznana za źródło informacji. Następujące słowa kluczowe były używane w różnych kombinacjach: subkliniczne zmiany siatkówki lub subkliniczne uszkodzenie siatkówki lub subkliniczna choroba siatkówki lub subkliniczne zajęcie siatkówki i SLE lub toczeń rumieniowaty układowy i/lub angiografia OCT lub OCTA. Autorzy przeanalizowali wszystkie artykuły w języku angielskim znalezione przy użyciu wspomnianych słów kluczowych. Odnaleziono czternaście badań, ale tylko siedem spełniało warunki pełnego włączenia do badania. Kryteria włączenia obejmowały: rozpoznanie SLE, brak retinopatii, metodologia badania z użyciem angiografii OCT. Artykuły, których przedmiotem byli pacjenci także z innymi chorobami ogólnoustrojowymi, nie tylko ze SLE, zostały wyłączone z przeglądu.

Badanie oryginalne podzielono na dwa etapy. W pierwszym etapie dokonano oceny parametrów dostępnych w OCT z opcją angiografii, a w drugim w OCT bez funkcji angiografii w celu ustalenia przewagi opcji angiografii nad powszechnie dostępnym i stosowanym OCT. Do badań oryginalnych zostało włączonych 64 pacjentów (113 oczu), w tym 33 pacjentów (57 oczu) z rozpoznanym toczniem rumieniowatym układowym będących pod opieką Katedry i Kliniki Reumatologii i Chorób Wewnętrznych Uniwersyteckiego Szpitala Klinicznego we Wrocławiu oraz 31 zdrowych osobników (56 oczu). Ze względu na słabą jakość skanów z grupy badanej wykluczono 3 pacjentów (4 oczy).

W pracach oryginalnych wykorzystano następujące metody badawcze:

1. pełne badanie okulistyczne,
2. OCT,
3. Angio-OCT,
4. wyniki badań laboratoryjnych i diagnostycznych,
5. skalę SLEDAI-2K (The Systemic Lupus Erythematosus Disease Activity Index 2000),
6. skalę SLICC/ACR DI (The Systemic Lupus International Collaborating Clinics/American, Indeks College of Rheumatology Damage).

Do badań wykorzystano urządzenie DRI OCT Triton Plus (Topcon Corp., Tokio, Japonia, 2015). Wbudowane oprogramowanie i algorytm urządzenia wykorzystano do zautomatyzowanej segmentacji warstw siatkówki oraz pomiaru ich grubości oraz gęstości naczyń w splocie powierzchownym i głębokim. Aby wyznaczyć parametry FAZ ze splotu powierzchownego (wskaźnik powierzchni, obwodu i kolistości), obrazy Angio-OCT zostały wyeksportowane jako obraz o rozdzielczości 320 x 320 pikseli, ręcznie obrysowane i obliczone przy użyciu programu Adobe Photoshop w wersji 23.0.1 (Adobe, Inc., San Jose, Kalifornia, USA, 2021) przez tego samego, zamaskowanego, doświadczonego okulistę.

Analizę statystyczną przeprowadzono przy użyciu programu STATISTICA 13.3 (StatSoft, Inc., Tulsa, OK, Stany Zjednoczone, 2017). We wszystkich analizach za istotne statystycznie uznano wyniki, w których poziom istotności $p<0.05$. Do oceny normalności rozkładu badanych cech ilościowych zastosowano test Kołmogorowa-Smirnowa. Analizę statystyczną badającą różnice pomiędzy poszczególnymi zmierzonymi parametrami w grupach przeprowadzono z zastosowaniem testu U-Manna-Whitney'a. Korelację pomiędzy zmierzonymi parametrami oraz danymi klinicznymi o charakterze ilościowym przeprowadzono z zastosowaniem testu korelacji rang Spearmana.

7. PUBLIKACJE

7.1. Optical Coherence Tomography Angiography as a New Tool for Evaluation of the Subclinical Retinal Involvement in Patients with Systemic Lupus Erythematosus—A Review

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Review

Optical Coherence Tomography Angiography as a New Tool for Evaluation of the Subclinical Retinal Involvement in Patients with Systemic Lupus Erythematosus—A Review

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Abstract: Knowing the proven relationship between lupus retinopathy and systemic changes and disease activity, it is crucial to find the possibility of early diagnosis of retinal changes at a subclinical level in order to provide faster medical intervention and protect the patient from irreversible changes in the eye and other organs. The aim of this review is an analysis of studies investigating early pathological changes in retinal vascularization obtained by optical coherence tomography angiography (OCTA) and their relationship to the systemic lupus erythematosus (SLE). A literature search was performed to identify all relevant articles, regarding detection of subclinical retinal changes using OCTA in systemic lupus erythematosus listed in PubMed database. Seven out of seven papers found showed a decrease in superficial capillary plexus in ocular asymptomatic patients diagnosed with SLE. A decrease in retinal vessel density measured by OCTA may be a good marker of SLE activity and poor prognosis. OCTA in a safe manner can give clinicians a new perspective on processes of vessel remodeling and answer the question of how SLE might impact the eye from a structural point of view. Adding OCTA to the standard diagnostic process of SLE patients, may detect systemic changes early and prevent further visual deterioration by stopping progression of lupus retinopathy.

Keywords: angiography (OCTA); retinal capillaries; subclinical retinal changes; vessel density; systemic lupus erythematosus

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1. Introduction

Systemic lupus erythematosus (SLE) is a chronic, systemic, autoimmune inflammatory connective tissue disease associated with the involvement of the majority of human organs, including eye vasculature [1]. The incidence of SLE varies between 1.0 per 100,000 in Denmark and 8.7 per 100,000 in Brazil [2]. Three main mechanisms responsible for SLE development are: impaired amount and presentation of nuclear antigens, production of antinuclear antibodies by T-cell-dependent B-cell stimulation, organ damage by anti-dsDNA antibodies or immune complexes [3]. Retinopathy in SLE is the second most common ophthalmic manifestation after keratoconjunctivitis sicca and the most common ocular complication affecting visual acuity [4]. The incidence of retinopathy in SLE ranges from 7% to 26%, depending on the disease control and activity [5]. Lupus retinopathy and its degree is a well-known risk factor of poor disease prognosis [6]. It is directly related to the activity of the disease and is more frequently detected in patients with renal failure and/or central nervous system involvement [1,7,8]. Its presence is a poor prognostic factor for both visual acuity and survival rate compared to patients without retinopathy. On the other hand, affection of the posterior segment of the eye in the course of SLE may precede systemic symptoms and therefore its detection may help in early diagnosis and prompt initiation of treatment [9].

Vascular changes in the course of SLE, referred to as lupus vasculopathy, may have a diverse character and their type is difficult to define unequivocally without detailed immunohistopathological tests. Appel et al. and D'Agati proposed a classification of vascular lesions in the course of SLE including: non-complicated vascular deposits of immune complexes, noninflammatory necrotic vasculopathy, trombotic microangiopathy, and true lupus vasculitis [10,11]. However, this detailed immunohistological division of the type of vascular involvement in the posterior segment of the eyeball is difficult to apply; hence, in daily practice the descriptions of vascular changes in the fundus and clinical presentations include: microangiopathy, vascular-occlusive changes, and true vasculitis.

Microangiopathy is caused by deposition of immune complexes in endothelium leading to complement activation, and enhanced phagocytosis, causing inflammatory mediators to release [7]. The early stage of the disease is characterized by presence of cotton wool spots with or without small intraretinal hemorrhages; sometimes focal retinal edema, vascular sheathing and narrowing, micro aneurysms, and capillary dilatation can be also detected. Vascular-occlusive changes can affect retinal vessels of various sizes: from involvement of central retinal vein or artery to extensive microembolisation in small vessels referred to as Purtscher-like retinopathy. Depending on the degree of retinal ischemia caused by these changes, neovascular lesions in the posterior and anterior segments, hemorrhage into the vitreous chamber, traction retinal detachment or neovascular glaucoma may be the consequence. An additional factor influencing the pathology of the retinal vessels in the course of SLE is also hypertension-related changes related to renal involvement by SLE.

In the case of severe vascular-occlusive lesions, the patient suffers from a significant decrease in visual acuity. Typical vasculitis, characterized by inflammation of retinal vessels is rarely seen. A more common symptom is the presence of vascular sheathing both in arterioles and venules. Fluorescein angiography typically shows leakage of dye at the site of affected vessels. Additionally, the presence of inflammatory cells in the vitreous body can be detected. Lupus vasculopathy is generally found significantly more often in patients with antiphospholipid syndrome [12].

Investigating the ocular microvasculature status is not only useful in well-known ophthalmic diseases like glaucoma, diabetic retinopathy, or age-related macular degeneration [13,14]. Recent studies have shown promising results in retinal vessel visualization in systemic diseases like SLE, multiple sclerosis, or Behcet disease [15–17]. For more than 50 years, the gold standard in the assessment of retinal circulation has been fluorescein angiography (FA), which is an invasive procedure involving the introduction of a dye, fluorescein, into the systemic circulation. FA is contraindicated in people with renal failure or known allergy to the fluoresceine or green indocyanine dye thus carrying a risk of adverse events including but not limited to anaphylaxis. The introduction of optical coherence tomography angiography of the retina (OCTA, OCT-A, Angio-OCT) in 2006 is considered a milestone in ophthalmic diagnostics [18]. OCTA is the newest, dyeless, non-invasive, and non-contact technique used for imaging the microcirculation of the retina and choroid with a resolution at the level of histopathological examination. It can detect subclinical vascular alterations in the retina and its microvasculature undetectable during fundus examination in a slit lamp [19]. Three-dimensional scans obtained by OCTA are automatically divided into OCT angiogram segments. Full-thickness retina is visualized from the internal limiting membrane (ILM) through the inner and outer retina, reaching the choroid and may be precisely analyzed. The vasculature projection of the retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) are considered as superficial retinal capillary plexus (SRCP) of the inner retina and the vascular plexuses from the border of the inner plexiform layer (IPL), inner nuclear layer (INL) to outer plexiform layer (OPL) are considered as the deep retinal capillary plexus (DRCP) of the inner retina [14].

This review analyzes research studies investigating early pathological changes in retinal vascularization and their relationship to the SLE. Knowing the proven relationship between lupus retinopathy and systemic changes and disease activity, it is crucial to find the possibility of early diagnosis of retinal changes at the subclinical level in order to

provide faster medical intervention and protect the patient from irreversible changes in the eye and other organs caused by inadequate or delayed treatment of SLE.

2. Materials and Methods

A literature search was performed to identify relevant articles, regarding subclinical retinal changes in systemic lupus erythematosus, listed in PubMed database up to the 15 March 2021. The authors did not use other databases. The reference lists of the analyzed articles were also considered a source of the literature information. The authors did not attempt to search for unpublished articles. The following keywords were used in various combinations: subclinical retinal changes or subclinical retinal impairment or subclinical retinal disease or subclinical retinal involvement and SLE or systemic lupus erythematosus and/or OCT angiography or OCTA. The authors analyzed all English articles found using the aforementioned keywords.

Fourteen studies were found, but only seven studies met the full study inclusion criteria: lack of symptomatic retinopathy in patients diagnosed with systemic lupus erythematosus with data obtained by OCT angiography. Studies in which patients were diagnosed with lupus retinopathy were not considered. Articles that also included patients with other systemic diseases, not only SLE, were excluded from the review. Studies in which patients were tested with OCT rather than OCTA were excluded from the review. No article published before 2018 was found. Review authors did not contact other study authors to expand on unpublished information or to obtain additional data. None of the studies included in the review were continued. Because of the scarce published data regarding this topic, all original studies considering subclinical retinal involvement in SLE patients detected by OCTA found by the authors were included in this work. All the publications were thoroughly reviewed to create a detailed overview of this issue.

3. Results

The first preliminary report regarding this topic was published by Conigliaro et al. in 2018 [20]. According to the study results, the eyes of SLE patients had a lower mean superficial and whole en face density, superficial parafoveal density, and superficial foveal density compared to the control group. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and Systemic Lupus International Collaborating Clinics (SLICC) were negatively correlated with superficial en face density, superficial parafoveal density, and deep whole en face density. Additionally, patients with kidney involvement displayed reduced parafoveal vessel density and parafoveal thickness compared with SLE patients without it, but this finding was not supported by the results presented by Işık et al., who have shown no difference between patients with SLE and kidney involvement and patients with SLE without kidney involvement in OCTA parameters [21]. Conigliaro et al. have shown a possible protective role of hydroxychloroquine (HCQ), an antimalarial drug, on retinal microvasculature despite its proven ocular toxicity. They found positive correlation between cumulative dose of hydroxychloroquine and vessel density (VD). The Mihailovic et al. study has shown a similar association, but only in patients with a low-risk profile for HCQ-induced toxic retinopathy [22]. They distinguished two study groups, using HCQ for >5 years (high-risk group) and <5 years (low-risk group), and only in patients using HCQ for less than 5 years does it seem to have a protective effect on the VD. This correlation was not confirmed in the high-risk group. Conigliaro et al. did not divide the groups in terms of HCQ treatment duration. Table 1 summarizes conclusions obtained by the aforementioned authors about the effects of HCQ on VD.

Table 1. Impact of the HCQ dose on vessel density.

Authors	HCQ, *n* (%) in Study Group	HCQ Subgroups	HCQ Cumulative Dose (g)	Result	Authors Conclusion
Conigliaro et al. [20]	16 out of 26 (61.5%)	No	738.8 ± 486.8	Positive correlation between the HCQ cumulative dose and VD	Possible protective effect of HCQ on retinal microvasculature
Forte et al. [23]	10 out of 10 (100%)	No; all patients treated with HCQ for more than 5 years	937.59 ± 332.37	Choroidal thinning and vascular abnormalities in the three retinal capillary plexuses and CC	OCTA could detect changes in the retina earlier than common screening tests
Mihailovic et al. [22]	19 out of 19 (100%)	Low-risk group-10 out of 19 High-risk group-9 out of 19	Total–819 ± 773 Low-risk group-265 ± 218 High-risk group-1317 ± 754	Positive correlation between the cumulative dose of HCQ and the VD in the low-risk group	Possible protective effect of HCQ on retinal microvasculature, but only in patients treated with HCQ < 5 years

HCQ-hydroxychloroquine, HCQ, *n* (%)-number of patients taking HCQ.

Bao et al. showed similar results to Conigliaro et al. regarding the density of superficial retina vessels [24]. Superficial retinal capillary plexus density was markedly decreased in the patients with SLE without any signs of lupus retinopathy. This pathology was not present in deep retinal capillary plexus. They found a decrease in the retinal microvascular density in both SRCP and DRCP only in patients with clinically diagnosed retinopathy. Similar results were presented by Işık et al., Mihailovic et al. and Pichi et al. [21,22,25]. Patients with SLE compared to the control group had a lower vascular density of the superficial capillary plexus. In the Arfeen et al. study, SLE patients had a decrease in VD in the deep capillary plexus in all sectors, but in superficial capillary plexus only in the upper and lower macular regions [26]. Table 2 compares the characteristics and results of the recent paper about VD impairment in patients with SLE. Table 3 includes patients characteristics.

Table 2. Comparison of impact of SLE on vessel density (VD) obtained by OCTA.

Authors	Year of Publication	Study Group	Control Group	SLE vs. Control Group	SLE and Nephropathy vs. SLE w/o Nephropathy
Conigliaro et al. [20].	2018	26 patients, 52 eyes	20 patients, 40 eyes	Lower superficial whole en face density, superficial parafoveal density and superficial foveal density Unknown FAZ parameters	Reduced parafoveal vessel density and parafoveal thickness
Forte et al. [23]	2019	10 patients, 20 eyes	18 patients, 36 eyes	Reduction of the vessel density in the 1 mm central, nasal and temporal subfields of DCP and in the 1 mm central subfield of CC Increased FAZ	Not compared
Bao et al. [24]	2019	32 patients, 58 eyes	50 patients, 50 eyes	Significant decrease in the superficial retinal capillary plexus density Unknown FAZ parameters	Not compared

Table 2. *Cont.*

Authors	Year of Publication	Study Group	Control Group	SLE vs. Control Group	SLE and Nephropathy vs. SLE w/o Nephropathy
Işık et al. [21]	2020	35 patients, 35 eyes	35 patients, 35 eyes	Lower inner, outer, and full vessel density and perfusion density No difference in FAZ	No difference
Pichi et al. [25]	2020	15 patients, 30 eyes	15 patients, 30 eyes	Decrease in the vascular density of the superficial capillary plexus Enlargement of the FAZ	Not compared
Mihailovic et al. [22]	2020	19 patients, 19 eyes	19 patients, 19 eyes	Significantly reduced VD in the en face superficial capillary plexus Larger FAZ area	Not compared
Arfeen et al. [26].	2020	20 patients, 20 eyes	20 patients, 20 eyes	Significant lower VD in superficial and deep capillary layers No difference in FAZ area	Not compared

SLE—Systemic lupus erythematosus, FAZ—Foveal avascular zone, DCP—Deep capillary plexus, CC—choriocapillary, VD—vessel density.

Table 3. Patient's characteristics.

Authors	Age (Years)	BCVA (LogMAR)	SLE Duration (Years)	SLEDAI	SLICC/ACR SDI
Conigliaro et al. [20]	49.6 ± 13.6	0.0 ± 0.1	15.1 ± 7.7	4.3 ± 4.4	1.9 ± 1.5
Forte et al. [23]	38.87 ± 8.6	0.01 ± 0.03	10.25 ± 3.28 (6–16)	Not calculated	Not calculated
Bao et al. [24]	34.9 ± 11.8	−0.01 ± 0.04	3.8± 3.0	7.7 ± 8.1	Not calculated
Işık et al. [21]	42.6 ± 9.2	0.02 ± 0.04	10.6 ± 4.4	Not calculated	Not calculated
Pichi et al. [25]	42.3 ± 13.4	[1] 20/25	11.3 ± 6.8	0 in 6 patients 1–8 in 8 patient [1] >8 in one patient (no clearly stated data in paper)	Not calculated
Mihailovic et al. [22]	40.1 ± 11.5	Not evaluated	Not evaluated	Not calculated	Not calculated
Arfeen et al. [26]	29.20 ± 7.90	[2] 0.85 ± 0.08	Unknown	No–8 patients Mild–2 patients Moderate–10 patients Severe–0 patients	0–10 patients 2–6 patients 3–2 patients 6–2 patients

[1] Authors evaluated only mean BCVA. [2] BCVA—Snellen decimal. Continuous variables were shown using mean and SD. BCVA–best corrected visual acuity. SLEDAI–Systemic Lupus Erythematosus Disease Activity Index. SLICC/ACR SDI–Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

In terms of the foveal avascular zone (FAZ), Forte et al., Pichi et al. and Mihailovic et al. had indicated that patients with SLE, with no ophthalmic symptoms, have enlargement of the FAZ while only the papers by Işık et al. and Arfeen et al. showed no difference in FAZ between study and control groups [21–23,25,26].

4. Discussion

This review analyzes seven papers considering the detection of early subclinical retinopathy by OCTA. Articles published within the last 3 years have proved that retinal

involvement is an important manifestation of systemic lupus erythematosus, even in the absence of ophthalmic symptoms and signs [20–26]. Seven out of seven papers showed a decrease in superficial capillary plexus in ocular asymptomatic patients diagnosed with SLE.

