• Clinical Research •

Choroidopathy in patients with systemic lupus erythematosus using enhanced depth imaging spectral domain optical coherence tomography and optical coherence tomography angiography

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Abstract

• **AIM:** To evaluate the choroidopathy in patients with systemic lupus erythematosus (SLE) using enhanced depth imaging spectral domain optical coherence tomography (EDI SD-OCT) and optical coherence tomography angiography (OCTA).

• **METHODS:** A total of 74 patients with SLE and 40 healthy volunteers were included in this cross-sectional study. SLE patients were further divided into three subgroups based on clinical and blood biochemistry findings. Ocular parameters obtained on ophthalmologic examination and optical imaging (EDI SD-OCT and OCTA) included the best corrected distance visual acuity (logMAR CDVA), subfoveal choroidal thickness (SCT), choroidal vascularity index (CVI) and vessel density (VD) of superficial capillary plexus (SCP) and deep capillary plexus (DCP).

• **RESULTS:** SLE patients had significantly lower values for CVI and VD of DCP (DVD) than control subjects. Amongst SLE patients, gender and chloroquine dose were found to be independent determinants of CVI while age predicted SCT. Steroid dose was a significant predictor for foveal VD of SCP (SVD), chloroquine dose for parafoveal SVD, gender for total DVD, and gender and steroid dose for perifoveal DVD. No correlation of logMAR CDVA and SCT was noted between SLE patients and control subjects. No correlation of SCT was noted with disease duration, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, hydroxychloroquine (HCQ) dose or steroid dose. No correlation of CVI was noted with patient age, disease duration, SLEDAI score, HCQ dose or steroid dose. No significant difference was noted between SLE subgroups in terms of any of the ocular parameters studied.

• **CONCLUSION:** The findings reveal the presence of ocular findings suggestive of early onset choroidopathy on EDI SD-OCT and OCTA in SLE patients, in the absence of ocular manifestations or active disease.

• **KEYWORDS:** systemic lupus erythematosus; choroidopathy; enhanced depth imaging spectral domain optical coherence tomography; optical coherence tomography angiography; vessel density

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease with heterogenous clinical manifestations and a chronic relapsing course[1-3]. SLE affects virtually every organ through direct autoimmune processes or secondary pathologic states such as hypercoagulability and vasculitis[1,3-4].

Ocular involvement, although not outlined in diagnostic criteria for SLE defined by the American College of Rheumatology, can occur in up to 30% of SLE patients and are primarily related to keratoconjunctivitis, retinopathy and optic neuritis in most of cases, while they may also appear as a complication of treatment [*i.e.*, hydroxychloroquine (HCQ) toxicity or drug-induced optic neuritis][5-10].

Ocular involvement in SLE depends on the activity of the disease and often precedes the involvement of other vital organs, while potentially hazardous complications may arise if not recognized early and treated in a timely manner[7-9,11]. Detection of posterior segment involvement (*i.e.*, retinopathy, optic neuritis, and choroidopathies) is particularly important in

this regard, given that these lesions are common and related to disease activity, in addition to the risk of permanent visual loss in case of delayed diagnosis and treatment[7-8,12-15].

Indeed, lupus retinopathy, albeit usually diagnosed in already well-advanced disease states, has become a more commonly detected ocular pathology than lupus choroidopathy in SLE patients, due to limited technical possibilities to analyze the deeper choroidal structures in the past[7,11-12,16-19].

In recent years, enhanced depth imaging (EDI) spectral domain optical coherence tomography (EDI SD-OCT) enabled to perform in-depth evaluations of the retina as well as the choroid *via* analysis of high-resolution three-dimensional images[8,10,20-22]. Similarly, optical coherence tomography angiography (OCTA), a fast and non-invasive imaging modality, is used to visualize vascular alteration in small vessels and capillaries of the retina and choriocapillar[13,16,19,23-25].

Choroidal thickness is suggested to decrease in SLE patients due to vasculitis and deposition of complement factors leading to a reduction in blood flow, while the choroidal vascularity index (CVI), as an upcoming method for assessment of choroidal vasculature and disease progression in SLE, is suggested to be less susceptible to physiological elements and thus to improve choroidal thickness assessment by providing more reliable data[10,20,26]. However, there are still limited number of studies with contradictory results on choroidal alterations in relation to disease activity or ongoing treatments in SLE patients[10,13,20,26-30].

Therefore, this study was designed to evaluate chorioretinal involvement *via* optical imaging (EDI SD-OCT and OCTA) in SLE patients in comparison to healthy controls, and to assess the choroidopathy in relation to disease activity, SLE subgroups and ongoing treatments.

PARTICIPANTS AND METHODS

Ethical Approval Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the Ankara City Hospital Clinical Research Ethics Committee (Date of Approval: 07/09/2022; Protocol No: E1/2765/2022).

Study Population A total of 74 patients with SLE and 40 healthy volunteers were included in this cross-sectional observational study conducted between September 12, 2022 and November 25, 2022 at a tertiary care rheumatology clinic. SLE patients were further divided into three subgroups including mucocutaneous involvement group (SLE-CUT; n=35), systemic involvement group (SLE-SYS; n=27) and antiphospholipid syndrome group (SLE-APS; n=12). In mucocutaneous involvement group affected area are restricted to the skin and mucosa; while systemic involvement group has extracutaneous manifestations like nephrological, musculoskeletal, serous, cardiopulmonary, neurologic and psychiatric involvements[31].

The antiphospholipid syndrome group is specified by the presence of antiphospholipid antibodies, namely lupus anticoagulant, anticardiolipin antibodies, or anti-b2-glycoprotein-I antibodies[32].

