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ORIGINAL RESEARCH

Foveal Avascular Zone Area in Patients with Systemic Lupus Erythematosus Using Optical Coherence Tomography Angiography

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Purpose: To evaluate the area of the superficial foveal avascular zone (SFAZ) and deep foveal avascular zone (DFAZ) in patients with systemic lupus erythematosus (SLE) using optical coherence tomography angiography (OCT-A) and to associate the SFAZ and DFAZ areas with medication.

Design: A cross-sectional observational study.

Patients and Methods: This study included 36 eyes of 36 SLE patients and 33 eyes of 33 healthy controls. SFAZ, DFAZ, and central retinal thickness (CRT) were measured using Spectralis OCT-A. Data on medical history and medications were collected to determine associations with SFAZ and DFAZ areas.

Results: SFAZ and DFAZ areas showed no significant association with hydroxychloroquine/chloroquine duration or immunosuppressive therapy ($p>0.05$).

Conclusion: The SFAZ and DFAZ areas in patients with SLE were not significantly larger than those in healthy controls. However, the CRT was significantly thinner.

Keywords: systemic lupus erythematosus, optical coherence tomography angiography, foveal avascular zone

Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease.[1] SLE affects multiple organs including skin, joints, lungs, kidneys, and CNS. SLE can also affect the periorbita, ocular adnexa, eye, and optic nerve.[2,3] Approximately one- third of SLE patients experience ocular involvement.[4] The most common ocular manifestation is keratoconjunctivitis sicca and retinopathy is a significant cause of vision- threatening complications.[2,5] The incidence of retinopathy is 3% to 29%, with a higher prevalence observed in patients with active systemic disease.[6] SLE retinal vasculopathy is associated with the presence of systemic disease activity, occult or overt. All findings of retinopathy are considered to reflect vascular damage such as vasculitis and thromboembolism.[7,8] However, fluorescein leakage on angiography can be detected even in eyes with a clinically unremarkable fundus examination.[8,9]

Optical coherence tomography angiography (OCT-A), a non-invasive retinal imaging technique, has recently been used for the study of the retinal and choroidal microvasculature. OCT-A is widely used to study diabetic retinopathy,[10] age-related macular degeneration, retinal vascular occlusions,[11] and sickle cell disease.[12] A few studies have revealed decreased retinal microvascular density[13] and enlargement of the foveal avascular zone (FAZ) in patients with SLE compared to normal subjects.[14–16]

Most studies have used the AngioVue OCT-A device (Optovue, Fremont, CA, USA). Our study provides device-specific evidence from Spectralis OCT-A, complementing recent reports (eg, 10.1186/s40942-024-00617-6) and contributing to the literature on microvascular changes in SLE.

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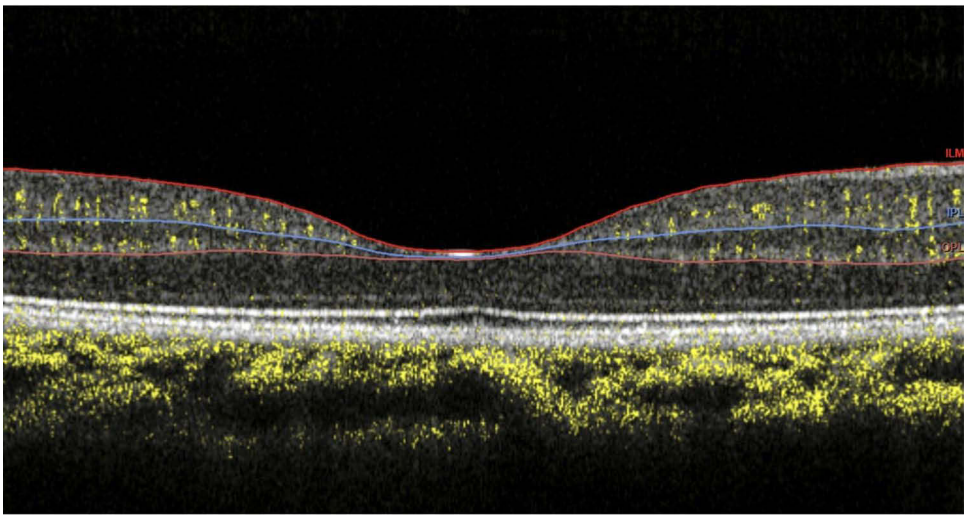

Figure 1 Cross sectional B-scan images show superficial vascular plexus layer and deep vascular plexus layer.