4.1. Retinal Testing in Subclinical Disease

OCTA is a new tool used to quantify tissue damage and published results confirm it is a promising method in detection of subclinical retinal involvement. Even though it is not the only diagnostic method, it seems quite sensitive compared to other methods. Some authors have also shown the possibility of detection of preclinical retinal involvement using OCT and automated perimetry, commonly used to detect antimalarial drug (HCQ) toxicity [15]. Conigliaro et al. have displayed lower visual field index values in totally asymptomatic SLE patients compared to healthy individuals. Mean defect obtained by standard automated perimetry was even higher and visual field index lower in SLE patients with nephropathy compared to patients without kidney involvement. The study confirms other authors' theses concerning the correlation between disease activity with nephropathy and retinal involvement [20]. Corticosteroids seem to have a protective role as, according to the authors, patients without a history of steroid use more often had disturbances in fundus perimetry [15]. The aforementioned studies have speculated on the protective role of both widely used drugs for SLE corticosteroids on functional retinal impairment and hydroxychloroquine on retinal microvasculature [15,20,22]. However, in the Forte et al. paper, no abnormalities were present in mfERG, OCT, automated visual field (AVF), and fundus autofluorescence (FAF) in patients with SLE treated with HCQ for more than 5 years [23]. They showed impairment only by means of OCTA in the three retinal capillary plexuses and CC. It seems that OCTA is a more precise method in subclinical change detection.

Researches confirm the relationship between changes in the retina captured by OCT and OCTA and the activity of the underlying disease, including the involvement of other systems, like the nervous system [15,27]. A study from 2015 suggested that there may be an association between the activity of neuropsychiatric SLE and OCT findings and that it may be a marker of early cognitive impairment in SLE. Unfortunately, there are no measures to quantify neuropsychiatric manifestations of SLE and to confirm SLE associated etiology of the aforementioned manifestations.

4.2. FAZ Area

Five out of seven reviewed publications have investigated the effect of SLE on the FAZ area. In the majority of studies (three out of five) authors have shown an enlargement of FAZ; in the two remaining ones, there was no difference compared to the control group. According to Pichi et al., subclinical SLE can cause hypoperfusion in the retinal vessels, tissue hypoxia, and retinal cell death. The simultaneous enlargement of the FAZ and the decrease in SCP density may be considered a precursor to the small vessel occlusion and blood flow deceleration [25].

4.3. Importance of Kidney Involvement

Conigliaro et al. demonstrated reduced VD in SLE patients with renal involvement compared to SLE patients without nephropathy [20]. Jallouli et al. showed significantly higher blood HCQ concentration in patients with renal insufficiency. These findings were also presented by Lee et al. [28,29]. However, Işık et al. did not confirm the Conigliaro et al. relationship in their study. According to Işık et al., this discrepancy in published results might be caused by differences in patients characteristics among studies: SLE duration, mean age, or HCQ cumulative dose [21].

4.4. HCQ Dose Influence

Three out of seven papers included in the review examined the relationship between the cumulative dose of HCQ and VD [20,22,23]. Two of seven have shown a possible protective effect of HCQ on retinal microvasculature. In the Conigliaro et al. and Forte et al. studies, it is not possible to clearly determine whether the changes in retinal vasculature are caused by underlying disease or the use of antimalarial drugs, because authors did not distinguish subgroups based on HCQ treatment duration. That is why, in our opinion, the Mihailovic et al. paper is of greater relevance and not biased by the HCQ therapy.

4.5. SLE Activity Index Influence

SLICC and SLEDAI were inversely correlated with superficial capillary plexus which is why Conigliaro et al. results showed not only the association between retinal vessels remodeling and the disease itself, but with its activity and other organs involvement. Arfeen et al. have supported Conigliaro et al. finding only in SLICC score. SLICC/SDI score was negatively correlated with vessel density in the superficial upper nasal sector, superficial central temporal sector, and the deep central middle sector, but the authors did not find a correlation between SLEDAI-2K and VD. Pichi et al. did not show a correlation between the SLEDAI score and OCTA parameters because of the small sample size. Bao et al. had calculated SLEDAI, but did not correlate it with VD. Işık et al., Mihailovic et al., and Forte et al. did not calculate SLEDAI score at all.

4.6. Stages of Subclinical Disease

Early changes in the retinal vessels, impossible to detect in a slit lamp examination, through disturbances in the inner layer of the retina, may promote the progression to full-blown lupus retinopathy. Deposition of immune complexes in the vessels' endothelium might cause microvasculature impairment and thus insufficient oxygen supply to the inner retina layer leading to structural and functional abnormalities [24]. Bao et al. speculate that DRCP impairment may be the second step of lupus retinopathy after SRCP impairment, which makes a decrease in SRCP VD a very early marker of disease. According to results from Pichi et al., hypoperfusion of the SCP may cause tissue hypoxia of retina. They did not show decreased VD in DRCP.

On the contrary, in the Forte et al. study, reduction of the vessel density was observed only in subfields of DCP when compared with control group; they did not show a reduction in SCP. Similar results were published by Arfeen et al. Some SCP quadrants did not show the difference in VD compared to the control group while the VD decrease was observed in whole DCP. It is speculated to be caused by its anatomical position at the termination of retinal capillaries, but exact etiology is still not confirmed [26].

4.7. Effect of Age on Vessel Density

Age-related changes in vascular density should be considered while analyzing the impact of the long-lasting disease on VD. Only three out of seven studies in the review considered age-related changes in retinal vascularity. Conigliaro et al. displayed a negative correlation in patients with SLE between age and superficial whole en face density, superficial foveal density, superficial parafoveal density, deep whole en face density, and deep parafoveal density. Işık et al. and Arfeen et al. did not support these findings. They did not find a correlation between OCTA parameters and age of the patients. The results of the Jo et al. study have displayed that all global and sectoral circumpapillary VDs decreased significantly with increasing age, except for those in the temporal superior sector [30]. It could alter research results, as decreased VD is frequently observed in chronic, long-lasting diseases, such as systemic lupus erythematosus.

Goker et al. published a very similar paper to those included in the review [31]. The review authors decided not to include the Goker et al. research article because it concerned not only patients with systemic lupus erythematosus, but the overall group of patients with connective tissue diseases treated with HCQ. However, the results of their study are similar

to the results of the above-mentioned studies included in the review. They revealed lower vessel densities of the fovea in both, the superficial capillary plexus and deep capillary plexus in patients taking HCQ. Patients in the study were on HCQ therapy for more than 5 years.

4.8. OCTA Types

Currently there are two main types of OCTA commonly used in clinical practice—swept source OCTA (SS-OCTA) and spectral domain OCTA (SD-OCTA). The first one uses a swept laser with 1050 nm wavelength and a single photodiode detector; the second one uses a superluminescent diode with 850 nm wavelength and spectrometer as the detector. The main advantages of SS-OCTA compared to SD-OCTA are faster scanning speed and, because of longer wavelength and higher power used, deeper penetration thus better visualization of structures below the retinal pigment epithelium though it reduces its axial resolution. The disadvantage of SS-OCTA is unfortunately the higher cost, which is why SD-OCTA devices are more widespread [32].

The parameters of upper and lower boundary of the generated slabs are preset by the software of OCTA device. Individual variations or alterations caused by retinal pathology may cause segmentation errors. To prevent that, each manufacturer of OCTA devices has its own technology and software to adjust for these changes or segmentation lines that may be adjusted manually by the operator.

One of the weaknesses of this relatively new diagnostic method is the fact that the quantitative parameters accompanying OCTA images may not be comparable when generated by different devices and parameters such as vessel density may even differ depending on the scan size (i.e., lower vessel density when comparing 6 mm × 6 mm scan with 3 mm × 3 mm scan); that is why all check-up exams should be carried out on the same device, using the same protocol [33].

Table 4 contains a summary of OCTA devices used in the reviewed articles.

Table 4. Summary of OCTA devices used in reviewed studies.

Name of OCTA	Methodology	Used in the Study by	Scan Speed	Wavelength	Optical Source	Axial Resolution
Optovue RTVue XR Avanti (Optovue, Inc., Fremont, CA, USA)	Spectral domain (SD)	Bao et al. [24], Pichi et al. [25], Conigliaro et al. [20], Mihailovic et al. [22], Arfeen et al. [26]	70,000 A-scans/s	840 nm	Superluminescent diode	Digital: 3 µm, in tissue 5 µm
Zeiss Cirrus 5000 system AngioPlexTM (Carl Zeiss Meditec, Dublin, CA, USA)	Spectral domain (SD)	Işık et al. [21]	68,000 A-scans/s	840 nm	Superluminescent diode	Digital: 1.95 µm, in tissue 5 µm
DRI OCT Triton plus (Topcon, Tokyo, Japan)	Swept Source (SS)	Forte et al. [23]	100,000 A-scans/s	1050 nm	Swept laser	Digital: 2.6 µm, in tissue 8 µm

Unfortunately, OCTA is not being widely used and recommended only in the specific clinical indications. We hope that in the future OCTA will be recommended in routine evaluation of patients with systemic diseases. Adding OCTA to the standard diagnostic process can lower the treatment cost of advanced SLE, enable earlier detection of organ changes, and protect the patient from serious complications.

The biggest limitation of the studies included in the review is a small number of patients enrolled and cross-sectional design. None of the studies performed a follow-up to detect the moment of retinopathy become symptomatic. The long-term nature of SLE disease and the prolonged use of the medications that can cause retinopathy may affect the results of the studies. In our opinion, further work should be designed to eliminate the

influence of HCQ on the results. The other limitations are: not calculating the cumulative dose of HCQ in four out of seven reviewed papers, not taking into account duration of HCQ therapy and age impact on VD, lack of disease activity indices, and a small field for the retinal microvasculature analysis.

The review itself is not free from limitations either. The authors did not obtain any additional data from the authors of the analyzed studies.

5. Conclusions

Retinal involvement in systemic lupus erythematosus may remain asymptomatic or mildly symptomatic for up to many years. Should its early detection prove beneficial in terms of further rheumatological treatment of SLE (i.e., controlling the disease activity with lower drug doses), it might be reasonable to introduce OCTA as a standard diagnostic tool in ophthalmic examination for all SLE patients. Studies on retinal microvasculature changes in asymptomatic SLE patients obtained by OCTA show a possible link between early stages of lupus retinopathy and decrease in retinal vessel density. It is reasonable to add OCTA to the standard diagnostic process of SLE patients, thanks to which it will be possible to detect systemic changes early and prevent further visual deterioration by stopping progression of lupus retinopathy. Results obtained by OCTA could be a good marker of SLE activity and prognosis. OCTA in a safe manner can give clinicians new perspective on a process of vessels remodeling and answer the question of how SLE might impact the eye in structural point of view. Longitudinal studies with patients divided into subgroups in terms of SLE and HCQ duration seem to better reflect the specific characteristics of the long-lasting disease and drug use and are necessary to measure the disease progression. SLE cohort seems to be a good study group to check new diagnostic possibilities in term of group homogeneity. Further research should answer the question of whether and when treatment should be started in patients with subclinical changes in the retina.

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References

1. Sitaula, R.; Narayan Shah, D.; Singh, D. The Spectrum of Ocular Involvement in Systemic Lupus Erythematosus in a Tertiary Eye Care Center in Nepal. *Ocul. Immunol. Inflamm.* **2011**, *19*, 422–425. [CrossRef]
2. Fortuna, G.; Brennan, M.T. Systemic Lupus Erythematosus. Epidemiology, Pathophysiology, Manifestations, and Management. *Dent. Clin. N. Am.* **2013**, *57*, 631–655. [CrossRef] [PubMed]
3. Herrmann, M.; Voll, R.E.; Kolowos, W.; Lorenz, H.M.; Kalden, J.R. Etiopathogenesis of Systemic Lupus Erythematosus (SLE). *Immunologist* **2000**, *8*, 66–71. [CrossRef]
4. Palejwala, N.V.; Walia, H.S.; Yeh, S. Ocular Manifestations of Systemic Lupus Erythematosus: A Review of the Literature. *Autoimmune Dis.* **2012**, *1*. [CrossRef] [PubMed]
5. Nangia, P.V.; Viswanathan, L.; Kharel, R.; Biswas, J. Retinal Involvement in Systemic Lupus Erythematosus. *Lupus Open Access* **2017**, *2*, 2–5.
6. Stafford-Brady, F.; Urowitz, M.; Gladman, D.; Easterbrook, M. Lupus Retinopathy: Patterns, Associations, and Prognosis. *Arthritis Rheum.* **1988**, *31*, 1105–1110. [CrossRef]
7. Seth, G.; Chengappa, K.G.; Misra, D.P.; Babu, R.; Belani, P.; Shanoj, K.C.; Kumar, G.; Negi, V.S. Lupus Retinopathy: A Marker of Active Systemic Lupus Erythematosus. *Rheumatol. Int.* **2018**, *38*, 1495–1501. [CrossRef]

8. Nguyen, Q.D.; Uy, H.S.; Akpek, E.K.; Harper, S.L.; Zacks, D.N.; Foster, C.S. Choroidopathy of Systemic Lupus Erythematosus. *Lupus* **2000**, *9*, 288–298. [CrossRef] [PubMed]
9. Bandyopadhyay, S.K.; Moulick, A.; Dutta, A. Retinal Vasculitis–an Initial Presentation of Systemic Lupus Erythematosus. *J. Indian Med. Assoc.* **2006**, *104*, 526–527.
10. Appel, G.B.; Pirani, C.L.; D'Agati, V. Renal Vascular Complications of Systemic Lupus Erythematosus. *J. Am. Soc. Nephrol.* **1994**, *4*, 1499–1515. [CrossRef] [PubMed]
11. D'Agati, V.D. Renal disease in systemic lupus erythematosus, mixed connective tissue disease, Sjogren's syndrome, and rhematoid arthritis. In *Heptinstall's Pathology of the Kidney*, 6th ed.; Jennette, J.C., Olson, I.L., Schwartz, M.M., Silva, F.G., Eds.; Lippincott Williams & Wilkins: Philadelphia, PA, USA, 2007.
12. Montehermoso, A.; Cervera, R.; Font, J.; Ramos-Casals, M.; García-Carrasco, M.; Formiga, F.; Callejas, J.L.; Jorfán, M.; Griñó, M.C.; Ingelmo, M. Association of Antiphospholipid Antibodies with Retinalvascular Disease in Systemic Lupus Erythematosus. *Semin. Arthritis Rheum.* **1999**, *28*, 326–332. [CrossRef]
13. Safi, H.; Safi, S.; Hafezi-Moghadam, A.; Ahmadieh, H. Early Detection of Diabetic Retinopathy. *Surv. Ophthalmol.* **2018**, *63*, 601–608. [CrossRef]
14. de Carlo, T.E.; Romano, A.; Waheed, N.K.; Duker, J.S. A Review of Optical Coherence Tomography Angiography (OCTA). *Int. J. Retin. Vitr.* **2015**, *1*, 1–15. [CrossRef]
15. Conigliaro, P.; Triggianese, P.; Draghessi, G.; Canofari, C.; Aloe, G.; Chimenti, M.S.; Valeri, C.; Nucci, C.; Perricone, R.; Cesareo, M. Evidence for the Detection of Subclinical Retinal Involvement in Systemic Lupus Erythematosus and Sjögren Syndrome: A Potential Association with Therapies. *Int. Arch. Allergy Immunol.* **2018**, *177*, 45–56. [CrossRef] [PubMed]
16. Lanzillo, R.; Cennamo, G.; Criscuolo, C.; Carotenuto, A.; Velotti, N.; Sparnelli, F.; Cianflone, A.; Moccia, M.; Brescia Morra, V. Optical Coherence Tomography Angiography Retinal Vascular Network Assessment in Multiple Sclerosis. *Mult. Scler.* **2018**, *24*, 1706–1714. [CrossRef] [PubMed]
17. Cheng, D.; Shen, M.; Zhuang, X.; Lin, D.; Dai, M.; Chen, S.; Lu, F.; Wang, Y. Inner Retinal Microvasculature Damage Correlates with Outer Retinal Disruption during Remission in Behçet's Posterior Uveitis by Optical Coherence Tomography Angiography. *Investig. Ophthalmol. Vis. Sci.* **2018**, *59*, 1295–1304. [CrossRef] [PubMed]
18. Makita, S.; Hong, Y.; Yamanari, M.; Yatagai, T.; Yasuno, Y. Optical Coherence Angiography. *Opt. Express* **2006**, *14*, 7821. [CrossRef] [PubMed]
19. Hosari, S.; Hohberger, B.; Theelke, L.; Sari, H.; Lucio, M.; Mardin, C.Y. OCT Angiography: Measurement of Retinal Macular Microvasculature with Spectralis II OCT Angiography-Reliability and Reproducibility. *Ophthalmologica* **2020**, *243*, 75–84. [CrossRef] [PubMed]
20. Conigliaro, P.; Cesareo, M.; Chimenti, M.S.; Triggianese, P.; Canofari, C.; Aloe, G.; Nucci, C.; Perricone, R. Evaluation of Retinal Microvascular Density in Patients Affected by Systemic Lupus Erythematosus: An Optical Coherence Tomography Angiography Study. *Ann. Rheum. Dis.* **2019**, *78*, 287–288. [CrossRef]
21. Işık, M.U.; Akmaz, B.; Akay, F.; Güven, Y.Z.; Solmaz, D.; Gercik, Ö.; Kabadayı, G.; Kurut, İ.; Akar, S. Evaluation of Subclinical Retinopathy and Angiopathy with OCT and OCTA in Patients with Systemic Lupus Erythematosus. *Int. Ophthalmol.* **2021**, *41*, 143–150. [CrossRef]
22. Mihailovic, N.; Leclaire, M.D.; Eter, N.; Brücher, V.C. Altered Microvascular Density in Patients with Systemic Lupus Erythematosus Treated with Hydroxychloroquine—An Optical Coherence Tomography Angiography Study. *Graefe Arch. Clin. Exp. Ophthalmol.* **2020**, *258*, 2263–2269. [CrossRef]
23. Forte, R.; Haulani, H.; Dyrda, A.; Jürgens, I. Swept Source Optical Coherence Tomography Angiography in Patients Treated with Hydroxychloroquine: Correlation with Morphological and Functional Tests. *Br. J. Ophthalmol.* **2019**, 1–6. [CrossRef] [PubMed]
24. Bao, L.; Zhou, R.; Wu, Y.; Wang, J.; Shen, M.; Lu, F.; Wang, H.; Chen, Q. Unique Changes in the Retinal Microvasculature Reveal Subclinical Retinal Impairment in Patients with Systemic Lupus Erythematosus. *Microvasc. Res.* **2020**, *129*, 103957. [CrossRef] [PubMed]
25. Pichi, F.; Woodstock, E.; Hay, S.; Neri, P. Optical Coherence Tomography Angiography Findings in Systemic Lupus Erythematosus Patients with No Ocular Disease. *Int. Ophthalmol.* **2020**, *40*, 2111–2118. [CrossRef] [PubMed]
26. Arfeen, S.A.; Bahgat, N.; Adel, N.; Eissa, M.; Khafagy, M.M. Assessment of Superficial and Deep Retinal Vessel Density in Systemic Lupus Erythematosus Patients Using Optical Coherence Tomography Angiography. *Graefe Arch. Clin. Exp. Ophthalmol.* **2020**, *258*, 1261–1268. [CrossRef]
27. Liu, G.Y.; Utset, T.O.; Bernard, J.T. Retinal Nerve Fiber Layer and Macular Thinning in Systemic Lupus Erythematosus: An Optical Coherence Tomography Study Comparing SLE and Neuropsychiatric SLE. *Lupus* **2015**, *24*, 1169–1176. [CrossRef]
28. Jallouli, M.; Galicier, L.; Zahr, N.; Aumaitre, O.; Frances, C.; Le Guern, V.; Liote, F.; Smail, A.; Limal, N.; Perard, L.; et al. Determinants of hydroxychloroquine blood con- centration variations in systemic lupus erythematosus. *Arthrit. Rheumatol.* **2015**, *67*, 2176–2184. [CrossRef]
29. Lee, J.Y.; Luc, S.; Greenblatt, D.J.; Kalish, R.; McAlindon, T.E. Factors associated with blood hydroxychloroquine level in lupus patients: Renal function could be important. *Lupus* **2013**, *22*, 541–542. [CrossRef]
30. Jo, Y.H.; Sung, K.R.; Shin, J.W. Effects of Age on Peripapillary and Macular Vessel Density Determined Using Optical Coherence Tomography Angiography in Healthy Eyes. *Investig. Ophthalmol. Vis. Sci.* **2019**, *60*, 3492–3498. [CrossRef] [PubMed]