SLE patients with regular follow up attendance and control subjects with no known systemic disease or ocular disease, who aged 18-65y were included in the study. Previous history for eye operation or intraocular injection for any reason, SLE patients with ocular involvement, presence of additional ocular disease, diabetes mellitus, or an ocular pathology such as media opacity that challenges ocular measurements were the exclusion criteria of the study.

Assessments Data on patient demographics (age, gender) were recorded in patient and control groups, while SLE characteristics (duration of disease, disease activity, SLE involvement) and ongoing medical treatments (HCQ and steroid) were recorded in the patient group. Ophthalmologic examination was performed for visual acuity testing with Snellen chart and biomicroscopic anterior segment and dilated fundus examination, while optical imaging was based on EDI SD-OCT and OCTA. All optical coherence tomography (OCT) scans were carried out between 9 *a.m.* and 11 *a.m.* to minimize the impact of diurnal variation. The ocular parameters recorded in both patient and control groups included best corrected distance visual acuity (logMAR CDVA), subfoveal choroidal thickness (SCT, μm), CVI (%) and vessel density (VD; total, foveal, parafoveal and perifoveal) of superficial capillary plexus (SCP) and deep capillary plexus (DCP).

Patient and control groups were compared in terms of demographic characteristics and ocular parameters, while SLE subgroups were compared in terms of both demographic and clinical characteristics in addition to ocular parameters. Appropriate statistical methods were used to control the effects of age and gender difference between patient and control groups while evaluating the ocular parameters. The independent determinants of CVI, SCT, VD of SCP (SVD) and VD of DCP (DVD) were also analyzed by multivariate regression analysis with inclusion of gender, age, HCQ dose, steroid dose and disease duration as independent variables in the model.

Disease Activity Disease activity was evaluated based on Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores and classified into no activity (score 0), mild activity (score 1-5), moderate activity (score 6-10), high activity (score 11-19) and very high activity (score ≥20) groups[33].

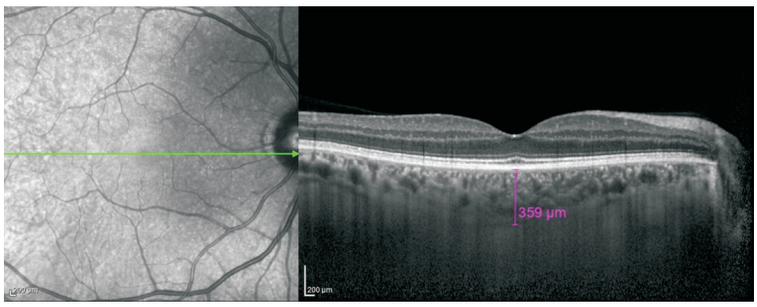

Figure 1 Enhanced-depth imaging spectral domain optical coherence tomography image.

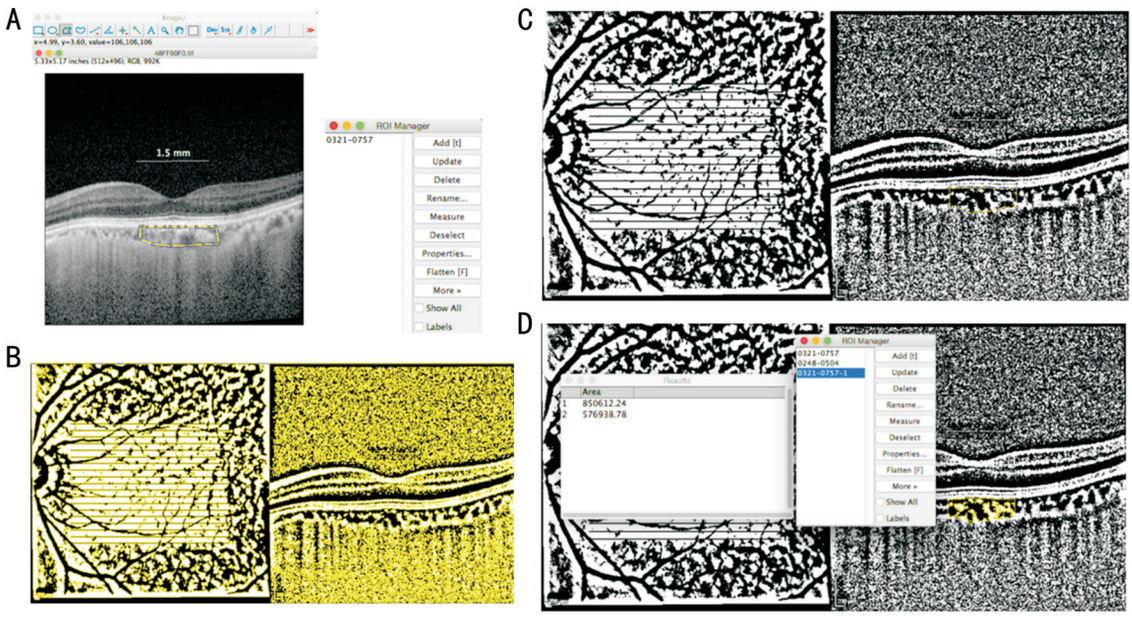

Figure 2 Choroidal vascularity index (CVI) calculation with binarization of enhanced-depth imaging spectral domain optical coherence tomography image Choroidal boundaries were traced using a region of interest of 1500 μm wide, centered on the fovea to identify the total choroidal area (A). The image was binarized using auto-local threshold (B). The image is converted to a red, green and blue image, and the color threshold tool is used to select the dark pixels, representing the luminal choroidal area (C). The CVI is calculated dividing luminal area by total choroidal area (D).

Ocular Imaging Analysis SD-OCT scans were obtained using Spectralis® SD-OCT (Heidelberg Engineering GmbH, Heidelberg, Germany) with EDI mode and single horizontal line scan through the central fovea. Choroidal thickness was measured manually from the subfoveal region, as the distance between the outer border of hyperreflective retina pigment epithelium (RPE) and the inner border of sclera using the software (Heidelberg Eye Explorer 1.7.0.0), by the same researcher (Figure 1).

