Open Access Rheumatology: Research and Reviews

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Ophthalmic Posterior Segment OCTA Metrics as Potential Biomarkers for Systemic Involvement in Systemic Sclerosis, Systemic Lupus Erythematosus, and Behçet Disease: A Systematic Review

Michael Drakopoulos, Hayden Flynn Sikora, Joseph D Fahey, Rukhsana G Mirza

Department of Ophthalmology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Correspondence: Rukhsana G Mirza, Department of Ophthalmology, Northwestern University Feinberg School of Medicine, 645 N Michigan Avenue, Suite 440, Chicago, IL, 60611, USA, Email r-mirza@northwestern.edu

Objective: To investigate the potential of quantitative ophthalmic posterior segment optical coherence tomography angiography (OCTA) imaging metrics to serve as biomarkers for systemic involvement in three rheumatologic diseases, systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and Behçet disease (BD), by reviewing the reported correlations between such OCTA metrics and clinically relevant features of systemic involvement in these diseases.

Methods: This review is a correlational study conducted through a systematic review of the PubMed database for articles reporting OCTA metrics in any of SSc, SLE, and BD. Articles correlating ophthalmic posterior segment OCTA metrics to clinically relevant features of systemic involvement, specifically serum, cerebrospinal fluid (CSF), or other established biomarkers; systemic symptom and severity scores; stage; non-ocular organ involvement; non-ocular imaging findings; and medication use were included.

Results: OCTA parameters have been significantly correlated to autoantibody presence, digit and pulmonary involvement, disease stage, and medication use in SSc with significance values ranging from $p = 0.008$ to $p = 0.048$. OCTA parameters have been significantly correlated to serum markers, renal and cardiac involvement, damage indices, and medication use in SLE with significance values ranging from $p < 0.0001$ to $p = 0.028$. OCTA parameters have been correlated to systemic vascular involvement in BD with significance value $p = 0.006$.

Conclusion: Ophthalmic posterior segment OCTA metrics may provide value in prognosis, stratification, and treatment monitoring of the examined rheumatologic conditions. These results warrant further study.

Keywords: optical coherence tomography angiography, oculomics, capillary plexus, systemic sclerosis, systemic lupus erythematosus, Behçet disease

Introduction

Optical coherence tomography angiography (OCTA) is an imaging modality that allows for non-invasive, quantitative imaging of the microvasculature, including of the eye and skin, in three dimensions. OCTA is widely used in ophthalmology in diagnosis and management, especially of retinal diseases. OCTA of the eye's posterior segment provides direct visualization of the microvasculature including the retinal superficial, intermediate, and deep capillary plexuses (SCP, ICP, and DCP, respectively), the radial peripapillary capillary plexus (RPCP), and the choriocapillaris (CC), which is the innermost layer of the choroid (Figure 1).

Quantitative metrics derived from en face OCTA images of the retinal and choroidal microvasculature have been developed and validated for use in ophthalmic diseases. Common OCTA metrics include vessel area density (VAD), vessel length density (VLD), foveal avascular zone (FAZ) area, FAZ circumference, and FAZ circularity. Table 1 defines