31. Goker, Y.S.; Ucgul Atılgan, C.; Tekin, K.; Kızıltoprak, H.; Yetkin, E.; Yesil Karahan, N.; Koc, M.; Kosekahya, P. The Validity of Optical Coherence Tomography Angiography as a Screening Test for the Early Detection of Retinal Changes in Patients with Hydroxychloroquine Therapy. *Curr. Eye Res.* **2019**, *44*, 311–315. [CrossRef] [PubMed]
32. Lane, M.; Moult, E.M.; Novais, E.A.; Louzada, R.N.; Cole, E.D.; Lee, B.; Husvogt, L.; Keane, P.A.; Denniston, A.K.; Witkin, A.J.; et al. Visualizing the choriocapillaris under Drusen: Comparing 1050-nm swept-source versus 840-nm spectral-domain optical coherence tomography angiography. *Investig. Ophthalmol. Vis. Sci.* **2016**, *57*, 585–590. [CrossRef] [PubMed]
33. Rabiolo, A.; Gelormini, F.; Marchese, A.; Cicinelli, M.V.; Triolo, G.; Sacconi, R.; Querques, L.; Bandello, F.; Querques, G. Macular perfusion parameters in different angiocube sizes: Does the size matter in quantitative optical coherence tomography angiography? *Investig. Ophthalmol. Vis. Sci.* **2018**, *59*, 231–237. [CrossRef] [PubMed]

7.2. Evaluation of Subclinical Retinal Disease in Patients Affected by Systemic Lupus Erythematosus with No Evidence of Ocular Involvement—An Optical Coherence Tomography Angiography Original Study

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Evaluation of Subclinical Retinal Disease in Patients Affected by Systemic Lupus Erythematosus with No Evidence of Ocular Involvement—An Optical Coherence Tomography Angiography Original Study

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Abstract: Lupus retinopathy is the second most common eye involvement in systemic lupus erythematosus (SLE), associated with significant visual deterioration and well-known negative prognostic factor for survival. Ocular manifestation in SLE, relating the retina, ranges from asymptomatic vascular involvement to vision devastating vascular occlusions. Subclinical microvascular changes are undetectable in slit lamp examination, hence are underdiagnosed. Optical coherence tomography angiography (OCTA) is a novel, easy to interpret and non-invasive technique that allows retinal vessels visualization. OCTA simplifies clinical approach and measures the severity of decreased perfusion. The aim of the study was to demonstrate the retinal vascularization in a subclinical stage of ocular involvement in a cohort of SLE patients. Thirty-three patients (57 eyes) diagnosed with SLE were enrolled into the study group and 31 healthy individuals (56 eyes) into the control group. Vessel density reduction in parafovea, inferior and nasal quadrants of superficial retinal capillary plexus in a cohort of SLE patients was found. Among study group kidney involvement was associated with further microvasculature reduction. Knowing that retinal involvement may precede other organs impairment, early detection of retinal impairment and use of OCTA as a screening modality, may decrease overall disease morbidity.

Keywords: angiography (OCTA); systemic lupus erythematosus; retinal capillaries; subclinical retinal changes; vessel density

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1. Introduction

Systemic lupus erythematosus (SLE) is a heterogeneous connective tissue disease primarily affecting young women. Clinical presentation of this autoimmune disease may vary from mild cutaneous involvement to severe cardiovascular life-threatening complications.

Lupus retinopathy is the second most common eye involvement in SLE, associated with significant visual deterioration and well-known negative prognostic factor for survival. Retinopathy may be secondary to insufficient disease control. It may have different clinical manifestations such as microangiopathy, vascular-occlusive changes or true vasculitis [1]. Immune complex-mediated microangiopathy is the most common manifestation, affecting from 3 to 29% patients, with typically mild course and good visual outcome, unless the macula is involved. It is caused by inflammatory reaction secondary to adhesion of immune complexes deposits to the basement membrane of endothelium [2–4]. In fundus it is characterized by cotton wool spots, small intraretinal hemorrhages, microaneurysms, hard exudates or retinal edema, as well as papilledema [1–3,5]. Retinal vascular occlusions are located mainly in arteries, or in veins. Lack of perfusion in retinal capillaries that

results in ischemia, may lead to neovascularization, hemorrhage in the vitreous chamber, retinal detachment, or neovascular glaucoma. Severe vaso-occlusive disease, such as central retinal artery occlusion and central retinal vein occlusion, is observed in less than 1% of patients but is related to significant visual loss [2]. It is associated with fibrinoid degeneration or necrosis and is more prevalent in patients with antiphospholipid syndrome and antiphospholipid antibodies [6]. True retinal vasculitis, inflammation of venules or arterioles, is uncommon with acute presentation [1,7].

Lupus choroidopathy is less common than retinopathy, but it is also an indicator of high disease activity [8]. Its manifestations include serous retinal detachment, detachment of retinal pigment epithelium or retinal pigment epitheliopathy [5,8]. Drusen-like-deposits are more frequent in SLE patients [9,10]. They were present regardless of kidney involvement, but patients without nephritis have smaller and less numerous drusen [10].

Optical coherence tomography angiography (OCTA) is safer, faster, and easier to perform than fluorescein angiography and is used for the same medical indications [11]. It is a novel, non-invasive technique that allows retinal vessels visualization, in form of a high-resolution angiographic maps. OCTA simplifies clinical approach and measures the severity of decreased perfusion. Forte et al. confirmed OCTA strength in the detection of early microangiopathy in the absence of changes in visual acuity [12].

Retinal manifestation in SLE ranges from asymptomatic vascular involvement to vision devastating vascular occlusions. Subclinical microvascular changes are undetectable in slit lamp, hence are underdiagnosed. Several authors have showed an impaired retinal vessel density (VD) and reduced foveal avascular zone (FAZ), measured by OCTA, in patients affected by SLE with no ocular symptoms and with no history of ocular disease [12–18]. In these papers, there were shown conflicting results regarding the effect of SLE on FAZ area, effect of nephritis on VD and correlation between the disease activity indices and OCTA parameters [1]. Considering promising papers, our aim was to confirm abovementioned results and correlate them with extended rheumatological data. Our hypothesis was that OCTA would show altered microcirculation in ophthalmologically asymptomatic SLE patients and that level of impairment is correlated with disease activity.

Primary objective was to describe the retinal vascularization, by means of VD and FAZ, in a subclinical stage of ocular involvement and secondary objective was to investigate association between the morphology of the retina, SLE activity and damage index, kidney and CNS involvement, hydroxychloroquine (HCQ) and chloroquine (CQ) cumulative doses.

2. Materials and Methods

The study was approved by the Bioethics Committee of the Wroclaw Medical University (Poland) and before the examination all participants provided written informed consent.

Thirty-three patients (57 eyes) diagnosed with SLE, according to the American College of Rheumatology classification criteria, were enrolled into the study group and 31 healthy individuals (56 eyes) into the control group. Because of the poor quality of the scans, 3 patients (4 eyes) were excluded from the study group. Exclusion criteria included: age over 75 and below 18 years, any signs or history of SLE retinopathy, other eye diseases, drug-induced retinal damage, refractive error greater than –5 diopters, history of trauma or history of eye surgery within last 6 months. Patients from study group were asymptomatic, with no evidence of ocular involvement on fundus examination and in OCT. The study lasted from July 2019 to October 2021. Each patient enrolled into the study, was provided with a full ophthalmological examination, including best corrected visual acuity (BCVA), air puff intraocular pressure measurement (IOP), examination of the anterior and posterior segment of the eye in a slit lamp after pharmacological pupil dilatation with 1% Tropicamide, and OCTA examination. The results of laboratory and diagnostic tests, as well as questionnaires regarding SLE, were analyzed by experienced rheumatologist to quantify disease damage. The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) and The Systemic Lupus International Collaborating Clinics/American

College of Rheumatology Damage index (SLICC/ACR DI) were used to assess the disease severity and activity.

Regarding the numerical values of some parameters—concentration of: anti dsDNA [IU/mL] < 10 were considered as 0, >800 as 801, ACL IgM, IgG [U/mL] and anti-β2 GPI IgM, IgG [RU/mL] < 2 were considered as negative, ≥2 as positive, C4 [g/L] < 0.08 were considered as negative, ≥0.08 as positive.

All the patients underwent detailed retinal analysis with an automatically centered on the fovea, 6 × 6 mm OCTA scan and a radial OCT B-scan, using Swept-Source Optical Coherence Tomography Angio DRI OCT Triton Plus (Topcon Corp., Tokyo, Japan, 2015). OCTA evaluation included VD measurement in superficial retinal capillary plexus (SRCP) and deep retinal capillary plexus (DRCP) in five regions, similar to the Early Treatment Diabetic Retinopathy Study (ETDRS) subfields: fovea, superior, inferior, nasal, temporal and then manually averaged by authors into parafoveal and whole en face vessel density. The built-in software and algorithm were used for automated layer segmentation and vessel density measurement. SRCP was defined from 2.6 µm below internal limiting membrane (ILM) to 15.6 µm below the inner plexiform (IPL) and inner nuclear layers (INL) (IPL/INL) and DRCP 15.6 µm to 70.2 µm below IPL/INL.

To determine FAZ parameters from the SRCP: area, perimeter and circularity index, the OCTA images were exported as 320 × 320 pixels image and manually outlined and calculated using Adobe Photoshop version 23.0.1 (Adobe, Inc., San Jose, CA, USA, 2021) by the same, masked, experienced ophthalmologist. Circularity index was defined by $4\pi \times \text{area}/\text{perimeter}^2$. Value equal to 1.0 indicates a perfect circle, while values below 1.0 less circular shape of FAZ.

Data from both eyes of each patient was averaged prior to statistical analysis. Authors decided to use averaged data, because of systemic character of the SLE that should evenly affect both eyes. The averaged values, in authors opinion, demonstrates the patient's condition more clearly. They also lower the impact of an atypical patient course—significant asymmetrical eye involvement—on the final results.

Statistical analysis was performed using a STATISTICA 13.3 (StatSoft, Inc., Tulsa, OK, USA, 2017). The results with $p < 0.05$ were considered statistically significant. The Kolmogorov-Smirnow test was used to assess the normality of the distribution of the investigated quantitative features. Statistical analysis examining the differences between the individual measured parameters in the groups was performed using the U-Mann-Whitney test. The correlation between the measured parameters and quantitative clinical data was performed using the Spearman's rank correlation test. ANOVA (analysis of variance) test was used for more than two groups comparison. We have performed multiple regression analysis between statistically significant differences between control and study group with a check for autocorrelation using Durbin-Watson test and have added this value to the footnote of each table (Supplementary Tables S1–S5). We have done power analysis for our main comparison (OCTA parameters between SLE patients and control group)—Supplementary Table S6, and for multiple regression analysis—Supplementary Table S7.

3. Results

All the collected data regarding patients' characteristics, SLE activity and treatment are summarized in Tables 1 and 2.

Table 1. Basic characteristics.

	Study Group (n = 30)	Control Group (n = 31)	p Value
Age (years)	46.07 ± 14.09	44.55 ± 14.11	0.69
Gender (male/female)	5/25	4/27	0.69
Visual acuity (logMAR)	0.01 ± 0.02	0.0	0.02
IOP (mmHg)	15.98 ± 2.4	16.04 ± 2.05	0.82
Disease duration (months)	101.8 ± 89.98	N/A	N/A
SLEDAI-2K	5.2 ± 4.39	N/A	N/A
SLICC/ACR DI	1.3 ± 1.2	N/A	N/A
HCQ cumulative dose (g)	391.23 ± 425.52	N/A	N/A
Anti dsDNA [IU/mL]	316.07 ± 263.16	N/A	N/A
ACL IgM (positive)	12	N/A	N/A
ACL IgG (positive)	29	N/A	N/A
anti-β2 GPI IgG [RU/mL]	28	N/A	N/A
anti-β2 GPI IgM [RU/mL]	19	N/A	N/A
LAC [s]	46.75 ± 31.2	N/A	N/A
C3 [g/L]	0.94 ± 0.31	N/A	N/A
C4 (positive)	5	N/A	N/A
ERS [mm/h]	19.97 ± 24.6	N/A	N/A

IOP—intraocular pressure, SLEDAI-2K—Systemic Lupus Erythematosus Disease Activity Index 2000, SLICC/ACR DI—The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage index, HCQ—hydroxychloroquine, Anti dsDNA—Anti-double stranded DNA antibodies, ACL—Anti-cardiolipin antibodies, anti-β2 GPI—Anti-β2-glycoprotein I antibodies, C3, C4—complement system, LAC—lupus anticoagulant, ERS—erythrocyte sedimentation rate, N/A—not applicable. Normal ranges: Anti dsDNA: 0–100 IU/mL—negative, >100 IU/mL—positive; ACL IgM: 0–20 U/mL, ACL IgG: 0–20 U/mL, anti-β2 GPI IgG: 0–20 U/mL, anti-β2 GPI IgM: 0–20 U/mL; LAC: 30.5–40.6 s, C3: 0.75–2.0 g/L, C4: 0.1–0.3 g/L, ERS: 1–15 mm/h.

Table 2. Rheumatological treatment.

	Positive	Negative
HCQ < 5 years/HCQ > 5 years	17/13	N/A
Kidney involvement	6	24
CNS involvement	3	27
HCQ	30	0
Chloroquine	12	18
Prednisolone	3	27
Azathioprine	11	19
Cyclophosphamide	4	26
Methotrexate	13	17
Leflunomide	1	29
Rituximab	1	29

HCQ—hydroxychloroquine, CNS—central nervous system, N/A—not applicable.

There was no significant difference in age, gender, IOP, vessel density in DRCP and FAZ perimeter between SLE patients and healthy controls. There was no difference among analyzed parameters between men (n—5) and women (n—25) in study group, as well as, in whole cohort of patients (n—52, n—9).

Visual acuity was significantly lower (p = 0.019) in SLE patients than in the control group. The eyes from SLE patients had lower superficial parafoveal vessel density (p = 0.018) as well as in inferior (p = 0.038) and nasal (p = 0.018) quadrants compared to the control group. FAZ area and FAZ circularity index (p = 0.035, p = 0.008) were reduced in patients suffering from SLE. Comparison of OCTA parameters between study and control group is shown in Table 3.

Table 3. Comparison of OCTA parameters.

	Study Group (n = 30)	Control Group (n = 31)	p Value
VD SRCP %—fovea	22.16 ± 3.63	20.14 ± 3.76	0.08
VD SRCP—superior	48.68 ± 2.69	49.52 ± 2.01	0.56
VD SRCP—inferior	48.82 ± 2.36	50.08 ± 2.44	0.04
VD SRCP—nasal	45.82 ± 1.83	46.99 ± 1.57	0.02
VD SRCP—temporal	46.7 ± 2.65	47.45 ± 2.5	0.19
VD SRCP—parafovea	47.51 ± 1.43	48.51 ± 1.5	0.02
VD SRCP—whole en face	44.69 ± 1.4	45.36 ± 1.32	0.13
VD DRCP %—fovea	20.88 ± 4.03	18.94 ± 3.89	0.16
VD DRCP—superior	52.27 ± 2.95	52.98 ± 2.42	0.52
VD DRCP—inferior	52.48 ± 2.43	53.59 ± 2.5	0.12
VD DRCP—nasal	50.08 ± 2.18	50.52 ± 1.99	0.37
VD DRCP—temporal	49.73 ± 2.86	50.31 ± 2.81	0.34
VD DRCP—parafovea	51.14 ± 1.7	51.85 ± 1.73	0.1
VD DRCP—whole en face	47.78 ± 1.59	48.2 ± 1.52	0.39
FAZ—area	0.16 ± 0.07	0.2 ± 0.08	0.03
FAZ—perimeter	1.53 ± 0.36	1.67 ± 0.36	0.11
FAZ—circularity index	0.79 ± 0.09	0.94 ± 0.63	0.01

VD—vessel density, SRCP—superficial retinal capillary plexus, DRCP—deep retinal capillary plexus, FAZ—foveal avascular zone.

Statistically significant positive correlation between HCQ cumulative dose and vessel density in SRCP (R = 0.422, p = 0.020) and DRCP (R = 0.382, p = 0.037) in superior quadrants was demonstrated. VD in superior quadrant of SRCP was also increased in SLE patients treated with HCQ for more than 5 years compared to patients with HCQ therapy for less than 5 years. (p = 0.022). Comparison of OCTA parameters among SLE patients based on HCQ treatment duration is shown in Table 4.

Table 4. Comparison of OCTA parameters among SLE patients based on HCQ treatment duration.

	>5 Years (n = 13)	<5 Years (n = 17)	p Value
VD SRCP %—fovea	21.8 ± 3.43	22.43 ± 3.86	0.56
VD SRCP—superior	49.74 ± 1.62	47.88 ± 3.09	0.02
VD SRCP—inferior	47.85 ± 2.12	49.57 ± 2.32	0.07
VD SRCP—nasal	46.1 ± 2.14	45.61 ± 1.6	0.65
VD SRCP—temporal	46.49 ± 1.58	46.86 ± 3.28	0.43
VD SRCP—parafovea	47.54 ± 1.23	47.48 ± 1.61	0.9
VD SRCP—whole en face	44.68 ± 1.32	44.69 ± 1.5	0.97
VD DRCP %—fovea	20.63 ± 3.47	21.06 ± 4.51	0.93
VD DRCP—superior	53.3 ± 1.73	51.49 ± 3.47	0.07
VD DRCP—inferior	51.61 ± 2.47	53.15 ± 2.26	0.12
VD DRCP—nasal	50.52 ± 2.34	49.75 ± 2.05	0.45
VD DRCP—temporal	49.62 ± 1.76	49.81 ± 3.53	0.48
VD DRCP—parafovea	51.26 ± 1.32	51.05 ± 1.98	0.97
VD DRCP—whole en face	47.86 ± 1.35	47.72 ± 1.8	0.9
FAZ—area	0.15 ± 0.08	0.16 ± 0.06	0.65
FAZ—perimeter	1.5 ± 0.43	1.55 ± 0.31	0.5
FAZ—circularity index	0.79 ± 0.07	0.78 ± 0.11	0.77

VD—vessel density, SRCP—superficial retinal capillary plexus, DRCP—deep retinal capillary plexus, FAZ—foveal avascular zone.