CVI was derived from OCT data using a technique to evaluate subfoveal luminal choroidal area and stromal choroidal area by an image binarization process of the EDI-SD-OCT foveal scan using the free software ImageJ (version 1.47, National Institutes of Health, Bethesda, MD, USA). The OCT image is opened in ImageJ, and the polygon tool is used to select a region of interest of 1500 μm wide, centered on the fovea. The upper boundary of the region of interest is traced along the choroidal-RPE junction and the lower boundary along the sclerochoroidal junction to identify the total choroidal area. After image brightness is set at the average value and conversion to an 8-bit image, auto-local threshold is applied to binarize the image and to demarcate luminal and stromal choroidal areas. The image is converted to a red, green and blue image, and the color threshold tool is used to select the dark pixels, representing the luminal choroidal area. The luminal area (dark pixels) and stromal and total choroidal areas (bright pixels) were automatically calculated. The ratio of luminal area to the total choroidal area is considered to indicate the vascular area of the choroid (CVI) with higher values indicating a greater vascular capacity (Figure 2).

OCTA imaging was performed using the RTVue XR Avanti system with AngioVue (Optovue Inc, Fremont, California, USA), which provides a 6×6 mm angiography image comprising 304 A-scans in 3s by performing 70 000 A-scans per second with light source centered at 840 nm and 45 nm bandwidth. It enables two orthogonal OCTA images to

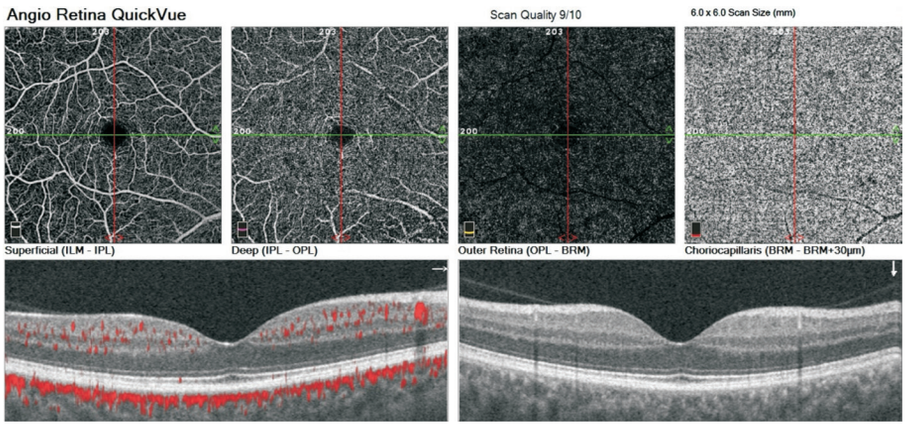

Figure 3 Optical coherence tomography angiography image.

minimize the motion artefacts. The macula was imaged using a fovea-centered 6×6 mm scan, focusing on two neuroretinal layers including SCP and DCP. The automated segmentation was performed using AngioVue module integrated to Optovue RTVue XR AVANTI software. Images with poor signal strength (signal strength <50) or those with motion artefact were not included in the study. After imaging, VD (foveal, parafoveal and perifoveal) in SCP and DCP OCT angiogram were analyzed using the AngioVue module of integrated device software (Optovue RTVue XR AVANTI, Optovue Inc, Fremont, California, USA; Figure 3).

Statistical Analysis Statistical analysis was made using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). Shapiro Wilks test was used to investigate normal distribution. Chi-square (χ^2) test and Fischer exact test were used for the comparison of categorical data, while numerical data were analyzed using Student's *t*-test and one-way ANOVA for variables with normal distribution and with Mann-Whitney *U* and Kruskal Wallis tests for non-normally distributed variables. Analysis of covariance (ANCOVA) was used to control the effects of age and gender difference between patient and control groups while evaluating the ocular parameters. Correlation between continuous variables was evaluated using Spearman's correlation analysis. Multivariate linear regression analysis was performed to determine the independent predictors of CVI, SCT, SVD, and DVD with inclusion of gender, age, chloroquine dose, steroid dose and disease duration as independent variables into the model, while "Enter" was selected as the method. Data were expressed as mean±standard deviation (SD), median (minimum-maximum) and *n* (%) where appropriate. $P<0.05$ was considered statistically significant.

RESULTS

Demographic Characteristics in SLE Patients and Controls A total of 74 patients with SLE (mean±SD age: 43.5±13.8y, 91.9% were females) and 40 healthy volunteers (mean±SD age: 33.5±9.9y, 75.5% were females) were included in this study. Significantly higher age [median (min-max) 41.5 (19.0-77.0) *vs* 29.0 (18.0-62.0)y, $P<0.001$] and higher percentage of females (91.1% *vs* 75.5%, $P=0.001$) were noted in the patient group compared with the control group (Table 1).

Table 1 Demographic characteristics in SLE patients and controls

Parameters	SLE patients (*n*=74)	Control subjects (*n*=40)	*P*
Demographics			
Age (y), mean±SD	43.5±13.8	33.5±9.9	<0.001[a]
Median (min-max)	41.5 (19.0-77.0)	29.0 (18.0-62.0)	
Gender, *n* (%)			0.001[b]
Female	68 (91.1)	27 (75.5)	
Male	6 (8.1)	13 (32.5)	

SLE: Systemic lupus erythematosus; [a]Mann Whitney *U* test, [b]Chi-Square test.