Received: 13 December 2024
Accepted: 22 March 2025
Published: 26 April 2025

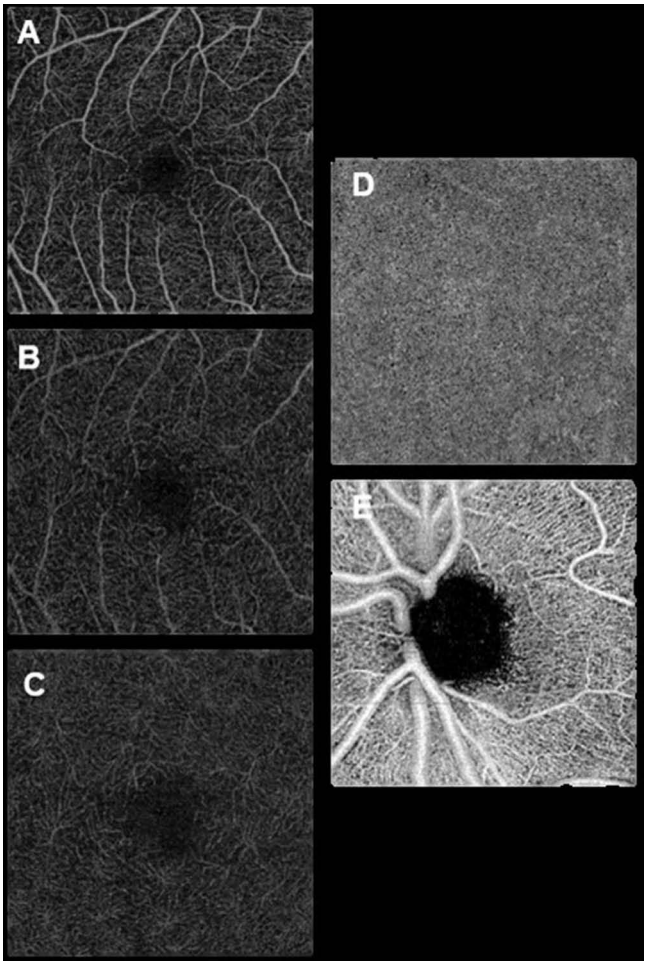

Figure 1 Optical coherence tomography angiography en face images of the superficial capillary plexus (SCP; **A**), intermediate capillary plexus (ICP; **B**; contains some projection artifact from retinal arterioles of the SCP), deep capillary plexus (DCP; **C**), radial peripapillary capillary plexus (RPCP; **E**), and the choriocapillaris (CC; **D**).

the OCTA metrics examined by the articles identified for inclusion in this review. These and other ophthalmic OCTA metrics have been found to change in individuals with a broad variety of systemic conditions, including rheumatologic conditions. Here, we omit a discussion of eye-specific OCTA findings in the included rheumatologic conditions, as these have been discussed elsewhere and we seek instead to examine the known correlations between eye OCTA metrics and features of systemic involvement in the included rheumatologic conditions. Our efforts are part of an emerging field of ophthalmology, oculomics, which seeks to identify eye imaging biomarkers for use in the study and management of non-ocular conditions. While rheumatologic diseases often affect the eye, we here examine what the eye can tell us about how rheumatologic diseases may be affecting the rest of the body. We examine such correlations to determine if ocular OCTA metrics may be useful in prognosis, stratification, and treatment monitoring of the included rheumatologic diseases, which could eventually offer rheumatologists a new tool in both clinical management and research in these conditions.

Materials and Methods

This review is a correlational study. We used PRISMA guidelines to conduct a systematic literature review of the PubMed database examining known correlations between the quantitative ophthalmic posterior segment OCTA metrics included in Table 1 and clinically relevant non-ocular features of systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and Behçet disease (BD). The following clinically relevant non-ocular features were considered: serum, cerebrospinal fluid (CSF), or other established biomarkers; systemic symptom and severity scores; stage; non-ocular organ involvement; non-ocular imaging findings; and medication use. SSc, SLE, and BD were selected for inclusion by

Table 1 Quantitative Ophthalmic Posterior Segment Optical Coherence Tomography Angiography Metrics Relevant to This Review, Including Metric Name, Abbreviation, and Definition