Twelve patients with SLE were taking chloroquine. There was lower VD in temporal quadrant of DRCP compared to patients without chloroquine therapy, but no difference between chloroquine cumulative dose and OCTA parameters, including VD. Eleven patients from study group were using azathioprine. There was no difference in analyzed

parameters compared to SLE patients that were not using azathioprine. Thirteen patients from study group were using methotrexate. Our study revealed lower VD in superficial capillary plexus in inferior quadrant in SLE patients treated with methotrexate ($p = 0.03$). Comparisons of OCTA parameters among SLE patient using methotrexate, azathioprine and chloroquine are summarized in Tables 5–7.

Table 5. Comparison of OCTA parameters among SLE patient using Methotrexate.

	Positive ($n = 13$)	Negative ($n = 17$)	p Value
VD SRCP %—fovea	21.33 ± 3	22.79 ± 4.03	0.34
VD SRCP—superior	49.29 ± 1.71	48.22 ± 3.22	0.43
VD SRCP—inferior	47.66 ± 2.24	49.71 ± 2.1	0.03
VD SRCP—nasal	45.99 ± 1.96	45.69 ± 1.78	0.9
VD SRCP—temporal	46.06 ± 1.48	47.19 ± 3.24	0.07
VD SRCP—parafovea	47.25 ± 1.29	47.7 ± 1.54	0.32
VD SRCP—whole en face	44.37 ± 1.18	44.93 ± 1.54	0.21
VD DRCP %—fovea	19.98 ± 3.53	21.56 ± 4.36	0.34
VD DRCP—superior	52.74 ± 1.77	51.92 ± 3.62	0.93
VD DRCP—inferior	51.5 ± 2.51	53.23 ± 2.16	0.05
VD DRCP—nasal	49.81 ± 1.68	50.29 ± 2.52	0.43
VD DRCP—temporal	49.38 ± 1.68	49.99 ± 3.54	0.19
VD DRCP—parafovea	50.86 ± 1.32	51.36 ± 1.96	0.3
VD DRCP—whole en face	47.43 ± 1.21	48.05 ± 1.82	0.18
FAZ—area	0.17 ± 0.07	0.15 ± 0.07	0.28
FAZ—perimeter	1.63 ± 0.34	1.46 ± 0.37	0.22
FAZ—circularity index	0.8 ± 0.07	0.78 ± 0.11	0.62

VD—vessel density, SRCP—superficial retinal capillary plexus, DRCP—deep retinal capillary plexus, FAZ—foveal avascular zone.

Table 6. Comparison of OCTA parameters among SLE patient using Azathioprine.

	Positive ($n = 11$)	Negative ($n = 19$)	p Value
VD SRCP %—fovea	23.44 ± 4.24	21.42 ± 3.11	0.16
VD SRCP—superior	48.02 ± 3.6	49.07 ± 2.01	0.23
VD SRCP—inferior	49.79 ± 2.39	48.26 ± 2.22	0.14
VD SRCP—nasal	45.22 ± 1.75	46.17 ± 1.83	0.26
VD SRCP—temporal	46.52 ± 3.91	46.8 ± 1.65	1
VD SRCP—parafovea	47.39 ± 1.72	47.57 ± 1.28	0.86
VD SRCP—whole en face	44.73 ± 1.74	44.67 ± 1.21	0.73
VD DRCP %—fovea	22.34 ± 4.95	20.03 ± 3.25	0.23
VD DRCP—superior	51.38 ± 4.06	52.79 ± 2.03	0.25
VD DRCP—inferior	53.11 ± 1.93	52.12 ± 2.66	0.41
VD DRCP—nasal	49 ± 2.13	50.71 ± 1.99	0.05
VD DRCP—temporal	49.02 ± 4.07	50.14 ± 1.87	0.55
VD DRCP—parafovea	50.63 ± 2.01	51.44 ± 1.48	0.21
VD DRCP—whole en face	47.48 ± 1.96	47.95 ± 1.37	0.37
FAZ—area	0.12 ± 0.07	0.18 ± 0.06	0.07
FAZ—perimeter	1.33 ± 0.39	1.65 ± 0.29	0.05
FAZ—circularity index	0.76 ± 0.14	0.8 ± 0.05	0.73

VD—vessel density, SRCP—superficial retinal capillary plexus, DRCP—deep retinal capillary plexus, FAZ—foveal avascular zone.

Lupus nephropathy was observed in 6 patients in our study group. Patients with SLE and nephritis had lower whole en face superficial vessel density ($p = 0.004$), superficial parafoveal density ($p = 0.007$) and superficial density in nasal ($p = 0.02$) and temporal ($p = 0.02$) quadrants compared with patients with SLE without kidney involvement. Comparison of OCTA parameters among SLE patient with kidney involvement is presented in Table 8.

Table 7. Comparison of OCTA parameters among SLE patient using Chloroquine.

	Positive (n = 12)	Negative (n = 18)	p Value
VD SRCP %—fovea	21.14 ± 3.19	22.83 ± 3.84	0.28
VD SRCP—superior	48.81 ± 3.6	48.6 ± 1.99	0.47
VD SRCP—inferior	48.63 ± 3.16	48.95 ± 1.73	0.75
VD SRCP—nasal	45.7 ± 2.22	45.9 ± 1.59	0.48
VD SRCP—temporal	45.6 ± 3.09	47.44 ± 2.08	0.09
VD SRCP—parafovea	47.18 ± 1.88	47.72 ± 1.03	0.39
VD SRCP—whole en face	44.29 ± 1.8	44.96 ± 1.04	0.46
VD DRCP %—fovea	20.02 ± 3.75	21.45 ± 4.22	0.43
VD DRCP—superior	52.11 ± 4	52.38 ± 2.12	0.85
VD DRCP—inferior	51.99 ± 3.06	52.81 ± 1.94	0.41
VD DRCP—nasal	49.68 ± 2.08	50.35 ± 2.26	0.45
VD DRCP—temporal	48.35 ± 3.44	50.64 ± 2.02	0.03
VD DRCP—parafovea	50.54 ± 2.14	51.55 ± 1.25	0.18
VD DRCP—whole en face	47.14 ± 2.03	48.2 ± 1.09	0.17
FAZ—area	0.17 ± 0.06	0.15 ± 0.07	0.69
FAZ—perimeter	1.58 ± 0.29	1.5 ± 0.4	0.78
FAZ—circularity index	0.81 ± 0.06	0.77 ± 0.11	0.11

VD—vessel density, SRCP—superficial retinal capillary plexus, DRCP—deep retinal capillary plexus, FAZ—foveal avascular zone.

Table 8. Comparison of OCTA parameters among SLE patient with kidney involvement.

	Positive (n = 6)	Negative (n = 24)	p Value
VD SRCP %—fovea	19.99 ± 2.76	22.7 ± 3.67	0.13
VD SRCP—superior	46.83 ± 3.76	49.15 ± 2.22	0.05
VD SRCP—inferior	49.26 ± 3.21	48.71 ± 2.18	0.82
VD SRCP—nasal	44.26 ± 1.61	46.21 ± 1.7	0.02
VD SRCP—temporal	44.23 ± 3.46	47.32 ± 2.05	0.02
VD SRCP—parafovea	46.14 ± 1.19	47.85 ± 1.29	0.01
VD SRCP—whole en face	43.24 ± 1.29	45.05 ± 1.19	<0.01
VD DRCP %—fovea	18.49 ± 2.02	21.47 ± 4.22	0.11
VD DRCP—superior	50.74 ± 4.73	52.66 ± 2.32	0.36
VD DRCP—inferior	52.96 ± 2.52	52.36 ± 2.45	0.98
VD DRCP—nasal	49.5 ± 2.96	50.23 ± 1.99	0.45
VD DRCP—temporal	47.56 ± 4.49	50.27 ± 2.1	0.14
VD DRCP—parafovea	50.19 ± 2.26	51.38 ± 1.5	0.22
VD DRCP—whole en face	46.67 ± 2.15	48.06 ± 1.34	0.13
FAZ—area	0.19 ± 0.03	0.15 ± 0.07	0.14
FAZ—perimeter	1.72 ± 0.17	1.48 ± 0.38	0.07
FAZ—circularity index	0.81 ± 0.03	0.78 ± 0.1	0.82

VD—vessel density, SRCP—superficial retinal capillary plexus, DRCP—deep retinal capillary plexus, FAZ—foveal avascular zone.

Among study group a parafoveal VD in DRCP decreased with age.

No correlations were revealed between examined OCTA parameters and C4, LAC, AnuA, anty-ß2 GPI IgM and IgG, Anti dsDNA and ACL IgG concentrations and ESR. Association between increase in ACL IgM concentration on decrease of VD in DRCP in fovea and increase in C3 on decrease VD in DRCP in superior quadrant was observed—but these results may be incidental because of small study group.

The effect of neuropsychiatric SLE, rituximab, leflunomide, cyclophosphamide and prednisolone usage on the retinal changes was also analyzed. Due to the insufficient size of these groups (neuropsychiatric SLE—3, rituximab—1, leflunomide—1, cyclophosphamide—4, prednisolone—3), the results are unreliable.

No correlation was found between the SLICC/ACR and the SLEDAI-2K scores and the retinal vessel density in superficial and deep retinal capillary plexus and FAZ.

We have performed multiple regression analysis between statistically significant differences between control and study group (VD SRCP inferior, VD SRCP nasal, VD SRCP parafovea, FAZ area and FAZ circularity index) with the following variables: age, gender, visual acuity, disease duration, disease severity, renal involvement, HCQ total dose, chloroquine use, azathioprine use, methotrexate use. The analysis showed that in the case of VD SRCP parafovea, only kidney involvement is a statistically significant predictor and almost reach statistical significance for VD SRCP nasal (p = 0.052773). For the FAZ area, such a predictor is the use of azathioprine. The FAZ circularity index does not have such a predictor among the listed data (Supplementary Tables S1–S5).

Values in Tables 1–8 are presented as mean ± standard deviation.

4. Discussion

The microvascular changes in SLE play an extremely important role in disease morbidity and mortality. The involvement of posterior segment of the eye may mirror other organs vascular involvement [19–21]. Well known clinical tools that can assess the morphological changes in patients' microvasculature are capillaroscopy, laser Doppler flowmetry and laser speckle contrast imaging [21]. The eye, through the pupil, allows for a view of small vessels and capillaries of the retina and choroid.

Our study revealed lower VD in parafovea, inferior and nasal quadrants of SRCP and reduction of FAZ area and FAZ circularity index in SLE patients. Our results concerning FAZ are at odds to Forte et al., Pichi et al., Mihailovic et al. and An et al. findings [12,14,15,22]. Some authors link enlargement of the FAZ with hypoperfusion in the retinal vessels, tissue hypoxia, and retinal cell death in patient with subclinical SLE [15]. However, large individual variations of the FAZ size and shape in healthy subject have been found [23]. Also, the measurement of the FAZ area may be challenging as the area is very irregular with many entering capillaries.

Bao et al. found out significant decrease in vascular density in the SRCP among patients diagnosed with lupus but without signs of lupus retinopathy and decrease in VD in both SRCP and DRCP in patients with lupus retinopathy [17]. According to Bao et al. subclinical retinal microvasculature impairment precedes proper lupus retinopathy development, making it the early marker of lupus retinopathy. The process may be caused by immune-complex deposition in vessels endothelium leading to retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) atrophy [15,17,24]. Authors speculate that SRCP and then DRCP impairment led to insufficient oxygen and nutrient supply to inner retina causing changes in the retina structure contributing to the development of lupus retinopathy. On the other hand, Arfeen et al. results showed the decrease VD in the DRCP in all sectors, while some of the quadrants in the SRCP showed no significant difference [16]. An et al. achieved similar results [22]. Authors suggest that DRCP is the most vulnerable to early impairment, because of its anatomical position and the role of inner retina blood supply, compared to other vessel networks. DRCP impairment can be consider as an early disease activity and damage biomarker. DRCP tends to gradual obstruction follows by hemodynamic dysfunction [16,25]. As a consequence, it may lead to photoreceptors integrity loss, but future studies are necessary to confirm the thesis [26].

Visual acuity was also statistically significant lower in SLE patients, which may be secondary to the degree of capillary loss, but this correlation is uncertain, and data is limited [27–29]. Some authors associate decreased visual acuity with the perfusion status of DRCP [28,30]. All enrolled patients were clinically asymptomatic—they did not report any impairment in visual acuity. Decreased BCVA (logMAR) in ophthalmological examination, was found only in five eyes—four eyes 0.1, one eye 0.2 in study group. This clinically insignificant difference happened to be statistically significant.

In contrast to Conigliaro et al. and Arfeen et al. results., our study has revealed no correlation between the SLICC/ACR and the SLEDAI-2K scores and the retinal microvascular alterations [13,16]. Our results were compatible with Pichi et al. [15]. However, the association between retinal vessels remodeling with the involvement of other organs was

shown. Patients with SLE and nephritis had lower whole en face superficial vessel density, superficial parafoveal density and superficial density in nasal and temporal quadrants compared with patients with SLE without kidney involvement. In Conigliaro et al. study patients with kidney involvement had also reduced superficial parafoveal vessel density compared with SLE patients without nephritis [13].

SLE patients are especially vulnerable group for retinal ischemia development. Both, SLE itself and SLE drug therapy (hydroxychloroquine, chloroquine, glucocorticosteroids, methotrexate, cyclosporine-A), can irreversibly damage the retina and be responsible for severe visual deterioration, as well as may overlap and confuse the study findings [31–33]. HCQ is widely used in SLE treatment with good efficacy, disease control, patient's tolerance but few side effects. Toxic drug-related retinopathy is one of the most dangerous side effects associated with HCQ cumulative dosage [34]. After 5 years of HCQ therapy, the risk of toxic retinopathy increases dramatically, while up to 5 years of treatment is less than 1% [35]. In the current study VD in superior quadrant of SRCP was increased in SLE patients treated with HCQ for more than 5 years compared to patients with HCQ therapy for less than 5 years. Our study revealed also positive correlation between HCQ cumulative dose and vessel density in SRCP and DRCP. These positive correlations might be indicative of protective function of HCQ on ocular microvasculature, even if it relates to longer SLE duration. Our study revealed lower VD in SRCP in inferior quadrant in SLE patients treated with methotrexate compared to SLE patients with no history of methotrexate therapy. Methotrexate may be responsible for ischemic retinal complications but futured studies are necessary to evaluate the correlation with VD [18].

Current paper found a negative correlation, among study group, between age and parafoveal VD in DRCP. Those findings are in alignment with Conigliaro et al. results where the correlation between age and superficial whole en face density, superficial foveal density, superficial parafoveal density and deep whole en face density was also showed [13]. VD tends to decline during process of aging [36,37]. Because vessel density correlates with age and may alternate the results obtained in studies detecting retinal microvascular changes in long-lasting systemic disease, this impact should be considered in futures studies.

Altered microcirculation in retina has been found in many autoimmune diseases, such as Crohn's disease, ulcerative colitis, and rheumatoid arthritis [38]. Debourdeau et al. have shown reduced VD in SRCP and radial peripapillary capillaries and larger FAZ in patients with severe Crohn's disease [38]. These patients had increased FAZ area and reduced VD in radial peripapillary capillaries compared to patients with moderate Crohn's disease. The study suggests that VD evaluated by OCTA, might be a useful biomarker of disease severity. Our study also showed reduced VD in SRCP in SLE group, but the measurements of FAZ area were opposite to Debourdeau et al. Despite no correlation of VD with disease severity index in our study, kidney involvement among SLE group was associated with further microvasculature reduction.

In Arnould et al. study, VD in SRCP was associated with the cardiovascular (CV) risk profile [39]. This suggests that retina impairment, measured by OCTA, may reflect increased CV risk thus may predict cardiac events. We have not collected data about past CV events nor coexisting CV risk factors e.g., smoking, dyslipidemia, obesity, hypertension, or diabetes. Further studies should collect data about patients CV and rheumatological status for more accurate results.

The strengths of the study were: the size of the rheumatological data, the patients division in terms of duration of HCQ therapy, the calculation of cumulative dose of HCQ and disease activity indices. The major limitations were small sample size and cross-sectional study design and lack of cardiovascular risk profile of patients.

5. Conclusions

In conclusion, we demonstrated vessel density reduction in a cohort of SLE patients compared to healthy individuals. Among study group kidney involvement was associated with further microvasculature reduction. FAZ area and FAZ circularity index were reduced

in patients suffering from SLE, however, in our opinion, they are not as informative as the VD and may vary among individuals.

Performing the eye angiography with OCTA procedure is considered a milestone in ophthalmology. In authors opinion, growing interest, availability, familiarity with OCTA, as well as awareness of the device advantages will be the reason of more common OCTA usage in interdisciplinary conditions, especially autoimmune diseases. Vessel density assessment obtained by OCTA should be considered at the time of SLE diagnosis and included in disease activity index. Knowing that retinal involvement may precede other organs impairment, the ophthalmological assessment is essential in the overall patient evaluation. Further studies are necessary to answer the question how to implement these findings into patient's care, including management and treatment modification. The multi-organ changes characterizing SLE emphasize the extremely important role of a holistic, interdisciplinary approach to both disease diagnosis, as well as its management and treatment. Early detection of retinal impairment and use OCTA as a screening modality, may decrease overall disease morbidity. Of great importance are novel diagnostic tools at the time of diagnosis and follow-up because of long-lasting character of all the autoimmune diseases.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11247417/s1, Table S1: Multiple regression analysis between VD SRCP nasal and the following variables; Table S2: Multiple regression analysis between VD SRCP parafovea and the following variables; Table S3: Multiple regression analysis between VD SRCP inferior and the following variables; Table S4: Multiple regression analysis between FAZ area and the following variables; Table S5: Multiple regression analysis between FAZ Circularity index and the following variables; Table S6: Power analysis for comparison of OCTA parameters between SLE and control group; Table S7: Power analysis for multiple regression analysis.