Demographic and Clinical Characteristics in SLE Patients and SLE Subgroups The disease duration was median 94mo (range, 10 to 394mo), while SLEDAI scores were consistent with no activity (40.6%) or mild activity (45.9%) in majority of patients. SLE-CUT, SLE-SYS and SLE-APS subgroups comprised the 47.3%, 36.5% and 16.2% of overall SLE patients. No significant difference was noted between SLE subgroups in terms of demographic characteristics, disease duration, SLEDAI scores and treatment doses (Table 2).

Ocular Parameters in Patient *vs* Control Groups and in SLE Subgroups SLE patients *vs* control subjects had significantly lower values for CVI [median (min-max) 63.9% (55.6-85.7)% *vs* 68.9% (57.4-76.8)%, $P=0.005$]. SLE patients *vs* control subjects also had significantly lower values for VD of DCP (DVD) including total [48.3% (31-60.9)% *vs* 52.4% (35.5-60.9)%, $P=0.032$], parafoveal [54.1% (33.5-64.0)% *vs* 57.9% (44.8-62.2)%, $P=0.020$] and perifoveal [49.3% (29.7-63.1)% *vs* 54.6% (35.6-63.4)%, $P=0.040$] quadrants. No significant difference was noted between SLE patients and controls in terms of logMAR CDVA, SCT, VD of SCP (SVD; Table 3).

Table 2 Demographic and clinical characteristics in SLE patients and SLE subgroups

Parameters	SLE patients (*n*=74)	SLE- subgroups			*P*
		SLE-CUT (*n*=35)	SLE-SYS (*n*=27)	SLE-APS (*n*=12)	
Demographics					
Age (y), median (min-max)	41.5 (19-77)	43 (19-69)	41 (22-77)	40 (19-60)	0.863[c]
Gender, *n* (%)					
Female	68 (91.9)	31 (88.6)	25 (92.6)	12 (100.0)	0.6353[c]
Male	6 (8.1)	4 (11.4)	2 (7.4)	0	
Clinical characteristics					
Disease duration (mo)	94 (10-394)	94 (10-370)	94 (10-394)	100 (10-310)	0.904[c]
SLEDAI score, median (min-max)	2.0 (0-14)	2 (0-10)	2 (0-14)	0 (0-6)	0.092[c]
SLEDAI classification, *n* (%)					
No activity	30 (40.6)	15 (42.9)	8 (29.6)	7 (58.3)	
Mild activity (scores 1-5)	34 (45.9)	17 (48.6)	13 (48.1)	4 (33.3)	
Moderate activity (scores 6-10)	8 (10.8)	3 (8.6)	4 (14.8)	1 (8.3)	0.454[d]
High activity (scores 11-19)	2 (2.7)	0	2 (7.4)	0	
Very high activity (scores ≥20)	0	0	0	0	
Treatment doses, median (min-max)					
Chloroquine dose (mg)	504000 (0-432000)	504000 (0-4320000)	504000 (0-2304000)	540000 (54000-3600000)	0.857[c]
Steroid dose (mg)	300 (0-51840)	0 (0-43200)	5760 (0-51840)	0 (0-37440)	0.193[c]

SLE: Systemic lupus erythematosus; SLE-CUT: Mucocutaneous involvement; SLE-SYS: Systemic involvement; SLE-APS: Antiphospholipid syndrome; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index. [a]Mann Whitney *U* test, [b]Chi-square test, [c]Kruskal Wallis variance analysis, [d]Fisher's exact test.

Table 3 Ocular parameters in patient *vs* control groups and in SLE subgroups

Parameters	SLE patients (*n*=74)	Control subjects (*n*=40)	*P*	SLE subgroups			*P*
				SLE-CUT (*n*=35)	SLE-SYS (*n*=27)	SLE-APS (*n*=12)	
Ocular parameters							
CDVA, logMAR	0 (0-52)	0 (0-0)	0.552[e]	0 (0-0.39)	0 (0-0.52)	0 (0-0.52)	0.246[c]
SCT (μm)	312.9±94.4	356.6±83.5	0.746[e]	313.1±88.7	303.0±113.0	334.6±80.9	0.635[d]
CVI (%)	63.9 (55.6-85.7)	68.9 (57.4-76.8)	0.005[e]	64.2 (56.1-85.7)	63.9 (55.7-72.7)	63.4 (59.1-73.6)	0.742[c]
Vessel density (%)							
SCP							
Total	49.9 (34.6-56.8)	51.3 (40.9-55.8)	0.189[e]	50.5 (40.7-55.8)	50.1 (37-56.8)	48.3 (34.6-52)	0.242[c]
Foveal	19.2 (4.8-34.0)	18.6 (4.9-39.5)	0.773[e]	18.7 (4.8-33.4)	19.3 (7.6-33.4)	21.1 (4.8-34.0)	0.852[c]
Parafoveal	53.1 (33.2-60.3)	53.9 (40.7-58.3)	0.377[e]	53.3 (41.1-60.3)	53.1 (38.3-58.0)	52 (33.2-58.2)	0.622[c]
Perifoveal	50.5 (34.9-58.6)	52.1 (41.7-57)	0.153[e]	50.8 (37.6-57.3)	50.7 (43.0-58.6)	49.5 (34.9-54.0)	0.235[c]
DCP							
Total	48.3 (31-60.9)	52.4 (35.5-60.9)	0.032[e]	49.6 (38.8-60.9)	46.1 (31.0-58.9)	48.4 (32.5-56.8)	0.256[c]
Foveal	37 (19.9-51.1)	35.7 (3.4-51.6)	0.752[e]	34.9 (19.9-51.1)	39.1 (24.8-48.2)	36.6 (25.8-50.8)	0.850[c]
Parafoveal	54.1 (33.5- 64.0)	57.9 (44.8-62.2)	0.020[e]	54.8 (45.3-64.0)	53.8 (33.5-62.5)	54.1 (42.4-61.2)	0.273[c]
Perifoveal	49.3 (29.7-63.1)	54.6 (35.6-63.4)	0.040[e]	51.2 (39.0-63.1)	46.7 (29.7-60.7)	49.6 (32.0-59.2)	0.354[c]

Data are expressed by mean±SD for SCT, and by median (min-max) for other ocular parameters. SLE: Systemic lupus erythematosus; SLE-CUT: Mucocutaneous involvement; SLE-SYS: Systemic involvement; SLE-APS: Antiphospholipid syndrome; CDVA: Best distance-corrected visual acuity; SCT: Subfoveal choroidal thickness; CVI: Choroidal vascularity index; SCP: Superficial capillary plexus; DCP: Deep capillary plexus. [e]Analysis of covariance (ANCOVA).