Metric (Abbreviation)	Definition
Vessel area density (VAD)	The ratio of the retinal area covered by blood vessels in an en face image to the total retinal area, sometimes after excluding the foveal avascular zone from analysis, and generally after binarization of the en face image
Vessel length density (VLD)	The ratio of the total length covered by 1-pixel-wide, skeletonized blood vessels in an en face image to the total retinal area, generally after excluding the foveal avascular zone from analysis
Foveal avascular zone area (FAZ area)	The area enclosed by the capillary ring surrounding the foveal avascular zone
Foveal avascular zone perimeter (FAZ perimeter)	The length of the capillary ring surrounding the foveal avascular zone
Foveal avascular zone circularity (FAZ circularity)	A ratio approximating the "roundness" of the FAZ, calculated as $4\pi * (\text{FAZ area}) / (\text{FAZ perimeter})^2$

the expert opinion of a single retina specialist (RGM) as a sample of rheumatologic disease both with (SLE, BD) and without (SSc) frequent eye involvement. While both SLE and BD have classic eye manifestations, including dry eye, retinopathy, and choroidopathy in SLE[1,2] and uveitis in BD,[3] SSc has not been reported to have classic eye findings.[4] Rheumatologic diseases both with and without classic eye manifestations were included to examine the ability of OCTA to identify ophthalmic involvement and its systemic correlates even in rheumatologic conditions where such correlations were less likely to be found. A set of search queries, one per included disease, were entered into the PubMed database on a single day, May 13th, 2024, by a single investigator. All searches were limited to articles published from January 1st, 2000, to May 13th, 2024, in English with human subjects. A sample search query, for Behçet disease, and the keywords used for each search query are presented in Table 2.

The identified articles were deduplicated and abstracts were screened by a single grader. Articles with abstracts describing the following study characteristics were excluded: case reports, case series with fewer than ten subjects with the rheumatologic disease of interest, clinical-trial protocols without data or other protocols without data, editorial publications not presenting new data, publications unrelated to OCTA, publications failing to discuss ophthalmic-posterior-segment OCTA, publications correlating ophthalmic OCTA findings only to diseases other than SSc, SLE, and BD, and any remaining non-English or non-human-subjects articles. The texts of the remaining articles were further screened by single-grader review to exclude those with no quantitative OCTA metrics, those irreversibly combining

Table 2 Sample PubMed Search Query (for Behçet Disease), Diseases Included in the Review, and Key Words Used for Each Search Query for Each Disease Included in the Review

Sample Search Query (Behçet disease): **((("OCTA") OR ("OCT-A") OR ("OCT angiography") OR ("optical coherence tomography angiography") OR ("OCT-angiography")) AND (("Behçet disease") OR (Behcet disorder) OR ("Behcet syndrome") OR ("Behcet's disease") OR (Behcet's disorder) OR ("Behcet's syndrome") OR (Behcet's disease) OR (Behcet's disorder) OR (Behcet's syndrome))**	
Disease Included:	**Key Words Used in Search Query:**
Behçet disease	Behcet disease, Behcet disorder, Behcet syndrome, Behcet's disease, Behcet's disorder, Behcet's syndrome, Behcet's disease, Behcet's disorder, Behcet's syndrome
Systemic lupus erythematosus	Systemic lupus erythematosus, lupus, systemic lupus, SLE, discoid lupus erythematosus, disseminated lupus erythematosus, lupus nephritis
Systemic sclerosis	Systemic sclerosis, SSc, scleroderma, CREST syndrome, diffuse systemic sclerosis, limited systemic sclerosis, progressive systemic sclerosis

OCTA metrics with laboratory or imaging metrics (for example, by creating a single artificial intelligence model taking both OCTA and color fundus photographs as inputs in predicting systemic disease severity, with no report on how the model performs with OCTA as a sole input), and those failing to correlate quantitative posterior segment OCTA metrics in the included rheumatologic diseases to the previously noted clinically relevant non-ocular metrics or markers of those diseases. Such articles were excluded as we sought to examine the known correlations between eye OCTA metrics and features of systemic involvement in the included rheumatologic conditions rather than to examine the eye-specific OCTA findings in the included diseases, which have been reported elsewhere.[5–9]

Results

Identified Articles

One hundred thirty articles were identified. One duplicate was identified and excluded. Thirty-five articles were excluded upon review of abstracts. Sixty-one articles were excluded upon review of article texts. A flowchart of articles included and excluded from the PubMed database search is presented in Figure 2. No studies fitting inclusion-exclusion criteria were excluded from this review.