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References

1. Mimier-Janczak, M.; Kaczmarek, D.; Janczak, D.; Kaczmarek, R. Optical Coherence Tomography Angiography as a New Tool for Evaluation of the Subclinical Retinal Involvement in Patients with Systemic Lupus Erythematosus—A Review. *J. Clin. Med.* **2021**, *10*, 2887. [CrossRef] [PubMed]
2. Seth, G.; Chengappa, K.G.; Misra, D.P.; Babu, R.; Belani, P.; Shanoj, K.C.; Kumar, G.; Negi, V.S. Lupus Retinopathy: A Marker of Active Systemic Lupus Erythematosus. *Rheumatol. Int.* **2018**, *38*, 1495–1501. [CrossRef] [PubMed]
3. Dammacco, R. Systemic Lupus Erythematosus and Ocular Involvement: An Overview. *Clin. Exp. Med.* **2018**, *18*, 135–149. [CrossRef] [PubMed]
4. Giorgi, D.; Pace, F.; Giorgi, A.; Bonomo, L.; Gabrieli, C.B. Retinopathy in Systemic Lupus Erythematosus: Pathogenesis and Approach to Therapy. *Hum. Immunol.* **1999**, *60*, 688–696. [CrossRef]
5. Conigliaro, P.; Cesareo, M.; Chimenti, M.S.; Triggianese, P.; Canofari, C.; Barbato, C.; Giannini, C.; Salandri, A.G.; Nucci, C.; Perricone, R. Take a Look at the Eyes in Systemic Lupus Erythematosus: A Novel Point of View. *Autoimmun. Rev.* **2019**, *18*, 247–254. [CrossRef]

6. Palejwala, N.V.; Walia, H.S.; Yeh, S. Ocular Manifestations of Systemic Lupus Erythematosus: A Review of the Literature. *Autoimmune Dis.* **2012**, *2012*, 290898. [CrossRef]
7. De Azevedo, L.G.B.; Biancardi, A.L.; Silva, R.A.; da Tavares, N.C.; de Abreu, M.M.; Bica, B.E.R.G.; de Moraes, H.V., Jr. Lupus Retinopathy: Epidemiology and Risk Factors TT—Retinopatia Lúpica: Epidemiologia e Fatores de Risco. *Arq. Bras. Oftalmol* **2021**, *84*, 395–401. [CrossRef]
8. Dias-Santos, A.; Tavares Ferreira, J.; Pinheiro, S.; Paulo Cunha, J.; Alves, M.; Papoila, A.; Moraes-Fontes, M.F.; Proença, R. Choroidal Thickness Changes in Systemic Lupus Erythematosus Patients. *Clin. Ophthalmol.* **2019**, *13*, 1567–1578. [CrossRef]
9. Baglio, V.; Gharbiya, M.; Balacco-Gabrieli, C.; Mascaro, T.; Gangemi, C.; Di Franco, M.; Pistolesi, V.; Morabito, S.; Pecci, G.P. Choroidopathy in Patients with Systemic Lupus Erythematosus with or without Nephropathy. *J. Nephrol.* **2011**, *24*, 522–529. [CrossRef]
10. Invernizzi, A.; dell'Arti, L.; Leone, G.; Galimberti, D.; Garoli, E.; Moroni, G.; Santaniello, A.; Agarwal, A.; Viola, F. Drusen-like Deposits in Young Adults Diagnosed With Systemic Lupus Erythematosus. *Am. J. Ophthalmol.* **2017**, *175*, 68–76. [CrossRef]
11. Savastano, M.C.; Rispoli, M.; Lumbroso, B.; Di Antonio, L.; Mastropasqua, L.; Virgili, G.; Savastano, A.; Bacherini, D.; Rizzo, S. Fluorescein Angiography versus Optical Coherence Tomography Angiography: FA vs OCTA Italian Study. *Eur. J. Ophthalmol.* **2021**, *31*, 514–520. [CrossRef] [PubMed]
12. Forte, R.; Haulani, H.; Dyrda, A.; Jürgens, I. Swept Source Optical Coherence Tomography Angiography in Patients Treated with Hydroxychloroquine: Correlation with Morphological and Functional Tests. *Br. J. Ophthalmol.* **2019**, *105*, 1297–1301. [CrossRef] [PubMed]
13. Conigliaro, P.; Cesareo, M.; Chimenti, M.S.; Triggianese, P.; Canofari, C.; Aloe, G.; Nucci, C.; Perricone, R. Evaluation of Retinal Microvascular Density in Patients Affected by Systemic Lupus Erythematosus: An Optical Coherence Tomography Angiography Study. *Ann. Rheum. Dis.* **2019**, *78*, 287–288. [CrossRef] [PubMed]
14. Mihailovic, N.; Leclaire, M.D.; Eter, N.; Brücher, V.C. Altered Microvascular Density in Patients with Systemic Lupus Erythematosus Treated with Hydroxychloroquine—An Optical Coherence Tomography Angiography Study. *Graefe's Arch. Clin. Exp. Ophthalmol.* **2020**, *258*, 2263–2269. [CrossRef]
15. Pichi, F.; Woodstock, E.; Hay, S.; Neri, P. Optical Coherence Tomography Angiography Findings in Systemic Lupus Erythematosus Patients with No Ocular Disease. *Int. Ophthalmol.* **2020**, *40*, 2111–2118. [CrossRef]
16. Arfeen, S.A.; Bahgat, N.; Adel, N.; Eissa, M.; Khafagy, M.M. Assessment of Superficial and Deep Retinal Vessel Density in Systemic Lupus Erythematosus Patients Using Optical Coherence Tomography Angiography. *Graefe's Arch. Clin. Exp. Ophthalmol.* **2020**, *258*, 1261–1268. [CrossRef]
17. Bao, L.; Zhou, R.; Wu, Y.; Wang, J.; Shen, M.; Lu, F.; Wang, H.; Chen, Q. Unique Changes in the Retinal Microvasculature Reveal Subclinical Retinal Impairment in Patients with Systemic Lupus Erythematosus. *Microvasc. Res.* **2020**, *129*, 103957. [CrossRef]
18. Işık, M.U.; Akmaz, B.; Akay, F.; Güven, Y.Z.; Solmaz, D.; Gercik, Ö.; Kabadayı, G.; Kurut, İ.; Akar, S. Evaluation of Subclinical Retinopathy and Angiopathy with OCT and OCTA in Patients with Systemic Lupus Erythematosus. *Int. Ophthalmol.* **2021**, *41*, 143–150. [CrossRef] [PubMed]
19. Hasanreisoglu, M.; Gulpinar Ikiz, G.D.; Kucuk, H.; Varan, O.; Ozdek, S. Acute Lupus Choroidopathy: Multimodal Imaging and Differential Diagnosis from Central Serous Chorioretinopathy. *Int. Ophthalmol.* **2018**, *38*, 369–374. [CrossRef]
20. Stafford-Brady, F.; Urowitz, M.; Gladman, D.; Easterbrook, M. Lupus Retinopathy: Patterns, Associations, and Prognosis. *Arthritis Rheum.* **1988**, *31*, 1105–1110. [CrossRef]
21. Saygin, D.; Highland, K.B.; Tonelli, A.R. Microvascular Involvement in Systemic Sclerosis and Systemic Lupus Erythematosus. *Microcirculation* **2019**, *26*, e12440. [CrossRef]
22. An, Q.; Gao, J.; Liu, L.; Liao, R.; Shuai, Z. Analysis of Foveal Microvascular Abnormalities in Patients with Systemic Lupus Erythematosus Using Optical Coherence Tomography Angiography. *Ocul. Immunol. Inflamm.* **2021**, *29*, 1392–1397. [CrossRef] [PubMed]
23. Chui, T.Y.P.; Zhong, Z.; Song, H.; Burns, S.A. Foveal Avascular Zone and Its Relationship to Foveal Pit Shape. *Optom. Vis. Sci.* **2012**, *89*, 602–610. [CrossRef] [PubMed]
24. Cao, X.; Bishop, R.J.; Forooghian, F.; Cho, Y.; Fariss, R.N.; Chan, C.-C. Autoimmune Retinopathy in Systemic Lupus Erythematosus: Histopathologic Features. *Open Ophthalmol. J.* **2009**, *3*, 20–25. [CrossRef] [PubMed]
25. Bek, T. Trans Retinal HistopathoIogical Changes in Capillary-Free Areas of Diabetic Retinopathy. *Acta Ophthalmol.* **1994**, *72*, 409–415. [CrossRef] [PubMed]
26. Scarinci, F.; Nesper, P.L.; Fawzi, A.A. Deep Retinal Capillary Nonperfusion Is Associated with Photoreceptor Disruption in Diabetic Macular Ischemia. *Am. J. Ophthalmol.* **2016**, *168*, 129–138. [CrossRef]
27. Samara, W.A.; Shahlaee, A.; Adam, M.K.; Khan, M.A.; Chiang, A.; Maguire, J.I.; Hsu, J.; Ho, A.C. Quantification of Diabetic Macular Ischemia Using Optical Coherence Tomography Angiography and Its Relationship with Visual Acuity. *Ophthalmology* **2017**, *124*, 235–244. [CrossRef]
28. Sultan, W.; Asanad, S.; Karanjia, R.; Sadun, A.A. Long-Term Attenuation of the Deep Capillary Plexus in SLE Utilizing OCTA. *Can. J. Ophthalmol.* **2019**, *54*, e207–e212. [CrossRef]
29. Dupas, B.; Minvielle, W.; Bonnin, S.; Couturier, A.; Erginay, A.; Massin, P.; Gaudric, A.; Tadayoni, R. Association between Vessel Density and Visual Acuity in Patients with Diabetic Retinopathy and Poorly Controlled Type 1 Diabetes. *JAMA Ophthalmol.* **2018**, *136*, 721–728. [CrossRef]

30. Moon, B.G.; Um, T.; Lee, J.; Yoon, Y.H. Correlation between Deep Capillary Plexus Perfusion and Long-Term Photoreceptor Recovery after Diabetic Macular Edema Treatment. *Ophthalmol. Retin.* **2018**, *2*, 235–243. [CrossRef]
31. Yusuf, I.H.; Sharma, S.; Luqmani, R.; Downes, S.M. Hydroxychloroquine Retinopathy. *Eye* **2017**, *31*, 828–845. [CrossRef] [PubMed]
32. Ding, H.J.; Denniston, A.K.; Rao, V.K.; Gordon, C. Hydroxychloroquine-Related Retinal Toxicity. *Rheumatology* **2016**, *55*, 957–967. [CrossRef] [PubMed]
33. Kruh, J.; Foster, C.S. Corticosteroid-Sparing Agents: Conventional Systemic Immunosuppressants. *Dev. Ophthalmol.* **2012**, *51*, 29–46. [CrossRef] [PubMed]
34. Ponticelli, C.; Moroni, G. Hydroxychloroquine in Systemic Lupus Erythematosus (SLE). *Expert Opin. Drug Saf.* **2017**, *16*, 411–419. [CrossRef]
35. Marmor, M.F.; Kellner, U.; Lai, T.Y.Y.; Melles, R.B.; Mieler, W.F.; Lum, F. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). *Ophthalmology* **2016**, *123*, 1386–1394. [CrossRef]
36. Wei, Y.; Jiang, H.; Shi, Y.; Qu, D.; Gregori, G.; Zheng, F.; Rundek, T.; Wang, J. Age-Related Alterations in the Retinal Microvasculature, Microcirculation, and Microstructure. *Investig. Ophthalmol. Vis. Sci.* **2017**, *58*, 3804–3817. [CrossRef]
37. Lin, Y.; Jiang, H.; Liu, Y.; Gameiro, G.R.; Gregori, G.; Dong, C.; Rundek, T.; Wang, J. Age-Related Alterations in Retinal Tissue Perfusion and Volumetric Vessel Density. *Investig. Ophthalmol. Vis. Sci.* **2019**, *60*, 685–693. [CrossRef]
38. Debourdeau, E.; Charmard, C.; Carriere, I.; Plat, J.; Villain, M.; Boivineau, L.; Altwegg, R.; Daien, V. Retinal Microcirculation Changes in Crohn's Disease Patients under Biologics, a Potential Biomarker of Severity: A Pilot Study. *J. Pers. Med.* **2022**, *12*, 230. [CrossRef]
39. Arnould, L.; Guenancia, C.; Azemar, A.; Alan, G.; Pitois, S.; Bichat, F.; Zeller, M.; Gabrielle, P.H.; Bron, A.M.; Creuzot-Garcher, C.; et al. The EYE-MI Pilot Study: A Prospective Acute Coronary Syndrome Cohort Evaluated with Retinal Optical Coherence Tomography Angiography. *Investig. Ophthalmol. Vis. Sci.* **2018**, *59*, 4299–4306. [CrossRef]

7.3. Subclinical Retinopathy in Systemic Lupus Erythematosus Patients—Optical Coherence Tomography Study

Original paper

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Subclinical retinopathy in systemic lupus erythematosus patients – optical coherence tomography study

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Abstract

Introduction: The aim was to detect subclinical structural retinal abnormalities in optical coherence tomography (OCT) in ophthalmologically asymptomatic systemic lupus erythematosus (SLE) patients without signs of lupus retinopathy or drug toxicity in fundus examination and in OCT and to assess the relationship between OCT parameters and disease activity, therapy type and burden on other organs to demonstrate the utility of OCT in early retinal impairment in SLE patients.
Material and methods: Cross-sectional study. Thirty-three SLE patients (57 eyes) and 31 healthy individuals (56 eyes) were enrolled in the study. We excluded patients with evidence of lupus retinopathy or hydroxychloroquine (HCQ) toxicity on OCT or fundus examination to reveal any subclinical changes. All patients underwent full ophthalmologic examination in the slit lamp including best corrected visual acuity, tonometry, and OCT. The Kolmogorov-Smirnov distribution test was used to assess the normal distribution in quantitative values. The differences between the individual measured parameters in the groups were analyzed using the Mann-Whitney *U* test. Spearman's rank correlation test was used to assess the correlation between the measured parameters and quantitative clinical data.
Results: There was no difference in the OCT findings between SLE and healthy control groups. Among the study group a negative correlation was found between disease duration and age and retinal nerve fiber layer thickness in the inferior quadrant ($p = 0.0063$, $p = 0.0036$). No correlations were observed between examined retinal parameters and duration of hydroxychloroquine therapy, hydroxychloroquine as well as chloroquine cumulative dose and disease activity indices.
Conclusions: Optical coherence tomography is a widespread ophthalmic modality used for SLE retinopathy and HCQ toxicity screening. Our study did not demonstrate its clinical potency in diagnosis of subclinical retinal involvement. An optical coherence tomography device seems to be less sensitive in subclinical retinal impairment detection than optical coherence tomography angiography.

Key words: optical coherence tomography, systemic lupus erythematosus, subclinical retinal disease, occult eye involvement.

Introduction

Systemic lupus erythematosus (SLE) is a chronic, multiorgan connective tissue disease characterized by variable dynamics of progression and broad diversity of organ involvement. Annually, SLE affects approximately 5 per 100,000 persons in the United States, and about half as many Europeans and Japanese [1].

Although the genetics, environmental factors, as well as a dysregulation of the immune system are mentioned as the main etiological factors, the exact etiopathogen-

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esis is still uncertain [2, 3]. About one-third of patients experience an ocular manifestation in the course of SLE and it may precede involvement of other organs [4]. Retinopathy, after keratoconjunctivitis sicca, is the second most common eye involvement in SLE [5].

Bashiri et al. [6] found 15.8% prevalence of retinopathy in patients newly diagnosed with ophthalmologically asymptomatic SLE. Diagnoses of retinopathy and, less expected, choroidopathy are proven negative prognostic factors for morbidity and mortality. Retinal and choroidal vascular disease may be concomitant to neuropsychiatric lupus and lupus nephritis [7].

Ophthalmological management of SLE patients is a challenge, because of different causes of eye involvement. It may be the reason for the disease itself, drug induced or due to a secondary disorder. Optical coherence tomography (OCT) is widely used for lupus retinopathy and hydroxychloroquine toxicity screening. Figure 1 presents a cross-section of a healthy retina OCT scan divided into layers.

It is a non-invasive device that uses near-infrared light to scan in vivo the posterior pole of the eye to provide high resolution retinal images. Cross-sectional pictures of the whole retina provide comprehensive data about the thickness of all individual layers divided into sections. Optical coherence tomography scans are fast and easy to perform, repeatable and low-cost. Optical coherence tomography is also widely used in glaucoma, macular degeneration and other eye disorders' diagnostics and follow-up, as well as being useful in multiple sclerosis (MS) and other neurodegenerative diseases [8–10].

Widespread OCT application in SLE patients, which is routinely used at each ophthalmology visit, induced the authors to use the device not only to detect apparent retinal damage, but also to find early, subclinical changes that preceded irreversible impairment and proper lupus retinopathy development.

The aim of the current study was to detect structural retinal abnormalities in OCT in asymptomatic SLE patients without signs of lupus retinopathy or drug toxicity in fundus examination and in OCT. Then, we aimed to assess the relationship between OCT parameters and disease activity, therapy type and burden on other organs to demonstrate the utility of OCT in early retinal impairment in SLE patients.

Material and methods

The study lasted from July 2019 to October 2021. Thirty-three SLE patients (57 eyes), diagnosed according to the American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria, and 31 healthy individuals (56 eyes) were enrolled in the study. For the study, data of both eyes were collected but averaged for statistical analysis.

Due to the systemic character of the disease, we used averaged data as, in our opinion, they better reflect the impact of SLE. Poor quality of OCT scans resulted in exclusion of 3 patients (4 eyes) from the study. We also

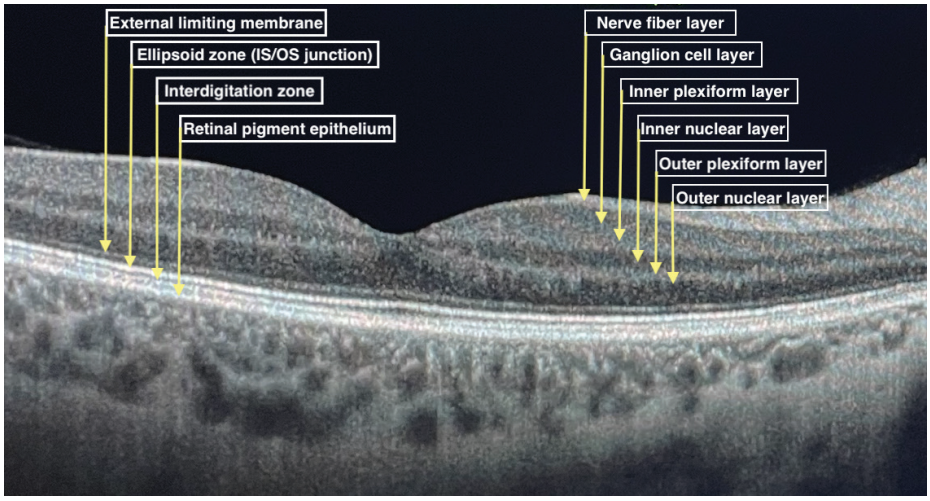

Fig. 1. Cross-section of a healthy retina optical coherence tomography scan.

excluded patients with evidence of lupus retinopathy or hydroxychloroquine (HCQ) toxicity on OCT or fundus examination on initial evaluation.

All the examined patients were ophthalmologically asymptomatic. Patients with glaucoma and other ocular disorders were excluded from the study as any underlying disease may have an impact on retinal nerve fiber layer (RNFL) thickness measurement. Patients with other eye disorders, over 75 or below 18 years old, with myopia greater than 5 diopters were also excluded from the study. All patients underwent full ophthalmologic examination in a slit lamp including best corrected visual acuity, tonometry, and OCT.