No significant difference was noted between SLE subgroups in terms of any of the ocular parameters studied (Table 3).

Correlation of SCT and CVI Parameters with Continuous Variables SCT values were negatively correlated with patient age (r=-0.435, P<0.001), while no correlation of SCT was noted with disease duration, SLEDAI score, HCQ dose or steroid dose. No correlation of CVI was noted with patient age, disease duration, SLEDAI score, HCQ dose or steroid dose (Table 4).

Multivariate Regression Analysis for Determinants of SCT and CVI Age (B=-2.918, 95%CI, -4.485 to -1.351, P<0.001)

Table 4 Correlation of SCT and CVI parameters with continuous variables

Parameters	SCT (μm)		CVI (%)	
	r	*P*	*r*	*P*
Age (y)	-0.435	<0.001	0.043	0.714
Disease duration (mo)	-0.180	0.125	0.153	0.193
SLEDAI score	0.062	0.599	-0.013	0.914
Chloroquine dose (mg)	-0.099	0.402	0.218	0.062
Steroid dose (mg)	-0.083	0.482	-0.042	0.721

SCT: Subfoveal choroidal thickness; CVI: Choroidal vascularity index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; *r*: Correlation coefficient. Spearman's correlation analysis.

Table 5 Multivariate regression analysis for determinants of subfoveal choroid thickness and choroidal vascular index

Parameters	Choroidal vascular index (%)					Subfoveal choroid thickness (μm)				
	B	SE	95%CI		*P*	*B*	SE	95%CI		*P*
Gender (female)	4.080	1.98	0.117	8.043	0.044	-53.466	38.003	-129.299	22.368	0.164
Age (y)	0.012	0.041	-0.070	0.094	0.774	-2.918	0.786	-4.485	-1.351	<0.001
Disease duration (mo)	-0.011	0.012	-0.035	0.013	0.356	-0.040	0.229	-0.497	0.418	0.864
Chloroquine dose (mg) ×1000	0.003	0.001	0.000	0.005	0.019	-0.003	0.023	-0.048	0.043	0.911
Steroid dose (mg) ×100	0.000	0.005	-0.010	0.009	0.944	-0.040	0.094	-0.226	0.147	0.673

B: Unstandardized regression coefficient; SE: Standard error; CI: Confidence interval.

Table 6 Multivariate regression analysis for determinants of vessel density in SCP and DCP

Items	Total					Foveal					Parafoveal					Perifoveal				
	B	SE	95%CI		*P*	*B*	SE	95%CI		*P*	*B*	SE	95%CI		*P*	*B*	SE	95%CI		*P*
VD-SCP (%)																				
Gender (female)	-2.489	1.709	-5.899	0.921	0.150	-3.111	2.958	-9.014	2.792	0.297	-2.625	0.949	-6.514	1.264	0.182	-2.231	1.796	-5.816	1.353	0.218
Age (y)	-0.035	0.035	-0.106	0.035	0.320	-0.044	0.061	-0.166	0.078	0.477	-0.050	0.040	-0.130	0.031	0.221	-0.019	0.037	-0.093	0.055	0.616
Disease duration (mo)	-0.012	0.010	-0.033	0.008	0.238	-0.010	0.018	-0.045	0.026	0.596	-0.015	0.012	-0.039	0.008	0.204	-0.008	0.011	-0.029	0.014	0.480
Chloroquine dose (mg) ×1000	0.002	0.071	0.000	0.004	0.071	0.002	0.002	-0.002	0.006	0.257	0.003	0.001	0.000	0.005	0.023	0.001	0.001	-0.001	0.003	0.340
Steroid dose (mg) ×100	-0.005	0.004	-0.013	0.004	0.254	0.016	0.007	0.001	0.030	0.037	-0.008	0.005	-0.018	0.001	0.089	-0.004	0.004	-0.013	0.005	0.334
VD-DCP (%)																				
Gender (male)	5.771	2.665	0.453	11.089	0.034	5.674	3.292	-0.894	12.242	0.089	2.604	2.304	-1.995	7.202	0.263	6.402	2.971	0.474	12.330	0.035
Age (y)	-0.035	0.055	-0.145	0.085	0.524	-0.097	0.068	-0.233	0.039	0.159	-0.077	0.048	-0.172	0.018	0.111	-0.054	0.061	-0.176	0.069	0.386
Disease duration (mo)	-0.008	0.016	-0.040	0.024	0.619	-0.003	0.020	-0.043	0.037	0.880	-0.012	0.014	-0.039	0.016	0.411	-0.009	0.018	-0.044	0.027	0.631
Chloroquine dose (mg) ×1000	0.002	0.002	-0.001	0.005	0.197	0.003	0.002	-0.001	0.007	0.188	0.002	0.001	0.000	0.005	0.085	0.002	0.002	-0.001	0.006	0.214
Steroid dose (mg) ×100	-0.013	0.007	-0.026	0.000	0.056	0.014	0.008	-0.002	0.031	0.081	-0.011	0.006	-0.022	0.001	0.063	-0.015	0.007	-0.030	0.000	0.044

VD: Vessel density; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; *B*: Unstandardized regression coefficient; SE: Standard error; CI: Confidence interval.

was found to be independent determinant of SCT (R^2=0.224, *F*=3.929, *P*=0.003), indicating 2.918 μm lower SCT values with each one year increase in age (Table 5).