Summary Tables

A summary of identified findings correlating OCTA ophthalmic posterior segment capillary plexus metrics with systemic markers and features of SSC, SLE, and BD for the SCP, ICP, DCP, and CC is presented in Table 3. A similar summary for FAZ metrics is presented in Table 4.

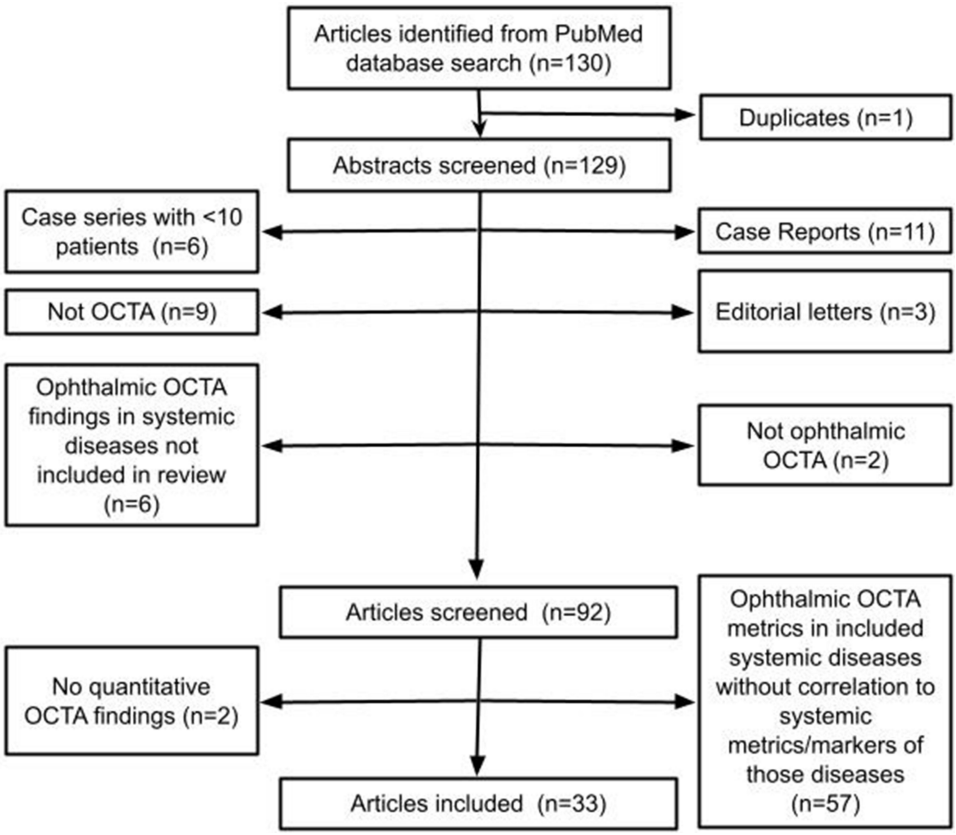

Figure 2 Flowchart of articles included and excluded after PubMed database search.

Systemic Sclerosis (SSc)

Systemic sclerosis (SSc) is a rheumatologic disease characterized by vascular dysfunction and fibroblast activation affecting multiple organ systems, with manifestations including digital ulcers and interstitial lung disease (ILD). Patients with SSc may be classified as having diffuse cutaneous SSc (dcSSc) or limited cutaneous SSc (lcSSc) depending on the extent of skin involvement. Consistent reductions in ophthalmic posterior segment OCTA metrics of vascularity have been identified in systemic sclerosis. We hypothesize that such findings reflect sub-clinical involvement of the ophthalmic vasculature in SSc, and that such end-organ vascular involvement in the eye should correlate to end-organ involvement elsewhere in the body. Consequently, ophthalmic OCTA metrics should correlate with other markers of systemic involvement in SSc, which is the focus of our review.