This study aims to evaluate and compare the FAZ area in the superficial (SFAZ) and deep (DFAZ) vascular plexus layers in SLE patients (Figure 1) and healthy controls using Spectralis OCT-A (Heidelberg Engineering, Heidelberg, Germany). We hypothesize that SLE patients will exhibit significant differences in SFAZ and DFAZ areas compared to healthy controls, potentially revealing novel patterns of retinal microvascular involvement in this disease.

Materials and Methods

Study Design and Setting

This cross-sectional observational study was conducted at Suddhavej Hospital, Faculty of Medicine, Mahasarakham University, from July 2020 to June 2021. This study was approved by the Mahasarakham University Review Board, and adhered to the tenets of the Declaration of Helsinki.

Study Participants

Inclusion Criteria

Patients with SLE and healthy controls older than 18 years of age. Patients with SLE were diagnosed by internists according to the American College of Rheumatology classification criteria.[14] All participants provided written informed consent prior to their inclusion in the study.

Exclusion Criteria

(1) poor quality of images and (2) ocular pathologies that affect the FAZ, such as macular edema secondary to diabetic retinopathy or retinal vein occlusion.

Based on previous studies reporting FAZ area measurements, a sample size of 30 eyes per group was estimated to achieve 80% power at a 0.05 significance level to detect a mean difference of 0.05 mm^2 in FAZ area, assuming a standard deviation of 0.1 mm^2. Our study exceeded this target with 36 SLE eyes and 33 control eyes. Thirty-six eyes of 36 patients with SLE (study group) and 33 eyes of 33 age- and sex-matched healthy subjects (control group) were included in this study. If both eyes of a participant were eligible, one eye was randomly selected for inclusion in the analysis to avoid inter-eye correlation. Data on age, sex, duration of hydroxychloroquine or chloroquine (HCQ/CQ) treatment, immunosuppressive drug use, and ocular findings were collected. All participants underwent a standard ophthalmic examination, including best-corrected visual acuity using Snellen's chart, intraocular pressure measurement using an air-puff tonometer due to the study population was deemed to have low risk of glaucoma, and the air puff was used for that reason, slit-lamp examination of the anterior segment, and fundus examination. OCT scans with spectral domain OCT (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) were performed to measure central retina thickness (CRT)

automatically from the software of the system and the area was corrected by the same retina specialist.CRT was defined as the average thickness of the macula in the central 1 mm diameter ring of the ETDRS grid. Data from the right eye were used for the analyses.

Five frames were averaged, with a distance of 6 μm between B-scans, to ensure high-quality imaging.

Study Outcome and Measures

The primary outcome was the comparison of the SFAZ and DFAZ areas between the study and control groups.

The secondary outcomes were (1) comparison of CRT between the study and control groups. (2) To determine the possible relationship between the SFAZ and DFAZ and the duration of HCQ/CQ use. (3) To determine the possible relationship between SFAZ, DFAZ, and immunosuppressive therapy.

Statistical Analysis

STATA version 15 (Stata Corp., College Station, Texas, USA) was used for statistical analyses. Categorical data are presented as percentages (%) and numbers (n). Continuous variables were presented as means with standard deviations (SD) according to their normal distribution patterns. Differences between the two groups were compared using the *t*-test for continuous data and Fisher's exact test for categorical data. The intraclass correlation coefficient (ICC) was calculated to assess the inter-rater reliability. Statistical significance was set at $p < 0.05$.

Results

Baseline characteristics between study group and control group were similar. In the study group, the mean age was 31.80 ±10.96 years. Thirty-four patients were female (Table 1). All enrolled SLE patients were asymptomatic for ocular complaints, and the clinical ophthalmic examination, including dilated funduscopy, revealed no signs of active retinopathy, macular edema, or other pathologies that would meet the exclusion criteria. Thirty-three patients (91.67%) were having CQ/HCQ.

The mean area of SFAZ and DFAZ in study group were 0.38±0.10 mm2 and 0.39 ±0.10 mm2, respectively (Table 2). Both areas were larger than those in control group (0.35±0.10 mm2, 0.36±0.10 mm2). However, there was no significant difference between the groups (SFAZ: p=0.311; DFAZ: p=0.158). Figure 2 shows representative images of the FAZ and DFAZ in patients with SLE. The inter-rater reliability for FAZ area measurement by the two retinal specialists was excellent (SFAZ: ICC = 0.992, 95% CI: 0.988–0.994; DFAZ: ICC = 0.987, 95% CI: 0.981–0.990).