Gender (*B*: 4.080, 95%CI, 0.117 to 8.043, *P*=0.044) and HCQ dose (*B*: 0.003, 95%CI, 0.000 to 0.005, *P*=0.019) were found to be independent determinants of CVI (R^2=0.201, *F*=3.415, *P*=0.008), indicating association of female gender with 4.08% higher CVI and, 0.3% higher CVI with each 1000 mg increase in cumulative HCQ dose (Table 5).

Disease duration had no significant association with SCT or CVI, while HCQ dose had no significant impact on SCT (Table 5).

Multivariate Regression Analysis for Determinants of SCP and DCP Vessel Density Gender, age and disease duration were not amongst the significant determinants of SVD. Steroid dose (*B*: 0.016, 95%CI, 0.001 to 0.030, *P*=0.037) was found to be independent determinant of foveal SVD (R^2=0.103, *F*=1.562, *P*=0.183), indicating 1.6% higher foveal SVD with each 100 mg increase in cumulative steroid dose. HCQ dose (*B*: 0.003, 95%CI, 0.000 to 0.005, *P*=0.023) was found to be independent determinant of parafoveal SVD (R^2=0.155, *F*=2.497, *P*=0.039), indicating 0.3% higher parafoveal SVD with each 1000 mg increase in cumulative HCQ dose (Table 6).

Age, disease duration and HCQ dose were not amongst the significant determinants of DVD. Gender (*B*: 5.771, 95%CI, 0.453 to 11.089, *P*=0.034) was found to be independent determinant of total DVD (R^2=0.152, *F*=2.447, *P*=0.042), indicating association of male gender with 5.771% higher total DVD. Gender (*B*: 6.402, 95%CI, 0.474 to 12.330, *P*=0.035) and steroid dose (*B*: -0.015, 95%CI, -0.030 to 0.000, *P*=0.044)

were found to be independent determinants of perifoveal DVD (R^2=0.159, F=2.564, P=0.034), indicating association of male gender with 6.402% higher perifoveal DVD, while 1.5% lower perifoveal DVD with each 100 mg increase in cumulative steroid dose (Table 6).

DISCUSSION

Our findings revealed the association of SLE with adverse ocular findings including CVI and total, parafoveal and perifoveal DVD compared to healthy controls. No correlation was noted between disease activity (SLEDAI scores) and SCT or CVI, while SLE subgroups were also similar in terms of SLEDAI scores and ocular findings.

Similarly, in a study by Altinkaynak *et al*[20], SLE patients in an inactive state of disease were reported to have lower choroidal thickness compared with control subject, and this lower choroidal thickness was suggested to be a consequence of vasculitis and immune-deposits leading to a decrease in blood flow and thus atrophy in the choroid. In a study by Kukan *et al*[10], while lower choroid volumes were reported in SLE patients compared with control subjects, significant lower values for CVI and a tendency for greater choroid volumes were noted in SLE patients with *vs* without drusen-like deposits. Greater choroid volumes and lesser CVI in the presence of drusen-like deposits was suggested to be a likely consequence of a more active inflammatory state in these patients, which leads to vasculitis, immunocomplex, and complement depositions in the capillary systems[10].

Notably, in a study by Invernizzi *et al*[6] higher choroidal thickness was reported in patients with SLE compared to controls, as explained by the increase in choroidal thickness by active disease and active inflammatory state in SLE. Other studies also reported thicker choroidal thickness in SLE patients compared with healthy controls, while in juvenile SLE patients the finding of similar CVI with healthy controls is explained by concurrent inflammatory deposition in the stroma and vasodilation[28,30].

Immune complex deposition, inflammatory process and vasoocclusion are considered amongst the mechanisms underlying chorioretinal involvement in SLE[3,27,34]. Choroidal vasculitis with choroidal infiltration of mononuclear inflammatory cells and immunoglobulin and complement deposition in the choroidal vasculature, in addition to long-term atrophy of choroidal stroma due to chronic ischemia are considered responsible for compromised choroidal blood supply, leading to choroidal thinning[35-37]. Indeed, while atrophy through capillary luminal obstruction leads to a choroidal thinning, active inflammation is considered to be associated with increase in choroidal thickness via inflammatory cell infiltration[6,10,20,25]. Hence, lower CVI in our SLE patients seems to be a finding consistent with absence of active inflammatory state in majority of our study population. In addition, while previous studies reporting higher CVI in SLE patients included those with concomitant posterior uveitis findings, none of our patients had acute uveitis or previous history of uveitis attack, and therefore higher CVI secondary to inflammation was not a likely condition in our patients[20,38].

Considering SVD and DVD, there were significant lower values for DVD including total area and parafoveal and perifoveal quadrants in our SLE patients, but no significant difference was noted in SVD, compared with control subjects. Previous studies regarding OCTA analysis also revealed an impaired retinal VD in SLE patients with no ocular symptoms or history of ocular disease, while there were conflicting results, such as an apparent reduction in both SVD and DVD reported in some studies, while demonstration of either an impaired SVD or impaired DVD in others[10,13,16,23,39-43].

Bao *et al*[42] reported significant decrease in SVD in SLE patients without signs of lupus retinopathy, while both SVD and DVD were reported to be decreased in those with lupus retinopathy. Hence, SCP impairment followed by the DCP impairment is suggested to lead to decreased blood supply to inner retina causing structural changes in the retina and subsequent development of lupus retinopathy[42]. These findings are considered suggestive of subclinical retinal microvasculature impairment to precede proper lupus retinopathy development, making it the early marker of lupus retinopathy[42].