OCTA metrics have been correlated to presence and risk of organ involvement in SSc. SCP VAD was lower in SSc patients with digital ulcers than those without in the whole, perifoveal, superior, inferior, temporal, and nasal regions (n = 20; 9 with digital ulcers, 11 without; p = 0.03, 0.03, 0.04, 0.03, 0.04, 0.03, respectively).[10] Further a negative correlation was identified between SCP VAD and modified Rodnan skin score (n = 22, Spearman coefficient (rSp)=−0.504; p = 0.017), indicative of increased systemic dermatologic involvement in SSc,[11] and a positive correlation was found between CC VAD and more positive assessment on qualitative nailfold capillaroscopy (n = 22, rSp = 0.456, p = 0.011),[11] mean capillary number in the digits (n = 32, Pearson coefficient (r)=0.23, p = 0.01),[27] and mean digit perfusion (n = 32, r = 0.28, p = 0.01).[27] Further, a negative correlation was found between VAD in Haller's layer, comprising the large vessels of the choroid, and capillaroscopic skin ulcer risk index (CSURI), a risk score for predicting new skin ulcers in SSc (n = 15, r = −0.406, p = 0.026).[28] Thus, OCTA metrics have been correlated to not only presence and severity of digit ulcers in SSc but also to risk score for developing this complication. Additionally, SSc patients with ILD with a nonspecific interstitial pneumonia pattern (NSIP) had greater SCP VAD and greater DCP FAZ area than those with ILD with a usual interstitial pneumonia pattern (UIP) (n = 11; 7 with NSIP, 4 with UIP; p = 0.0471 and p = 0.0484, respectively).[12] Furthermore, patients with dcSSc presented with decreased CC VAD compared to those with lcSSc (n = 32; 10 with dcSSc, 22 with lcSSc; p = 0.033), correlating CC metrics to extent of organ involvement.[27] Such findings suggest that OCTA metrics might be useful in predicting and subtyping systemic complications in SSc. However, not all studies have been significant. One found no correlation between SCP VAD and nailfold capillary vessel density (n = 22, rSp = 0.342, p = 0.064),[11] and another found no differences in SCP, DCP, and CC VAD between SSc patients with versus without ILD (n = 20; 7 with ILD, 13 without).[10] It is possible that prognosis of SSc organ involvement with OCTA metrics may be limited to certain systemic complications.

OCTA metrics have also been found to differ among SSc patients according to their use of medication therapy for this disease. Patients using hydroxychloroquine, calcium channel blockers, or corticosteroids had greater RPCP VAD than patients not using these drugs (n = 61, p = 0.021, p = 0.027, p = 0.043, respectively).[29] SSC patients using vasodilators (sildenafil, nifedipine, pentoxifylline, or diltiazem) had decreased FAZ area and increased FAZ circularity compared to those not using vasodilators (n = 40; 11 using vasodilators, 29 not using vasodilators; p = 0.040 and p = 0.035, respectively).[33] Such findings suggest that OCTA may allow clinicians to assess the efficacy of systemic therapies for SSc by monitoring ocular vascular metrics, though caution in interpreting these results as causal is warranted given the possibility of selection bias.

OCTA metrics have been correlated to serum markers in SSc, with peripapillary RPCP VAD decreasing as antinuclear antibody titer increased and with lower mean RPCP VAD in SSc patients positive for anti-Scl-70 (anti-topoisomerase I) antibody relative to those who were negative (n = 61, r =- 0.267, p=0.037, and n = not reported, p = 0.021, respectively).[29] Considering known correlations between such antibodies and SSc phenotype and complications,[37,38] we hypothesize these findings may suggest a possible pathophysiologic mechanism involving an effect of these antibodies on the microvasculature systemically.