Patients' laboratory and index results were consulted with an experienced rheumatologist to evaluate the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) and the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI).

Optical coherence tomography imaging

Patients from study and control groups underwent a radial OCT B-scan by means of Swept-Source Optical Coherence Tomography Angio (Topcon Corp, Tokyo, Japan, 2015). All patients enrolled in the study had their blood collected for laboratory tests and then the OCT scan was performed within 3 months. Systemic lupus erythematosus pharmacotherapy was not considered during enrollment.

Full retinal thickness, RNFL thickness, ganglion cell layer (GCL) + (GCL with IPL), and GCL++ (RNFL and GCL and IPL) were evaluated in nine Early Treatment Diabetic Retinopathy Study (ETDRS) subfields. All the parameters obtained from scanning were automatically calculated by the device. Retinal thickness, GCL+ and GCL++ were grouped into central subfield (CSF) (circular foveal area with 1 mm diameter), inner ring (average value of four inner quadrants with 3 mm diameter) and outer ring (average value of four outer quadrants with 6 mm diameter).

In the course of neurogenerative diseases such as multiple sclerosis, deterioration of fibers in temporal sector may be seen. Therefore, in this study, the division into sectors typical to the optic nerve was maintained. Retinal nerve fiber layer thickness was evaluated as follows: central, superior, inferior, nasal, temporal quadrants and average of superior, inferior, nasal, and temporal.

Statistical analysis

The statistical analysis was performed using STATISTICA 13.3 (StatSoft, Inc., Tulsa, OK, USA, 2017). The results with $p < 0.05$ were considered statistically significant. The Kolmogorov–Smirnov distribution test was used to assess the normal distribution in quantitative values. The differences between the individual measured parameters in the groups were analyzed using the Mann-Whitney *U* test. Spearman's rank correlation test was used to assess the correlation between the measured parameters and quantitative clinical data.

Bioethical standards

The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Bioethical Committee (number 9/2019, date 11/01/2019). Informed consent was obtained from all patients involved in the study.

Results

All the patients from study group were treated with HCQ and 12 of them (12/30) were previously treated with chloroquine that was withdrawn prior to administration of HCQ. Rheumatological treatment data are summarized in Table I. The clinical characteristics of the groups are presented in Table II.

There was no significant difference in gender, age, intraocular pressure, retinal thickness, RNFL, GCL+, GCL++ in all sectors, between SLE patients and healthy controls (HC). Comparison of OCT parameters between study and control groups is summarized in Table III.

Significantly lower ($p = 0.019$) visual acuity was demonstrated in SLE patients than in the control group. Among the study group a negative correlation was found between disease duration and age and RNFL thickness in the inferior quadrant ($p = 0.0063$, $p = 0.0036$). Among the control group a negative correlation was revealed between age and retinal thickness (RT) in the whole outer ring, superior quadrant of RNFL and outer ring of GCL++ ($p = 0.0248$, $p = 0.0136$, $p = 0.0079$).

Kidney involvement was observed in 6 patients in a cohort of SLE patient. The retinal nerve fiber layer in nasal quadrant was increased in patients with SLE and

Table I. Systemic lupus erythematosus treatment summary

Treatment	Positive	Negative
HCQ Including: HCQ < 5 years/HCQ > 5 years	30 17/30	0 N/A
Chloroquine	12	18
Azathioprine	11	19
Methotrexate	13	17

HCQ – hydroxychloroquine.

Table II. Clinical characteristic of patients

Variable	Study group (n = 30)	Control group (n = 31)	p-value
Age [years]	46.07 ±14.09	44.55 ±14.11	0.69
Gender, male/female	5/25	4/27	0.69
Visual acuity [logMAR]	0.01 ±0.02	0.0	0.02
IOP [mmHg]	15.98 ±2.4	16.04 ±2.05	0.82
Disease duration [months]	101.8 ±89.98	N/A	N/A
SLEDAI-2K	5.2 ±4.39	N/A	N/A
SLICC/ACR DI	1.3 ±1.2	N/A	N/A
HCQ cumulative dose [g]	391.23 ±425.52	N/A	N/A
Anti-dsDNA [IU/ml]	316.07 ±263.16	N/A	N/A
ACL IgM (positive)	12	N/A	N/A
ACL IgG (positive)	29	N/A	N/A
Anti-β2 GPI IgG [RU/ml]	28	N/A	N/A
Anti-β2 GPI IgM [RU/ml]	19	N/A	N/A
LAC [s]	46.75 ±31.2	N/A	N/A
C3 [g/l]	0.94 ±0.31	N/A	N/A
C4 (positive)	5	N/A	N/A
ERS [mm/h]	19.97 ±24.6	N/A	N/A

ACL – anti-cardiolipin antibodies IgM and IgG, anti-dsDNA – anti-double stranded DNA antibodies, anti-ß2-GPI – anti-ß2-glycoprotein I antibodies IgM and IgG, ERS – erythrocyte sedimentation rate, HCQ – hydroxychloroquine, IOP – intraocular pressure, SLEDAI-2K – Systemic Lupus Erythematosus Disease Activity Index 2000, SLICC/ACR DI – Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

Table III. Comparison of optical coherence tomography parameters between study and control groups

OCT parameters	Study group (n = 30)	SD	Control group (n = 31)	SD	p-value
Average retinal thickness	283.26	13.99	281.37	13.99	0.65
RT CST	253.58	18.74	250.82	18.74	0.42
RT inner ring	311.06	14.65	309.96	14.65	0.85
RT outer ring	276.18	14.69	272.76	14.69	0.33
RNFL centrum	7.38	2.77	6.73	2.77	0.41
RNFL superior	36.55	6.83	35.69	6.83	0.90
RNFL inferior	40.18	7.97	39.85	7.97	0.90
RNFL temporal	26.47	6.98	24.51	6.98	0.14
RNFL nasal	42.19	7.48	42.94	7.48	0.60
RNFL average	36.35	4.56	35.74	4.56	0.47
GCL++ CST	59.70	9.90	57.82	9.90	0.57
GCL++ inner ring	118.96	8.18	116.83	8.18	0.33
GCL++ outer ring	110.69	9.09	107.15	9.09	0.06
GCL+ CST	52.43	8.44	50.69	8.44	0.57
GCL+ inner ring	89.99	6.08	88.71	6.08	0.62
GCL+ outer ring	66.63	5.16	64.14	5.16	0.12

CST – central subfield thickness, GCL – ganglion cell layer, OCT – optical coherence tomography, RNFL – retinal nerve fiber layer, RT – retinal thickness, SD – standard deviation.

Table IV. Comparison of optical coherence tomography parameters – subgroups based on hydroxychloroquine duration

OCT parameters	> 5 years (n = 13)	SD	< 5 years (n = 17)	SD	p-value
Average retinal thickness	282.49	17.15	282.49	11.55	0.93
RT CST	255.73	17.29	255.73	20.14	0.50
RT inner ring	312.88	14.39	312.88	15.13	0.48
RT outer ring	274.57	18.70	274.57	11.20	0.83
RNFL centrum	6.88	3.04	6.88	2.57	0.29
RNFL superior	36.13	7.44	36.13	6.54	0.45
RNFL inferior	38.23	5.49	38.23	9.33	0.44
RNFL temporal	25.27	7.51	25.27	6.62	0.38
RNFL nasal	41.42	6.68	41.42	8.19	0.79
RNFL average	35.26	4.29	35.26	4.72	0.24
GCL++ CST	59.58	8.85	59.58	10.91	0.98
GCL++ inner ring	118.53	8.11	118.53	8.46	0.66
GCL++ outer ring	108.28	9.76	108.28	8.37	0.15
GCL+ CST	52.85	7.88	52.85	9.07	0.75
GCL+ inner ring	89.84	5.69	89.84	6.54	0.69
GCL+ outer ring	65.82	6.52	65.82	3.91	0.59

CST – central subfield thickness, GCL – ganglion cell layer, OCT – optical coherence tomography, RNFL – retinal nerve fiber layer, RT – retinal thickness, SD – standard deviation.

nephritis compared with SLE patients without nephritis (p = 0.02).

No correlations were observed between examined retinal layers parameters and C3, C4, erythrocyte sedimentation rate (ESR), lupus anticoagulant (LAC), anti-nucleosome antibody (ANuA), anti-ß2-glycoprotein I antibodies (anti-ß2-GPI) IgM and IgG, anti-double stranded DNA antibodies (anti-dsDNA), anti-cardiolipin antibodies (ACL) IgM and IgG, duration of HCQ therapy, HCQ cumulative dosage, chloroquine cumulative dose, methotrexate, SLICC/ACR and the SLEDAI-2K scores. Azathioprine was associated with lower RNFL thickness in inferior and nasal quadrants. Comparison of OCT parameters among SLE patients based on HCQ duration and chloroquine use are presented in Tables IV and V.

Data about the impact of central nervous system (CNS) involvement, leflunomide (1 patient), cyclophosphamide (4 patients), rituximab (1 patient) and prednisolone (3 patients) therapy on retinal microstructure were also collected. Because of the small sample size from these subgroups, these results were unreliable.

Discussion

Retinal structures, especially RNFL and GCL, may be altered in the course of the disease or administered treatment [9]. Systemic lupus erythematosus is an insidious entity and, even though advanced retinal injuries are visible in OCT scans, they do not cause visible changes in the retina in a standard ophthalmological examination in the subclinical stage.

Over time, visual acuity decreases significantly and alterations in the fundus become apparent, but then treatment is difficult, and the visual outcomes are often unsatisfactory. Finding a solid biomarker used for early SLE diagnosis, disease monitoring and preceding exacerbation of the disease has been a purpose of many research studies [11].

Our study revealed no difference between SLE and HC groups in retinal thickness, RNFL, GCL+, GCL++, and no correlation between OCT parameters and disease activity and therapy type. The results of Fouad et al. [12] were comparable to ours. In their study, no significant correlation between disease activity and OCT abnormalities were detected. Optical coherence tomography was able to detect only significant changes that resulted from HCQ therapy longer than 5 years. The study showed that OCT is not able to detect subtle changes in early retina involvement [12].

In many neurogenerative disorders, such as Parkinson disease, Alzheimer disease, multiple sclerosis and schizophrenia, RNFL thinning is observed [13]. Our study found a negative correlation between disease duration and RNFL thickness in the inferior quadrant, but there

Table V. Comparison of optical coherence tomography parameters – subgroups based on chloroquine use

OCT parameters	Positive (n = 12)	SD	Negative (n = 18)	SD	p-value
Average retinal thickness	282.43	14.25	283.82	14.21	0.63
RT CST	256.38	21.36	251.72	17.16	0.50
RT inner ring	312.64	14.84	310.01	14.85	0.78
RT outer ring	274.53	14.54	277.28	15.11	0.43
RNFL centrum	8.29	3.12	6.78	2.41	0.14
RNFL superior	37.83	7.42	35.69	6.48	0.39
RNFL inferior	38.52	4.57	41.29	9.57	0.55
RNFL temporal	27.98	9.30	25.46	4.94	1.00
RNFL nasal	42.81	7.08	41.78	7.90	0.75
RNFL average	36.79	3.54	36.06	5.22	0.69
GCL++ CST	61.46	11.30	58.53	9.00	0.36
GCL++ inner ring	121.66	4.99	117.16	9.45	0.16
GCL++ outer ring	110.77	7.84	110.64	10.06	0.80
GCL+ CST	53.00	9.63	52.06	7.82	0.90
GCL+ inner ring	91.64	4.46	88.89	6.86	0.34
GCL+ outer ring	66.79	5.08	66.51	5.35	0.90

CST – central subfield thickness, GCL – ganglion cell layer, OCT – optical coherence tomography, RNFL – retinal nerve fiber layer, RT – retinal thickness, SD – standard deviation.

was no significant difference in RNFL thickness between SLE patients and HC.

Conigliaro et al. [14] revealed thinning in the temporal-inferior quadrant of RNFL in a cohort of SLE patients with neuropsychiatric involvement. In our study, because of the small sample size, data about the impact of CNS involvement on OCT abnormalities were not significant.

Liu et al. [9] detected significant RNFL thinning in global, temporal superior and nasal quadrants in NPSLE (neuropsychiatric systemic lupus erythematosus) patients compared to the control group. This correlation was not confirmed in NPSLE patients compared to the non-NPSLE group. It supports the thesis that NPSLE patients, as well as non-NPSLE, differ from healthy controls and had some early abnormalities in RNFL thickness.

As confirmation, the authors also found a correlation between the cognitive function test and thickness of the temporal quadrant of the RNFL. According to the aforementioned authors, abnormalities in OCT parameters, in the form of RNFL thinning, may be indicative of cognitive impairment in SLE and may serve as an early biomarker. They also suggest that changes in the CNS in SLE patients are more common, which reflects on RNFL thinning in the whole SLE group, not only in the NPSLE cohort specifically.

Retinal nerve fiber layer thinning may by the reason for RNFL microinfarcts because of immune complex deposition in retinal vessel walls [15]. A correlation between RNFL thinning and white matter damage was suspected, but it was not confirmed [16].

Bao et al. [17] also revealed decreased RNFL thickness compared to controls. In the non-lupus retinopathy group, it was evaluated in superior and nasal quadrants, and in patients with confirmed lupus retinopathy additionally in the inferior region.

In contrast, Işık et al. [18] did not find a difference in RNFL thickness in the SLE group compared to the control one. The study authors included all SLE patients, not only NPSLE patients.

Hydroxychloroquine therapy is considered safe with good disease control but associated with dose-dependent toxicity [6]. Hydroxychloroquine retinopathy tends to increase with long-term therapy (5 or more years), high daily dose (more than 5 mg/kg per day), chronic renal disease, use of tamoxifen and preexisting retinal or macular disease [6–8].

Early retinopathy detection is crucial to prevent vision-threatening complications. The timetable for HCQ toxicity screening, for patients with no risk factors, includes baseline fundus examination to detect coexistent retinal disease and annual screening after 5 years from SLE diagnosis [6].

Primary screening tests are automated visual fields (standard automated perimeter) and spectral-domain optical coherence tomography (SD OCT), as well as

the multifocal electroretinogram (mfERG) and fundus autofluorescence (FAF). In our study, we divided the SLE group based on the duration of HCQ therapy.

Conigliaro et al. [14], in their study, did not observe HCQ toxicity in OCT in SLE patients. In our study also no significant changes were observed in OCT parameters based on the duration of HCQ therapy and HCQ cumulative dosage. The authors detected functional alterations rather than morphological ones. It seems that standard automated perimetry better reflects subclinical changes in the SLE cohort group than OCT. According to the authors, changes in perimetry were possibly associated with nephritis.

In the current study there was no significant difference in GCL+ and GCL++ thickness between SLE patients and HC. However, Işık et al. [18] observed thinner GC-IPL and mean macular thickness in the SLE group compared to HC. Bao et al. [17] compared lupus retinopathy (LR) and non-lupus retinopathy (NLR) patients with HC and found decreased temporal GCL+ in the NLR group and decreased central, superior, temporal, and inferior GCL+ in LR. Compared to NLR, GCL+ in the temporal and inferior quadrants of LR patients was associated with further thickness reduction. At the early stage of LR, microstructure of the retina seen in OCT is not so vulnerable to disease fluctuation to detect subclinical disease.

Average RT, in the 1 mm center and in the whole 6 mm ring (including the inner and outer ring), was similar in study and control groups. Our results are accordant with Conigliaro et al. [14], who found similar RT in SLE and control groups. Interestingly, they detected a reduction in retinal thickness exclusively in Sjögren syndrome patients compared to both control group and SLE patients.

In contrast to our study, Liu et al. [9] observed lower mean macular thickness in patients with SLE and Bao et al. [17] found decreased RT in the temporal region in the non-lupus retinopathy group and in the superior, temporal, inferior and nasal regions in patients with lupus retinopathy.

Thinning of the retinal layers such as the RNFL and GCL is a confirmed, age-related alteration in retinal microstructure [19]. Our study confirmed a negative correlation between age and RNFL in the inferior quadrant in the study group and between age and retinal thickness in the whole outer ring, the superior quadrant of the RNFL and the outer ring of GCL++ among the control group.

All the patients from the study group were treated with HCQ, making the study cohort homogeneous. Hydroxychloroquine has a protective effect on the course of SLE, and studies show that HCQ might have a protective effect on ocular microvasculature [20].

Another novel, promising method for diagnosis of subclinical retinal alterations is optical coherence tomography angiography (OCTA). It scans the retina in a non-contact way and provides data about retinal vessels and the status of all the retina layers in easy to follow-up images and quantitative data. Introduction of OCTA was a milestone in ophthalmology and, in the authors' opinion, may replace fundus fluorescein angiography entirely. Recent papers have pointed out the potential of OCTA in early subclinical microvasculature changes in SLE patients [14, 17, 18, 20–25].

The biggest strengths of the study are the evaluation of different retinal layers divided into sectors and big rheumatological data.

Study limitations

The study is not free of limitations, including the small sample size, small number of patients with kidney and CNS involvement, lack of follow-up data, absence of standard automated perimetry data and lack of choroidal thickness.

Conclusions

In the current study we did not find any subclinical morphological differences in OCT between SLE patients and the healthy control group. Despite its well-established position in neurodegenerative diseases, RNFL thickness in SLE patients did not differ significantly from the control group. Optical coherence tomography is a widespread ophthalmic modality used for SLE retinopathy and HCQ toxicity screening.

Our study did not demonstrate its clinical potency in diagnosis of subclinical retinal involvement. The optical coherence tomography device seems to be less sensitive in subclinical retinal impairment detection than OCTA.

In patients with SLE and no lupus retinopathy, changes in microstructure of the retina are not evident in OCT, in contrast to changes in microvasculature in OCTA. The role of optical coherence tomography in ophthalmology is well established and our study did not change this status.

The authors declare no conflict of interest.

References

1. Cunningham ET, Tabbara KF, Zierhut M. Systemic lupus erythematosus and the eye. Ocul Immunol Inflamm 2018; 26: 1143–1145, DOI: 10.1080/09273948.2018.1539589.
2. Dammacco R. Systemic lupus erythematosus and ocular involvement: an overview. Clin Exp Med 2018; 18: 135–149, DOI: 10.1007/s10238-017-0479-9.