In fact, lower VD of choriocapillaris on OCTA was also shown in SLE patients without HCQ retinopathy compared to controls, indicating that choroidopathy is one of the possible ophthalmic manifestations in patients with SLE and VD of choriocapillaris can be affected even in patients with SLE without retinopathy[13].

The association of SLE specifically with lower DVD rather than SVD in our study seems notable given that lower DVD is suggested to be related with vascular occlusion or overall decrease of blood flow in retinal vessels, while histological studies indicate DCP to be more prone to progressive occlusion than SCP, as explained in OCTA studies by anatomical position of DCP which is at the terminal of retinal capillary units[40,44-45]. In this regard, DCP is considered the most vulnerable capillary plexus to early impairment amongst the other vessel networks, because of its anatomical position and the role of inner retina blood supply, and thus DCP impairment is suggested to be an early disease activity and damage biomarker, while some authors also considered the association of decreased visual acuity with the perfusion status of DCP[16,18,46-47].

Presence of subtle and subclinical changes in choroidal circulation including lower CVI and DVD in our patients with SLE, in the absence of high disease activity or ocular

manifestations, suggests the likelihood of choroidal vascular bed to be affected early in the course of SLE, and thus the ischemic change and reduced blood flow in the choroidal vasculature may precede the proper retinopathy and micro-vasculopathy in other organ systems[7-8,12,14-15,17-18,25,27]. Hence, use of EDI SD-OCT and OCTA as screening modalities in SLE patients, even in the absence of relevant complaints, seems to be of key importance in this regard, enabling early recognition of choroidopathy in SLE patients, even in those with no ophthalmologic manifestations or active inflammatory state[11,16,30]. As reported by Bashiri *et al*[8], the prevalence of retinopathy (15.8%) in newly-diagnosed asymptomatic SLE patients is considered an alarmingly-high rate which emphasizes the need for incorporating assessment of ocular involvement as a screening test for all patients who are diagnosed with SLE.

Retinal and choroidal alterations are considered to be correlated to disease activity in SLE, and the presence and severity of ocular manifestations have been linked to poor prognosis[8-9,11,15-17]. However, while VD measurement is suggested to serve as a potential biomarker for disease activity on the basis of correlation of a lower VD with a higher disease activity, some authors indicated no correlation of SLEDAI scores with the retinal microvascular alterations including VD in SLE patients[10,16,27,30,39-41,48].

In a study by Ağın *et al*[30] in juvenile SLE patients, while total subfoveal choroidal, luminal and stromal area were found to be higher in patients than in control subjects, the two groups were similar in terms of CVI and retinal nerve fiber layer thickness. Also, no correlation was noted between OCT findings, SLEDAI and the immunological parameters (antinuclear antibodies, anti-double-stranded DNA, complements 3 and 4, extracted nuclear antigen antibody, antiphospholipid antibody)[30]. Notably, in a study by Dias-Santos *et al*[27], lower choroidal thickness was observed in the subset of SLE patients with biopsy-proven lupus nephritis and in those on anticoagulant therapy, reflecting the burden of systemic microvascular damage, particularly at the renal vasculature in SLE patients with lupus nephritis. However, the authors reported that choroidal thickness was not significantly associated with disease duration, SLEDAI, neuropsychiatric SLE, anti-phospholipid syndrome or HCQ treatment duration or dosage[27]. In the current study no correlation of disease activity (SLEDAI scores) was noted with SCT or CVI, along with no significant difference between SLE subgroups (mucocutaneous involvement, systemic involvement and antiphospholipid syndrome) in terms of disease activity or any of the ocular parameters studied (SCT, CVI, SVD or DVD).

Ocular manifestations, although not part of American College of Rheumatology diagnostic criteria, have long been reported as common findings in SLE, along with their highest possible effect on the disease activity on SLEDAI assessment which scores ocular involvement as a marker of disease severity[8]. Hence, it has been suggested that use of SLEDAI as the gold-standard disease activity index may not be feasible to infer the correlation between retinopathy and disease activity, since visual disturbance adds 8 points to the index, and any patients with retinopathy were expected to have a significantly higher SLEDAI[8]. Lack of correlation of disease activity with choroidopathy findings in our study may also be related to the fact that considerable proportion of SLE patients had either no disease activity (SLEDAI score of 0, 40.6%) or mild activity (SLEDAI scores of 1-5, 45.9%), possibly reflecting the likelihood of better disease control via new treatment alternatives in the current SLE practice.

Antiphospholipid syndrome (APS) is characterized by recurrent infarcts and thromboembolic diseases in several organs, while ocular involvement differs between primary APS (*i.e.*, ocular vasculopathy) and APS secondary to SLE (*i.e.*, thrombophilia)[11,49]. As detected in 77% *vs* 29% of SLE patients with *vs* without ocular involvement, antiphospholipid antibodies are considered likely to play a key role in some patients in the pathogenesis of lupus retinopathy[11,49-50]. However, while our patients with APS are expected to have more significant vascular occlusion findings, neither the SLEDAI scores nor the ocular involvement differed with respect to SLE subgroups in our study.