The mean CRT in the study group and control group were 248.86±18.82 μm and 259.31± 7.90 μm, respectively. The CRT in the study group was significantly lower than that in the control group (p=0.022).

Table 1 Demographic and Clinical Characteristics of the Study Participants

	Control (n=33)	SLE (n=36)	*p* value
Mean age (years)±SD	31.27±10.11	31.80±10.96	0.835
Sex			
Female, n	31	34	
Male, n	2	2	
SFAZ area (mm2)	0.35±0.10	0.38±0.10	0.311
DFAZ area (mm2)	0.36±0.10	0.39±0.10	0.158
CRT (μm)	259.31±17.90	248.86±18.82	0.022

Notes: Table 1 presents the demographic and clinical characteristics of the study participants. No statistically significant differences were observed between the study and control groups in terms of age, sex, SFAZ area, DFAZ area, or CRT. In the study group, the mean age was 31.80±10.96 years. Thirty-four patients were female (Table 1). In all patients, no ocular symptoms were reported and ocular examination results, including retinal examination, were normal. Thirty-three patients (91.67%) patients received CQ/HCQ.

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Table 2 Comparison of the Area of Superficial Foveal Avascular Zone and Deep Foveal Avascular Zone Between Patients Using HCQ/CQ for <5 years and ≥ 5 years and Immunosuppressive Therapy

	Duration of HCQ/CQ use			IMT		
	< 5 year (n=28)	**≥ 5 years (n=5)**	***p value***	**No (n=16)**	**Yes (n=20)**	***p value***
SFAZ area (mm2)	0.38±0.11	0.37±0.07	0.731	0.39±0.12	0.36±0.10	0.518
DFAZ area (mm2)	0.40±0.10	0.39±0.07	0.771	0.41±0.10	0.38±0.09	0.458

Notes: Table 2 presents the comparison of superficial and deep foveal avascular zone (SFAZ and DFAZ) areas among patients with SLE according to the duration of chloroquine/hydroxychloroquine (CQ/HCQ) therapy and the use of immunosuppressive therapy (IMT). No statistically significant differences were observed in either SFAZ or DFAZ area between patients treated with CQ/HCQ for <5 years compared with ≥5 years (SFAZ: 0.38±0.11 vs 0.37±0.07 mm², p=0.731; DFAZ: 0.40±0.10 vs 0.39±0.07 mm², p=0.771). Similarly, no significant differences were found between patients receiving IMT and those not receiving IMT (SFAZ: 0.36±0.10 vs 0.39 ±0.12 mm², p=0.518; DFAZ: 0.38±0.09 vs 0.41±0.10 mm², p=0.458).

Comparison of SFAZ and DFAZ areas between patients treated with HCQ/CQ for <5 years and ≥5 years did not show statistically significant differences (SFAZ: p=0.731, DFAZ: p=0.771).

Discussion

SLE retinopathy may present with cotton-wool spots, retinal hemorrhages, and vascular changes. Fluorescein angiography can reveal leakage or capillary nonperfusion even in clinically normal eyes. OCT-A provides a non-invasive approach to detect such microvascular abnormalities at an early stage.

The FAZ was devoid of retinal blood vessels. Size and shape of the FAZ have been studied and demonstrated to be an indicator of retinal pathology.[18] Enlargement of FAZ was found in diseases involving macular circulation deficiency such as diabetic retinopathy and retinal vein occlusion.[19–21,22,23] Previous studies in SLE patients showed enlarged FAZ area in comparison with controls.[14–16,24] In contrast to previous studies, our result found enlargement of SFAZ area and DFAZ area in patients with SLE, but no statistically significant difference from controls. However, the interpretation should be cautioned because of differences in the device and segmentation. Corvi et al suggested that the comparison between instruments should be evaluated with concern, and the set of measurements from the various instruments is not interchangeable regarding FAZ for both the superficial and deep capillary plexus.[25,26] Our results should be used for comparison with the data produced by the Spectralis OCT-A device.