3. Herrmann M, Gaipl U, Lorenz H, et al. Etiopathogenesis of systemic lupus erythematosus. Int Arch Allergy Immunol 2000; 123: 28–35, DOI: 10.1159/000024421.
4. Hasanreisoglu M, Gulpinar Ikiz GD, Kucuk H, et al. Acute lupus choroidopathy: multimodal imaging and differential diagnosis from central serous chorioretinopathy. Int Ophthalmol 2018; 38: 369–374, DOI: 10.1007/s10792-016-0433-y.
5. Palejwala NV, Walia HS, Yeh S. Ocular manifestations of systemic lupus erythematosus: a review of the literature. Autoimmune Dis 2012; 2012: 290898, DOI: 10.1155/2012/290898.
6. Bashiri H, Karimi N, Mostafaei S, et al. Retinopathy in newly-diagnosed systemic lupus erythematosus: should we screen for ocular involvement? BMC Rheumatol 2021; 5: 34, DOI: 10.1186/s41927-021-00203-5.
7. Stafford-Brady F, Urowitz M, Gladman D, et al. Lupus retinopathy: patterns, associations, and prognosis. Arthritis Rheum 1988; 31: 1105–1110, DOI: 10.1002/art.1780310904.
8. Britze J, Frederiksen JL. Optical coherence tomography in multiple sclerosis. Eye (Lond) 2018; 32: 884–888, DOI: 10.1038/s41433-017-0010-2.
9. Liu GY, Utset TO, Bernard JT. Retinal nerve fiber layer and macular thinning in systemic lupus erythematosus: an optical coherence tomography study comparing SLE and neuropsychiatric SLE. Lupus 2015; 24: 1169–1176, DOI: 10.1177/0961203315582285.
10. Pula JH, Towle VL, Staszak VM, et al. Retinal nerve fibre layer and macular thinning in spinocerebellar ataxia and cerebellar multisystem atrophy. Neuroophthalmology 2011; 35: 108–114, DOI: 10.3109/01658107.2011.580898.
11. Zucchi D, Elefante E, Calabresi E, et al. One year in review 2019: systemic lupus erythematosus. Clin Exp Rheumatol 2019; 37: 715–722.
12. Fouad SA, Esmat Mahmoud Ali SM, Rezk Alnaggar ARL, et al. Structural retinal assessment using optical coherence tomography and fundus fluorescein angiography in systemic lupus erythematosus patients. J Clin Rheumatol 2021; 27: 34–39, DOI: 10.1097/RHU.0000000000001162.
13. Chhablani PP, Ambiya V, Nair AG, et al. Retinal Findings on OCT in Systemic Conditions. Semin Ophthalmol 2018; 33: 525–546, DOI: 10.1080/08820538.2017.1332233.
14. Conigliaro P, Triggianese P, Draghessi G, et al. Evidence for the detection of subclinical retinal involvement in systemic lupus erythematosus and Sjögren Syndrome: a potential association with therapies. Int Arch Allergy Immunol 2018; 177: 45–56, DOI: 10.1159/000488950.
15. Karpik AG, Schwartz MM, Dickey LE, et al. Ocular immune reactants in patients dying with systemic lupus erythematosus. Clin Immunol Immunopathol 1985; 35: 295–312, DOI: 10.1016/0090-1229(85)90091-1.
16. Shulman S, Shorer R, Wollman J, et al. Retinal nerve fiber layer thickness and neuropsychiatric manifestations in systemic lupus erythematosus. Lupus 2017; 26: 1420–1425, DOI: 10.1177/0961203317703496.
17. Bao L, Zhou R, Wu Y, et al. Unique changes in the retinal microvasculature reveal subclinical retinal impairment in patients with systemic lupus erythematosus. Microvasc Res 2020; 129: 103957, DOI: 10.1016/j.mvr.2019.103957.
18. Işık MU, Akmaz B, Akay F, et al. Evaluation of subclinical retinopathy and angiopathy with OCT and OCTA in patients with systemic lupus erythematosus. Int Ophthalmol 2021; 41: 143–150, DOI: 10.1007/s10792-020-01561-8.
19. Wei Y, Jiang H, Shi Y, et al. Age-related alterations in the retinal microvasculature, microcirculation, and microstructure. Investig Ophthalmol Vis Sci 2017; 58: 3804–3817, DOI: 10.1167/iovs.17-21460.
20. Mimier-Janczak M, Kaczmarek D, Proc K, et al. Evaluation of subclinical retinal disease in patients affected by systemic lupus erythematosus with no evidence of ocular involvement – an optical coherence tomography angiography original study. J Clin Med 2022; 11: 7414, DOI: 10.3390/jcm11247417.
21. Pichi F, Woodstock E, Hay S, Neri P. Optical coherence tomography angiography findings in systemic lupus erythematosus patients with no ocular disease. Int Ophthalmol 2020; 40: 2111–2118, DOI: 10.1007/s10792-020-01388-3.
22. Mimier-Janczak M, Kaczmarek D, Janczak D, Kaczmarek R. Optical coherence tomography angiography as a new tool for evaluation of the subclinical retinal involvement in patients with systemic lupus erythematosus – a review. J Clin Med 2021; 10: 2887, DOI: 10.3390/jcm10132887.
23. Mihailovic N, Leclaire MD, Eter N, Brücher VC. Altered microvascular density in patients with systemic lupus erythematosus treated with hydroxychloroquine – an optical coherence tomography angiography study. Graefes Arch Clin Exp Ophthalmol 2020; 258: 2263–2269, DOI: 10.1007/s00417-020-04788-4.
24. Arfeen SA, Bahgat N, Adel N, et al. Assessment of superficial and deep retinal vessel density in systemic lupus erythematosus patients using optical coherence tomography angiography. Graefes Arch Clin Exp Ophthalmol 2020; 258: 1261–1268, DOI: 10.1007/s00417-020-04626-7.
25. Forte R, Haulani H, Dyrda A, Jürgens I. Swept source optical coherence tomography angiography in patients treated with hydroxychloroquine: correlation with morphological and functional tests. Br J Ophthalmol 2021; 105: 1297–1301, DOI: 10.1136/bjophthalmol-2018-313679.

8. PODSUMOWANIE WYNIKÓW

W niniejszej pracy przeglądowej przeanalizowano siedem artykułów, których przedmiotem badania była subkliniczna retinopatia w przebiegu SLE. Wykazano luki w dotychczas opublikowanych badaniach, które polegały na nieobliczaniu skumulowanej dawki HCQ, braku podziału pacjentów ze względu na czas trwania leczenia HCQ, nieobliczaniu indeksów aktywności SLE. We wszystkich analizowanych pracach wykazano zmniejszenie gęstości naczyń włosowatych splotu powierzchownego u pacjentów z rozpoznanym SLE bez cech retinopatii w badaniu okulistycznym oraz bez obniżenia ostrości wzroku w porównaniu ze zdrową grupą kontrolną.

Pierwsze badanie oryginalne potwierdziło wyniki powyższych autorów. Wykazano mniejszą gęstość naczyń (VD) mikrokrążenia siatkówki w dolnym i nosowym kwadrancie splotu powierzchownego oraz w jej strefie okołodołkowej w porównaniu do grupy kontrolnej. W grupie badanej zajęcie nerek związane było z dalszą redukcją mikrokrążenia w porównaniu do pacjentów ze SLE bez zajęcia nerek. Powierzchnia FAZ i wskaźnik kolistości FAZ zostały zmniejszone u pacjentów cierpiących na SLE, jednak parametry te cechuje duża zmienność osobnicza. Ostrość wzroku była także istotnie statystycznie niższa u pacjentów ze SLE, co może być wtórne do stopnia utraty naczyń włosowatych. Badanie nie wykazało korelacji pomiędzy skalami SLICC/ACR i SLEDAI-2K a VD i FAZ, jednakże stwierdzono związek między VD a zajęciem innych narządów. Pacjenci ze SLE i zajęciem nerek mieli mniejszą gęstość naczyń w kwadrantach nosowych i skroniowych, a także całkowitą i okołodołkową splotu powierzchownego w porównaniu z pacjentami ze SLE bez zajęcia nerek. Gęstość naczyń w górnym kwadrancie splotu powierzchownego była zwiększona u pacjentów ze SLE leczonych HCQ przez ponad 5 lat w porównaniu z pacjentami leczonymi HCQ mniej niż 5 lat. Badanie wykazało również dodatnią korelację między skumulowaną dawką HCQ oraz gęstością naczyń w splocie powierzchownym i głębokim.

W drugim badaniu oryginalnym nie znaleziono różnic morfologicznych w OCT między grupą chorującą na SLE a zdrową grupą kontrolną. Grubość RNFL u chorych na SLE nie różniła się statystycznie od grupy kontrolnej. Nie zaobserwowano korelacji między badanymi parametrami siatkówkowymi a czasem trwania terapii hydroksychlorochiną, jak również skumulowaną dawką HCQ i chlorochiny oraz wskaźnikami uszkodzenia i aktywności SLE.

9. WNIOSKI

9.1. Angiografia OCT jest obiecującą metodą diagnostyczną do bezinwazyjnej oceny zaburzeń unaczynienia siatkówki u pacjentów ze SLE.

9.2. Kontynuacja badań z większą ilością pacjentów jest kluczowa do określenia jak wdrożyć wyniki powyższych badań w opiekę nad pacjentem.

9.3. Zmniejszenie gęstości naczyń siatkówki może być uważane za wczesny marker retinopatii w przebiegu SLE.

9.4. Wyniki uzyskane za pomocą Angio-OCT mogą być dobrym wskaźnikiem rokowania SLE.

9.5. Hydroksychlorochina może pełnić funkcję ochronną dla mikrokrążenia siatkówki.

9.6. Angio-OCT może przyczynić się do wczesnej diagnozy i monitorowania progresji retinopatii w przebiegu SLE.

9.7. U pacjentów ze SLE i bez retinopatii zmiany w mikrostrukturze siatkówki nie są widoczne w OCT.

9.8. OCT bez funkcji angiografii jest mniej czułe niż Angio-OCT w wykrywaniu subklinicznych uszkodzeń siatkówki u pacjentów ze SLE.

10. BIBLIOGRAFIA

1. Sitaula, R.; Narayan Shah, D.; Singh, D. The Spectrum of Ocular Involvement in Systemic Lupus Erythematosus in a Tertiary Eye Care Center in Nepal. Ocul. Immunol. Inflamm. 2011, 19, 422–425. DOI: 10.3109/09273948.2011.610023.
2. Dammacco R. Systemic lupus erythematosus and ocular involvement: an overview. Clin Exp Med 2018; 18: 135–149. DOI: 10.1007/s10238-017-0479-9.
3. Hasanreisoglu M, Gulpinar Ikiz GD, Kucuk H, et al. Acute lupus choroidopathy: multimodal imaging and differential diagnosis from central serous chorioretinopathy. Int Ophthalmol 2018; 38: 369–374. DOI: 10.1007/s10792-016-0433-y.
4. Palejwala NV, Walia HS, Yeh S. Ocular manifestations of systemic lupus erythematosus: a review of the literature. Autoimmune Dis 2012; 2012: 290898. DOI: 10.1155/2012/290898.
5. Nangia, P.V.; Viswanathan, L.; Kharel, R.; Biswas, J. Retinal Involvement in Systemic Lupus Erythematosus. Lupus Open Access 2017, 2, 2–5. DOI: 10.35248/2684-1630.17.2.129.
6. Stafford-Brady F, Urowitz M, Gladman D, et al. Lupus retinopathy: patterns, associations, and prognosis. Arthritis Rheum 1988; 31: 1105–1110. DOI: 10.1002/art.1780310904.
7. Mimier-Janczak, M.; Kaczmarek, D.; Janczak, D.; Kaczmarek, R. Optical Coherence Tomography Angiography as a New Tool for Evaluation of the Subclinical Retinal Involvement in Patients with Systemic Lupus Erythematosus—A Review. J. Clin. Med. 2021, 10, 2887. DOI: 10.3390/jcm10132887.
8. Butendieck RR, Parikh K, Stewart M, Davidge-Pitts C, Abril A. Systemic lupus erythematosus-associated retinal vasculitis. J Rheumatol. 2012;39(5):1095-6. DOI: 10.3899/jrheum.111462.
9. Davies JB, Rao PK. Ocular manifestations of systemic lupus erythematosus. Curr Opin Ophthalmol. 2008;19(6):512-8. DOI: 10.1097/icu.0b013e3283126d34.
10. Preble JM, Silpa-Archa S, Foster CS. Ocular involvement in systemic lupus erythematosus. Curr Opin Ophthalmol. 2015;26(6):540-5. DOI: 10.1097/ICU.0000000000000209.
11. Cao X, Bishop RJ, Forooghian F, Cho Y, Fariss RN, Chan CC. Autoimmune retinopathy in systemic lupus erythematosus: histopathologic features. Open Ophthalmol J. 2009;3:20-5. DOI: 10.2174/1874364100903010020.

12. Chen JJ, Kumar N, McEvoy KM, Leavitt JA. Papilloedema and autoimmune retinopathy from systemic lupus erythematosus. Neuroophthalmology. 2017;18.42(2):117-21. DOI: 10.1080/01658107.2017.1355395.
13. Azevedo LGB, Biancardi AL, Silva RA, Tavares NC, Abreu MM, Bica BERG, et al. Retinopatia lúpica: epidemiologia e fatores de risco. Arq. Bras. Oftalmol. 2021;84(4):395-401. DOI: 10.5935/0004-2749.20210076.
14. Giorgi, D.; Pace, F.; Giorgi, A.; Bonomo, L.; Gabrieli, C.B. Retinopathy in Systemic Lupus Erythematosus: Pathogenesis and Approach to Therapy. Hum. Immunol. 1999, 60, 688–696. DOI: 10.1016/s0198-8859(99)00035-x.
15. Seth, G.; Chengappa, K.G.; Misra, D.P.; Babu, R.; Belani, P.; Shanoj, K.C.; Kumar, G.; Negi, V.S. Lupus Retinopathy: A Marker of Active Systemic Lupus Erythematosus. Rheumatol. Int. 2018, 38, 1495–1501. DOI: 10.1007/s00296-018-4083-4.
16. Montehermoso, A.; Cervera, R.; Font, J.; Ramos-Casals, M.; García-Carrasco, M.; Formiga, F.; Callejas, J.L.; Jorfán, M.; Griñó, M.C.; Ingelmo, M. Association of Antiphospholipid Antibodies with Retinalvascular Disease in Systemic Lupus Erythematosus. Semin. Arthritis Rheum. 1999, 28, 326–332. DOI: 10.1016/s0049-0172(99)80017-1.
17. Ushiyama, O. (2000). Retinal disease in patients with systemic lupus erythematosus. Annals of the Rheumatic Diseases, 59(9), 705–708. DOI: 10.1136/ard.59.9.705.
18. Azevedo, L. G., Biancardi, A. L., Silva, R. A., Tavares, N. da, Abreu, M. M., Bica, B. E., & Moraes Júnior, H. V. (2021). Lupus retinopathy: Epidemiology and risk factors. Arquivos Brasileiros De Oftalmologia, 84(4). DOI: 10.5935/0004-2749.20210076.
19. Hasanreisoglu, M.; Gulpinar Ikiz, G.D.; Kucuk, H.; Varan, O.; Ozdek, S. Acute Lupus Choroidopathy: Multimodal Imaging and Differential Diagnosis from Central Serous Chorioretinopathy. Int. Ophthalmol. 2018, 38, 369–374. DOI: 10.1007/s10792-016-0433-y.
20. Saygin, D.; Highland, K.B.; Tonelli, A.R. Microvascular Involvement in Systemic Sclerosis and Systemic Lupus Erythematosus. Microcirculation 2019, 26, e12440. DOI: 10.1111/micc.12440.
21. Makita, S.; Hong, Y.; Yamanari, M.; Yatagai, T.; Yasuno, Y. Optical Coherence Angiography. Opt. Express 2006, 14, 7821. DOI: 10.1364/OE.14.007821.
22. Hosari, S.; Hohberger, B.; Theelke, L.; Sari, H.; Lucio, M.; Mardin, C.Y. OCT Angiography: Measurement of Retinal Macular Microvasculature with Spectralis II OCT Angiography-Reliability and Reproducibility. DOI: 10.1159/000502458.

23. Lanzillo, R.; Cennamo, G.; Criscuolo, C.; Carotenuto, A.; Velotti, N.; Sparnelli, F.; Cianflone, A.; Moccia, M.; Brescia Morra, V. Optical Coherence Tomography Angiography Retinal Vascular Network Assessment in Multiple Sclerosis. Mult. Scler. 2018, 24, 1706–1714. DOI: 10.1177/1352458517729463.
24. Conigliaro, P.; Triggianese, P.; Draghessi, G.; Canofari, C.; Aloe, G.; Chimenti, M.S.; Valeri, C.; Nucci, C.; Perricone, R.; Cesareo, M. Evidence for the Detection of Subclinical Retinal Involvement in Systemic Lupus Erythematosus and Sjögren Syndrome: A Potential Association with Therapies. Int. Arch. Allergy Immunol. 2018, 177, 45–56. DOI: 10.1159/000488950.
25. Cheng, D.; Shen, M.; Zhuang, X.; Lin, D.; Dai, M.; Chen, S.; Lu, F.;Wang, Y. Inner Retinal Microvasculature Damage Correlates with Outer Retinal Disruption during Remission in Behçet's Posterior Uveitis by Optical Coherence Tomography Angiography. Investig. Ophthalmol. Vis. Sci. 2018, 59, 1295–1304. DOI: 10.1167/iovs.17-23113.

11. ZAŁĄCZNIKI

11.1. Zgoda komisji bioetycznej

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

OPINIA KOMISJI BIOETYCZNEJ Nr KB – 9/2019

Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu, powołana zarządzeniem Rektora Uniwersytetu Medycznego we Wrocławiu nr 133/XV R/2017 z dnia 21 grudnia 2017 r. oraz działająca w trybie przewidzianym rozporządzeniem Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. (Dz.U. nr 47, poz. 480) na podstawie ustawy o zawodzie lekarza z dnia 5 grudnia 1996 r. (Dz.U. nr 28 z 1997 r. poz. 152 z późniejszymi zmianami) w składzie:

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

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

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

„Zastosowanie badania angiografii OCT w ocenie gęstości mikrokrążenia siatkówki u pacjentów z układowym toczniem rumieniowatym"

zgłoszonym przez **lek. Małgorzatę Mimier** uczestnika studiów doktoranckich w Katedrze i Klinice Okulistyki Uniwersytetu Medycznego we Wrocławiu oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła **wyrazić zgodę** na przeprowadzenie badania w Klinice Okulistyki i w Klinice Reumatologii i Chorób Wewnętrznych Uniwersyteckiego Szpitala Klinicznego im. Jana Mikulicza-Radeckiego we Wrocławiu oraz Centrum Okulistycznym M-MED we Wrocławiu pod nadzorem dr hab. Radosława Kaczmarka **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.

Wrocław, dnia 11 stycznia 2019 r.