SLE patients are considered to be especially vulnerable group for retinal ischemia development, given the adverse effects of both SLE itself and SLE drug therapy on retinal structures and subsequent visual deterioration[16,51]. Toxic drug-related retinopathy is one of the most dangerous side effects associated with HCQ cumulative dosage, particularly after 5y of HCQ therapy[51-52]. Some authors suggested no significant association between duration or cumulative dosage of HCQ treatment and choroid thickness, lower DVD or choroid thickness in SLE patients with *vs* without HCQ treatment, and a negative correlation between increasing HCQ dose and DVD[27,53-54]. However, others indicated that duration or cumulative dosage of HCQ was positively correlated with choroidal thickness as well as with SVD and DVD in SLE patients, indicating a potential protective effect of HCQ on the ocular microvasculature, even if it relates to longer SLE duration[13,16,28-39]. Similarly, greater cumulative HCQ dose was found to be an independent determinant of higher parafoveal SVD as well as higher CVI in our SLE patients, while disease duration had no significant impact on ocular parameters. Also, higher steroid dose was independently associated with higher foveal SVD but lower perifoveal DVD. Such differences between studies may be explained by the variations in the

concomitant immunosuppressive treatment received by patients[43].

In a study by Mimier-Janczak *et al*[16], SLE patients were reported to have significantly lower visual acuity and lower SVD in parafoveal, inferior and nasal quadrants compared to the control group. The authors also noted significant positive correlation between HCQ cumulative dose and SVD and DVD in superior quadrants, while SVD in superior quadrant was also higher in SLE patients treated with HCQ for more than 5y compared to those receiving HCQ therapy for less than 5y[16]. In a study by Mihailovic *et al*[13], SVD was reported to be significantly lower in SLE patients compared with the control group, as well as in SLE patients using HCQ for >5y (high-risk group) *vs* those using HCQ for <5y (low-risk group). The authors also reported a significant positive correlation between VD and cumulative dose of HCQ only in the low-risk group, indicating that HCQ might have a protective effect on retinal microvasculature leading to a reduced disease activity only in the early stage of the disease[13]. Importantly, given that even patients with a low-risk profile for HCQ-induced toxic retinopathy (HCQ therapy <5y) show a significantly lower VD than healthy controls measured by OCTA, they also suggested that SLE itself leads to a lower VD in affected patients, regardless of HCQ therapy[13]. Likewise, the association of HCQ dose with higher CVI and parafoveal SVD in our SLE patients with median 94mo of disease duration and lack of disease activity seem to indicate the direct role of SLE in the observed choroidopathy (reduction in CVI, SCT, SVD and DVD), and a likelihood of a protective effect of HCQ on SVD in particular, in inactive state and early stage of the disease.

One of the important aspects of our study is the inclusion of multivariate analysis for identifying independent determinants of SCT, CVI, SVD and DVD, and consideration of factors with likely effects on ocular findings (*i.e.*, age, gender, disease duration, HCQ dose, steroid dose) in the model. Accordingly, our multivariate analysis revealed the female gender and higher HCQ dose as determinants of higher CVI, while younger age predicted higher SCT in SLE patients. For VD, higher steroid dose (foveal SVD), higher HCQ dose (parafoveal SVD), male gender (total and perifoveal DVD) and lower steroid dose (perifoveal DVD) were the independent determinants of higher VD in SLE patients. Disease duration had no significant impact on any of the ocular parameters, while both age and gender had no significant impact on SVD.

In another study on multiple regression analysis including age, gender, disease duration, disease severity, renal involvement and HCQ total dose amongst the other variables, authors reported that kidney involvement is significant predictor of SVD (nasal, parafoveal), while younger age was significant predictor of DVD (parafoveal)[16]. VD is considered to decline during process of aging, while the correlation between age and SVD (total, foveal, parafoveal) and DVD (total) was also reported in SLE patients[40,55-56]. Although, SCT but not VD was found to be related to age in our patients, our findings support that age may alternate the results obtained in studies detecting retinal microvascular changes in long-lasting systemic disease[16]. Notably, in a study by Ostanek *et al*[57] age was found to be associated with lower visual acuity, cornea involvement and retinopathy, and presence of anti-double stranded DNA antibodies were associated with increased risk of retinopathy, while high activity of disease, late diagnosis of SLE, arterial hypertension, glucose metabolism disorders were also reported as the risk factors for ocular involvement in their series of SLE patients.

Certain limitations to this study should be considered. First, the significant difference between patient and control groups in terms of age and gender seems to be the major limitation given the likely impact of both younger age and female gender on ocular findings. Despite, we have found lower DVD in the patient group after we had statistically adjusted the gender and age difference. Second, potential lack of generalizability due to relatively small sample size seems an important limitation. Third, lack of data on HCQ duration and presence of moderate or high disease activity only in minority of population seem to be another limitation which otherwise would extend the knowledge achieved in the current study. Fourth, single-point measurement of SCT and CVI using only the inferior foveal quadrant is another limitation with measurements from a larger choroidal are to reveal potentially different results, while measurement of SCT by a single researcher is also questionable in terms of test-re-test reliability.

In conclusion, our findings revealed the presence of ocular findings suggestive of early onset choroidopathy on EDI SD-OCT (lower CVI) and OCTA (lower for total, parafoveal and perifoveal DVD) in SLE patients, in the absence of ocular manifestations or active disease, compared to healthy control subjects. No correlation of disease activity (SLEDAI scores) was noted with SCT or CVI, along with no significant difference between SLE subgroups in terms of disease activity or ocular findings. DCP seems to be more vulnerable to early impairment than SCP, and thus impaired DVD may represent an early disease activity and damage biomarker. The cumulative HCQ dose seems to have a protective effect on CVI and parafoveal SVD, while disease duration or disease activity had no significant impact on ocular parameters. Accordingly, given the likelihood of choroidal vascular bed to be affected early in the course of SLE preceding the proper retinopathy, non-invasive ophthalmic imaging *via* EDI SD-OCT and OCTA seems to be of key prognostic importance,

enabling early recognition and monitoring of choroidopathy in SLE patients. Further prospective ophthalmic imaging studies in SLE patients across a wider spectrum of disease activity are needed for better understanding of the pathogenesis and clinical consequences of SLE choroidopathy in relation to systemic vasculopathy, disease progression and treatment modifications.

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