In this study, patients with HCQ/CQ underwent ophthalmic examination following the American Academy of Ophthalmology recommendations for screening for HCQ and CQ retinopathy in 2016. The risk of HCQ retinal toxicity is < 1% with recommended doses up to 5 years and increases sharply after 5 years.[22] Bulut et al found that FAZ area in

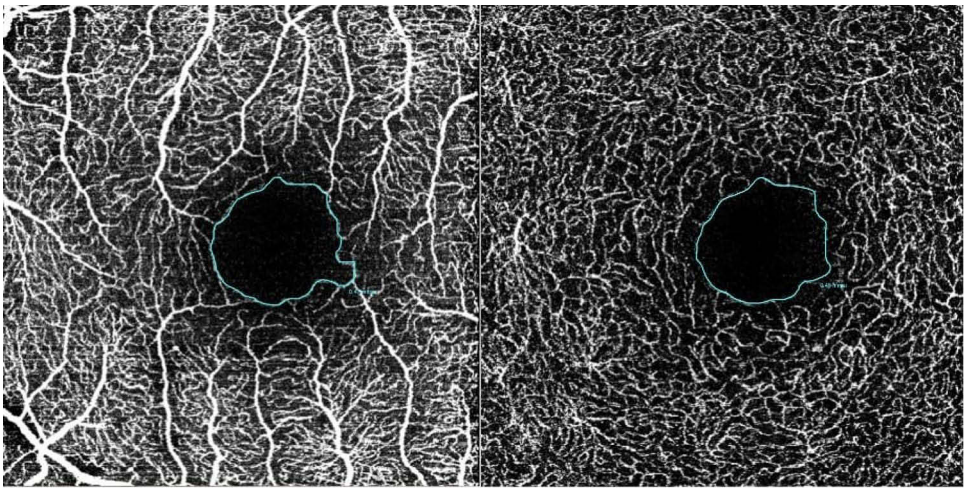

Figure 2 Representative images of the SFAZ (left) and DFAZ (right) in a patient with SLE.

patients using HCQ for ≥ 5 years was wider than patients using HCQ for < 5 years.[24] We could not detect the difference between those groups probably because of too few patients in taking HCQ/CQ for ≥ 5 years group.

Immunosuppressive drugs are primarily used to treat inflammatory ocular disorders. In SLE, immunosuppressive drugs are used to control disease and ocular inflammation. Drug regimens for the initial therapy typically include high-dose oral corticosteroids that are tapered if the disease is quiet. An immunosuppressive drug is added to an oral corticosteroid regimen for a patient with chronic disease to control inflammation in response to corticosteroids alone and to prevent corticosteroid-induced toxicity.[27,28] Common ocular side effects of IMT include cataracts and glaucoma due to corticosteroids, and reactivation of cytomegalovirus retinitis and toxoplasmic chorioretinitis have been reported; however.[29] We were unable to find any literature that found an association between the FAZ area and IMT. However, we did not find a difference in FAZ area between patients with SLE with and without IMT.

We found a significant reduction in CRT in patients with SLE compared with that in controls. An et al also found that foveal retinal thickness significantly decreased in with SLE patients.[14] Bulet et al detected slight thinning of the foveal, parafoveal, and perifoveal macular thickness in patients treated with HCQ/CQ for ≥ 5 years.[23] Several studies have reported that HCQ/CQ retinopathy commonly involves the parafoveal and perifoveal regions. Retinal thinning is an early sign of retinal toxicity despite normal fundus.[30,31] CRT thinning related to SLE, HCQ/CQ retinal toxicity, or both, requires further investigation.

A key limitation of this study is its cross-sectional design and small sample size. Furthermore, a significant methodological limitation is the lack of data on axial length and intraocular pressure. We were therefore unable to perform magnification correction (eg, using the Littmann-Bennett formula), which is important as ocular axial length can significantly affect the dimensions of OCT-A measurements. The use of an air-puff tonometer rather than Goldmann applanation tonometry also provided less precise IOP measurements. Future prospective studies with larger cohorts and correction for ocular magnification are warranted to confirm these findings.

Conclusion

In this cohort, SLE was not associated with a statistically significant enlargement of the SFAZ or DFAZ when measured with Spectralis OCT-A. However, a significant thinning of the CRT was observed. These findings underscore the importance of considering device-specific differences in OCT-A measurements and suggest that CRT thinning may be a more sensitive biomarker of early retinal changes than FAZ area in some SLE populations.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The author(s) report no conflicts of interest in this work.

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