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

11.2. Curriculum vitae

Małgorzata Mimier-Janczak

Urodzona 22 marca 1990 we Wrocławiu

Wykształcenie i przebieg pracy zawodowej:

2016 – obecnie	specjalizacja lekarska
	Katedra i Klinika Okulistyki, Uniwersytecki Szpital Kliniczny we Wrocławiu
2016 – obecnie	studia doktoranckie
	Katedra i Klinika Okulistyki, Uniwersytecki Szpital Kliniczny we Wrocławiu
	Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu
2015 – 2016	staż podyplomowy
	Uniwersytecki Szpital Kliniczny we Wrocławiu
2013 – 2014	Program Erasmus
	Università degli Studi di Perugia, Włochy
2009 – 2015	studia wyższe
	Wydział Lekarski, Uniwersytet Medyczny we Wrocławiu
2006 – 2009	szkoła średnia
	VII Liceum Ogólnokształcące we Wrocławiu

Praktyki zagraniczne i staże:

01.2018	The Basic Science Course in Ophthalmology
	Columbia University, New York City, USA
05.2016	Staż naukowy (research trainee)
	Mayo Clinic, Rochester, Minnesota, USA

Przynależność do towarzystw naukowych:

2016 – obecnie	Polskie Towarzystwo Okulistyczne

11.3. Dorobek naukowy

Sumaryczny Impact Factor	27,776
Sumaryczna liczba punktów MEiN	667,0
Liczba cytowań	89
Indeks Hirscha	3
Liczba pełnych prac	19
Liczba doniesień zjazdowych	21

1. Publikacje w czasopismach naukowych

1.1 Publikacje w czasopiśmie z IF

Lp.	Opis bibliograficzny	IF	Punkty
1	Janczak Dariusz, **Mimier Małgorzata**, Mimier Aleksandra, Janczak Dawid, Chabowski Mariusz, Mularz Katarzyna, Jeleń Michał: Huge alveolar soft part sarcoma of the retroperitoneum - case report, Polish Journal of Pathology, 2014, vol. 65, nr 4, s. 327-330, DOI:10.5114/pjp.2014.48195	1,128	15
2	Mulak Małgorzata, Czak Wojciech A., **Mimier Małgorzata**, Kaczmarek Radosław: A comparison of intraocular pressure values obtained using a Goldmann applanation tonometer and a handheld version of applanation resonance tonometer: a preliminary report, Advances in Clinical and Experimental Medicine, 2018, vol. 27, nr 4, s. 481-485, DOI:10.17219/acem/68559	1,227	15
3	Lenz Charles J., McBane Robert D., Cohoon Kevin P., Janczak Dawid T., Simmons Benjamin S., Saadiq Rayya A., **Mimier Małgorzata**, Casanegra Ana I., Daniels Paul R., Wysokiński Waldemar E.: Testicular vein thrombosis: incidence of recurrent venous thromboembolism and survival, European Journal of Haematology, 2018, vol. 100, nr 1, s. 83-87, DOI:10.1111/ejh.12985	2,217	25
4	Janczak Dawid T., **Mimier Małgorzata** K., McBane Robert D., Kamath Patrick S., Simmons Benjamin S., Bott-Kitslaar Dalene M., Lenz Charles J., Vargas Emily R., Hodge David O., Wysokiński Waldemar E.: Rivaroxaban and apixaban for initial treatment of acute venous thromboembolism of atypical location, Mayo Clinic Proceedings, 2018, vol. 93, nr 1, s. 40-47, DOI:10.1016/j.mayocp.2017.10.007	7,091	45
5	**Mimier Małgorzata** K., Janczak Dawid T., McBane Robert D., Houghton Damon E., Wysokiński Waldemar E.: Thrombosis of atypical location: how to treat patients in the era of direct oral anticoagulants?, Polskie Archiwum Medycyny Wewnętrznej, 2018, vol. 128, nr 10, s. 604-608, DOI:10.20452/pamw.4333	2,882	30
6	Grzybowski Andrzej E., **Mimier Małgorzata** K.: Evaluation of the association between the risk of central retinal artery occlusion and the concentration of environmental air pollutants, Journal of Clinical Medicine, 2019, vol. 8, nr 2, art.206 [8 s.], DOI:10.3390/jcm8020206	3,303	140
7	**Mimier-Janczak Małgorzata**, Kaczmarek Dorota, Janczak Dawid, Kaczmarek Radosław: Optical coherence tomography angiography as a new tool for evaluation of the subclinical retinal involvement in patients with systemic lupus erythematosus - a review, Journal of Clinical Medicine, 2021, vol. 10, nr 13, art.2887 [11 s.], DOI:10.3390/jcm10132887	4,964	140

1

8	**Mimier-Janczak Małgorzata**, Kaczmarek Dorota, Proc Krzysztof, Misiuk-Hojło Marta, Kaczmarek Radosław: Evaluation of subclinical retinal disease in patients affected by systemic lupus erythematosus with no evidence of ocular involvement - an optical coherence tomography angiography original study, Journal of Clinical Medicine, 2022, vol. 11, nr 24, art.7417 [12 s.], DOI:10.3390/jcm11247417	4,964*	140
	**IF 2021* Podsumowanie	27,776	550

1.2 Publikacje w czasopiśmie bez IF

Lp.	Opis bibliograficzny	Punkty
1	Janczak Dariusz, Leśniak Michał, **Mimier Małgorzata**, Janczak Dawid: Nowoczesne poglądy na temat leczenia ostrej zakrzepicy żył głębokich kończyn dolnych, Chirurgia po Dyplomie, 2016, vol. 11, nr 4, 4-8, 34	4
2	Janczak Dariusz, Leśniak Michał, **Mimier Małgorzata**, Janczak Dawid: Zakrzepica żył centralnych - etiologia, symptomatologia, diagnostyka i leczenie, Chirurgia po Dyplomie, 2016, vol. 11, nr 5, s. 37-41	4
3	**Mimier Małgorzata**, Janczak Dawid, Hill-Bator Aneta, Sebastian Agata, Wiland Grażyna, Misiuk-Hojło Marta: Management of corneal melting in a patient with long-standing rheumatoid arthritis - case report, Klinika Oczna, 2016, vol. 118, nr 3, s. 235-237, DOI:10.5114/ko.2016.71711	10
4	Janczak Dariusz, **Mimier Małgorzata**, Leśniak Michał, Janczak Dawid: Porównanie wyników leczenia tętniaków aorty piersiowo-brzusznej metodą endowaskularną i klasyczną, Chirurgia po Dyplomie, 2017, vol. 12, nr 1, s. 29-32	4
5	Janczak Dariusz, Leśniak Michał, **Mimier Małgorzata**, Janczak Dawid: Leczenie zespołu pozakrzepowego - co mówią wytyczne? Podsumowanie dla internisty, Medycyna po Dyplomie, 2017, vol. 26, nr 1, 9-10, 12-14	5
6	Grzybowski Andrzej, **Mimier Małgorzata**, Misiuk-Hojło Marta: Farmakologiczne metody leczenia starczowzroczności, OphthaTherapy. Terapie w Okulistyce, 2017, vol. 4, nr 4, s. 237-240, [Publikacja w czasopiśmie spoza listy MNiSW], DOI:10.24292/01.OT.291217.07	1
7	**Mimier Małgorzata**, Bator Kaja, Hill-Bator Aneta: Nowe metody leczenia biologicznego nieinfekcyjnego zapalenia błony naczyniowej, Przegląd Reumatologiczny, 2017, vol. 13, nr 2, s. 1-2	0
8	Sebastian Agata, Wojtala Patryk, Łubiński Łukasz, **Mimier Małgorzata**, Chlebicki Arkadiusz, Wiland Piotr: Disease activity in axial spondyloarthritis after discontinuation of TNF inhibitors therapy, Reumatologia, 2017, vol. 55, nr 4, s. 157-162, DOI:10.5114/reum.2017.69775	14
9	Misiuk-Hojło Marta, **Mimier Małgorzata**: Wpływ hialuronianu sodu i witaminy B_{12} na pozabiegową suchość oczu, Przegląd Okulistyczny, 2018, vol. 15, nr 5-6, s. 4	0
10	Mulak Małgorzata, Szumny Dorota, Czak Wojciech, **Mimier Małgorzata**, Bujak Henryk, Misiuk-Hojło Marta: Decrease corneal hysteresis in early glaucoma patients measured with ocular response analyzer (ORA) helps in early diagnosis of glaucoma, Current Trends in Biomedical Engineering & Biosciences, 2019, vol. 19, nr 1, art.556004 [6 s.], [Publikacja w czasopiśmie spoza listy MNiSW], DOI:10.19080/CTBEB.2019.19.556004	5

11	Rusiecka-Ziółkowska Jolanta Barbara, Hill-Bator Aneta, Piątkowska Elżbieta, **Mimier-Janczak Małgorzata**, Bator Kaja, Misiuk-Hojło Marta: The eye wipes with polyhexanide (HexaClean) in preoperative prophylaxis of cataract surgery, Ophthalmology Journal, 2023, vol. 8, s. 38-45, DOI:10.5603/oj.2023.0009	70
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3. Varia

3.1 Komentarz

3.2 Inne

Lp.	Opis bibliograficzny
1	**Mimier Małgorzata**: Zastosowanie nanocząsteczkowych kropli do oczu - polsko-islandzka wymiana wiedzy, Przegląd Okulistyczny, 2017, vol. 14, nr 5-6, s. 6

4. Abstrakty

Lp.	Opis bibliograficzny
1	**Mimier Małgorzata**, Janczak Dawid, Simmons Benjamin, Lenz Charlez, Bott-Kitslaar Dalene, Saadiq Rayya, Ransone Teresa, Kamath Patrick, McBane Robert, Wysokiński Waldemar: Rivaroxaban and apixaban for treatment of venous thrombosis of atypical location, Circulation, 2016, vol. 134, nr suppl.1, poz.A19736, [The American Heart Association 2016 - Scientific Sessions and Resuscitation Science Symposium. New Orleans (Louisiana), 12-14 November 2016. Abstracts]
2	**Mimier Małgorzata**: Wpływ marihuany na ciśnienie wewnątrzgałkowe, W: Konferencja "Interdyscyplinarność przyszłością nauki". Zieleniec, 4-6.11.2016. Księga abstraktów 2016, s. 39
3	Czak Wojciech, Piróg-Mulak Małgorzata, Ejma Maria, Gurański Konstanty, Nowakowski Jonatan, **Mimier Małgorzata**, Misiuk-Hojło Marta: Wpływ przezblaszkowego gradientu ciśnień na ustawienie blaszki sitowej twardowki, W: XLVII Zjazd Okulistów Polskich. Wrocław, 16-18.06.2016 r. Streszczenia prac naukowych [CD-ROM] 2016, 117 poz.II/4
4	**Mimier Małgorzata**, Hill-Bator Aneta, Janczak Dawid, Czak Wojciech, Piróg-Mulak Małgorzata: Wysoka wartość ciśnienia wewnątrzgałkowego jako czynnik diagnostyczny herpetycznego zapalenia błony naczyniowej oka - opis przypadku, W: XLVII Zjazd Okulistów Polskich. Wrocław, 16-18.06.2016 r. Streszczenia prac naukowych [CD-ROM] 2016, 271 poz.1
5	Bott-Kitslaar Dalene, Simmons Benjamin, Janczak Dawid, **Mimier Małgorzata**, Saadiq Rayya, McBane Robert, Wysokiński Waldemar: Efficacy and safety of rivaroxaban verses apixaban in the treatment of acute VTE, W: 18th Meeting of the European Venous Forum. Porto, Portugal, 29 June - 1 July 2017. Scientific programme and book of abstracts, Torino 2017, Edizioni Minerva Medica, 12-13 poz.2.2
6	Misiuk-Hojło Marta, **Mimier Małgorzata**: Jaskra w przebiegu zespołu pseudoeksfoliacji = Pseudoexfoliative glaucoma, W: III Międzynarodowa Konferencja Naukowo-Szkoleniowa - Akademia Optegra "Okulistyka na co dzień". Warszawa, 19-20 maja 2017. Program i streszczenia, Wrocław 2017, InspireCongress Sp. z o.o. ; SR-Poligrafia, 52 poz.II/4, ISBN 978-83-947480-2-9
7	**Mimier Małgorzata**: Choroby oczu kiedyś i dziś, W: Konferencja "Interdyscyplinarność przyszłością nauki". Zieleniec, 10-12 listopada 2017. Księga abstraktów 2017, s. 34

8	**Mimier Małgorzata**: Zespół suchego oka - problem nie tylko starszych osób, W: Konferencja "Interdyscyplinarność przyszłością nauki". Zieleniec, 7-9 kwietnia 2017. Księga abstraktów 2017, s. 52
9	**Mimier Małgorzata**, Bator Kaja, Hill-Bator Aneta: Zastosowanie lasera mikropulsowego w leczeniu cukrzycowego obrzęku plamki - opisy przypadków = The use of micropulse laser in the treatment of the diabetic macular edema - case reports, W: VII Międzynarodowa Konferencja "Okulistyka - kontrowersje". Wrocław, Poland, 19-21.10.2017. Program i streszczenia, (red.) Marta Misiuk-Hojło, Wrocław 2017, SR-Poligrafia ; InspireCongress Sp. z o.o., 162-163 poz.6, ISBN 978-83-947480-7-4
10	Misiuk-Hojło Marta, **Mimier Małgorzata**: Olbrzymiokomórkowe zapalenie tętnicy skroniowej widziane oczami okulisty = Giant cell temporal arteritis - ophthalmologist's vision, W: IX Śląski Meeting Siatkówkowy. Katowice, 29-30 listopada 2018. Program i streszczenia, Wrocław 2018, SR-Poligrafia ; InspireCongress Sp. z o.o., 72 poz.VI/1, ISBN 978-83-952446-1-2
11	**Mimier Małgorzata**: Jak okuliści wywołali II wojnę światową, W: Interdyscyplinarność przyszłością nauki. Zieleniec, 10-12 listopada 2018. Księga abstraktów 2018, s. 7, [[Dostęp 10.09.2019]. Dostępny w: http://www.doktoranci.umed.wroc.pl/wp-content/uploads/2019/09/Jesie%C5%84-2018-Biomed.pdf]
12	Zimmer Katarzyna, Pytrus W., **Mimier Małgorzata**, Zając-Pytrus Hanna, Turno-Kręcicka Anna: Chronic uveitis leading to ciliary body failure: case report, W: 37th Congress of the European Society of Cataract and Refractive Surgeons. Paris, France, 14-18 September 2019. Program - e-posters [online] 2019, [[Dostęp 18.09.2019]. Dostępny w: https://www.escrs.org/paris2019/programme/poster-village-details.asp?id=33429]
13	Mulak Małgorzata, Czak Wojciech, Szumny Dorota, **Mimier Małgorzata**, Bujak Henryk, Zimmer Katarzyna, Nowakowski Jonatan, Misiuk-Hojło Marta: Evaluation of corneal hysteresis in early glaucoma patients - a new tool for detection of the disease, W: 8th World Glaucoma Congress. Melbourne (Australia), March 27-30, 2019. Abstract book 2019, 177 poz.P-WT-066, [[Dostęp 27.08.2019]. Dostępny w: https://wga.one/download/228/2019/163907/wgc-2019_abstractbook.pdf]
14	Misiuk-Hojło Marta, **Mimier-Janczak Małgorzata**: Nowe możliwości postępowania w olbrzymiokomórkowym zapaleniu tętnicy skroniowej = New treatment methods in giant cell temporal arteritis, W: III Międzynarodowa Konferencja "Innowacje w okulistyce" ; Sympozjum Presbiopii - PRESBYMANIA. Katowice, 16-18.05.2019. Program i streszczenia 2019, 116 poz.IV/8
15	Pysz Marta, Zimmer Katarzyna, Krent Judyta, Czyszczoń Marek, **Mimier-Janczak Małgorzata**, Misiuk-Hojło Marta: Obustronna neuropatia n. II w przebiegu leczenia izotretinoiną = Bilateral optic nerve neuropathy secondary to the treatment with isotretinion, W: IX Międzynarodowa Konferencja "Okulistyka - kontrowersje". Wrocław, 24-26.10.2019. Program i streszczenia, (red.) Marta Misiuk-Hojło, Wrocław 2019, SR-Poligrafia ; InspireCongress Sp. z o.o., 124-125 poz.4, ISBN 978-83-952446-9-8
16	Zimmer Katarzyna, **Mimier-Janczak Małgorzata**, Zając-Pytrus Hanna, Adamiec-Mroczek Joanna, Turno-Kręcicka Anna: Trudności diagnostyczne w grzybiczym zapaleniu błony naczyniowej - opis przypadku = Diagnostic difficulties in fungal uveitis - a case report, W: IX Międzynarodowa Konferencja "Okulistyka - kontrowersje". Wrocław, 24-26.10.2019. Program i streszczenia, (red.) Marta Misiuk-Hojło, Wrocław 2019, SR-Poligrafia ; InspireCongress Sp. z o.o., 126-127 poz.5, ISBN 978-83-952446-9-8
17	**Mimier-Janczak Małgorzata**: Dlaczego chirurgia refrakcyjna doprowadza do samobójstwa?, W: Interdyscyplinarność przyszłością nauki. Zieleniec, 12-14 kwietnia 2019. Księga abstraktów 2019, s. 30, [[Dostęp 12.09.2019]. Dostępny w: http://www.doktoranci.umed.wroc.pl/wp-content/uploads/2019/09/Wiosna-2019-Biomed-1.pdf]

18	**Mimier-Janczak Małgorzata**: Okulistyczny folklor, W: Konferencja "Interdyscyplinarność przyszłością nauki". Zieleniec, 15-17.11.2019. Księga abstraktów, Wrocław 2019, s. 43
19	Zimmer Katarzyna, **Mimier-Janczak Małgorzata**, Szaliński Marek, Pomorska Maria, Gajdzis Małgorzata, Kaczmarek Radosław, Misiuk-Hojło Marta: Czy sport to zdrowie - przypadek powikłanego urazu nordic walking, W: Okulistyczny Festiwal Filmowy i Fotograficzny. Gdynia - Wrocław, 30-31.08.2019. Program i streszczenia, (red.) Marta Misiuk-Hojło, Wrocław 2019, InspireCongress Sp. z o.o. ; SR-Poligrafia, 64 poz.VII/37, ISBN 978-83-952446-8-1
20	Grzybowski A., **Mimier Małgorzata**: Association between the risk of central retinal artery occlusion and the concentration of environmental air pollutants - the original study, W: The Retina Society 52nd Scientific Meeting. London, England, 11-15 September 2019. Program [& abstracts online] 2019, [2 s.], [[Dostęp 03.09.2013]. Dostępny w: https://www.xcdsystem.com/retinasociety/program/5axOY6c/index.cfm?pgid=56]
21	Zimmer Katarzyna, **Mimier-Janczak Małgorzata**, Zając-Pytrus Hanna, Adamiec-Mroczek Joanna, Helemejko Iwona, Turno-Kręcicka Anna: The unknown enemy: diagnostic difficulties in the fungal uveitis, W: 38th Congress of the ESCRS. Online, 2-4 October 2020. Program - e-posters [online] 2020, poz.[35975], [[Dostęp 23.03.2021]. Dostępny w: https://www.escrs.org/amsterdam2020/programme/poster-overview.asp]
22	Misiuk-Hojło Marta, **Mimier-Janczak Małgorzata**: Powierzchnia oka a jaskra = Ocular surface and glaucoma, W: CORNEA 2021 online : XIII Międzynarodowe Sympozjum "Postępy w diagnostyce i terapii schorzeń rogówki", 8-10 kwietnia. Program i streszczenia, (red.) Edward Wylęgała, Wrocław 2021, InspireCongress Sp. z o. o. ; SR-Poligrafia, 79 poz.IX/2, ISBN ISBN 978-83-956061-7-5

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mój udział polegał na pomocy w zaprojektowaniu badania i metodologii, nadzorze merytorycznym oraz recenzji i korekcie ostatecznej wersji pracy.

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Subclinical retinopathy in systemic lupus erythematosus patients – Optical Coherence Tomography study. Reumatologia. https://doi.org/10.5114/reum/166296
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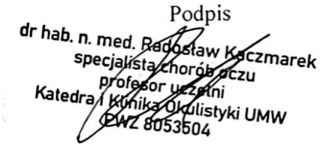

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