OCTA metrics have been found to differ according to stage of SSc,[12,30] though not all studies have been significant.[39] Patients with lcSSc had decreased RPCP VLD and significantly greater FAZ perimeter compared to very early diagnosis of systemic sclerosis (VEDOSS) patients (n = 44; 25 with lcSSc, 19 with VEDOSS; p < 0.001 and p = 0.017, respectively).[30] Similarly, patients with early SSc, as defined by nailfold videocapillaroscopy,[40] had greater SCP and

https://doi.org/10.2147/OARRR.S511810

Table 3 Findings Correlating Optical Coherence Tomography Angiography Ophthalmic Posterior Segment Capillary Plexus Metrics with Systemic Markers and Features of Systemic Sclerosis (SSc), Systemic Lupus Erythematosus (SLE) and Behçet Disease (BD)

Plexus	Disease	OCTA Metrics	Systemic Marker/Feature	Strength of Correlation or Comparison	Statistical Significance	Number of Subjects	Reference
SCP	SSc	VAD	Digital ulcers	Lesser with digital ulcers	**p=0.03**	20 (9 with ulcers, 11 without)	[10]
			Modified Rodnan Skin score	r=−0.504	**p=0.017**	22	[11]
			Nailfold capillary vessel density	(not significant)	p=0.064	22	[11]
			NSIP vs UIP in ILD	Greater with NSIP	**p=0.0471**	11 (7 with NSIP, 4 with UIP)	[12]
			Presence of ILD	(not significant)	p>0.05	20 (7 with ILD, 13 without)	[10]
		FAZ Area	Early SSc vs active/late SSc	Greater with early SSc	**p=0.0104**	26 (5 with early SSc, 12 with active SSc, 9 with late SSc)	[12]
	SLE	VAD	HCQ dosage (<5 years of use)	r=0.700	**p=0.035**	10	[13]
			HCQ dosage (≥ 5 years of use)	(not significant)	p=0.211	9	[13]
			Cumulative HCQ dose	r=0.4	**p=0.009**	26	[14]
			Cumulative HCQ dose	r=−0.383	**p=0.011**	43	[15]
			Cumulative HCQ dose	r=−0.78	**p=0.01**	10	[16]
			Cumulative HCQ dose	r=−0.332	**p=0.01**	60	[17]
			Duration of HCQ use	r=−0.85	**p=0.007**	10	[16]
			Duration of HCQ use	(not significant)	p=0.14	102	[18]
			C4 levels	r=−0.28	**p=0.013**	102	[18]
			C3 levels	(not significant)	p=0.07	102	[18]
			SLICC-DI	r=−0.5	**p=0.0001**	26	[14]
			SLICC-DI (upper nasal sector)	r=−0.593	**p=0.006**	20	[19]
			SLICC-DI (central temporal sector)	r=−0.456	**p=0.043**	20	[19]
			SLEDAI	r=−0.353	**p=0.015**	47	[20]
			SLEDAI	r=0.263	**p=0.02**	102	[18]
			SLEDAI	(not significant)	p>0.05	15	[21]
			SLEDAI	(not significant)	p>0.05	60	[17]
			Presence of nephritis	Lesser with presence	**p=0.02**	26	[14]
			Renal Involvement	Lesser with involvement	**p=0.004**	33	[22]
			Cardiac Involvement	Greater with involvement	**p=0.02**	78 (13 with, 65 without)	[18]
			Anti-dsDNA antibodies	Lesser with antibodies	**p=0.012**	48	[23]
		FAZ Area	Cumulative HCQ dose	r=0.71	**p=0.03**	10	[16]
ICP	SLE	VAD	Cumulative HCQ dose	r=−0.83	**p=0.02**	10	[16]
		FAZ Area	Cumulative HCQ dose	r=0.72	**p=0.01**	10	[16]

DCP	SSc	VAD	Presence of ILD	(not significant)	p>0.05	20 (7 with ILD, 13 without)	[10]
		FAZ Area	NSIP vs UIP in ILD	Greater with NSIP	**p=0.0484**	11 (7 with NSIP, 4 with UIP)	[12]
			Early SSc vs active/late SSc	Greater with early SSc	**p=0.0076**	26 (5 with early SSc, 12 with active SSc, 9 with late SSc)	[12]
	SLE	VAD	Cumulative HCQ dose	r=0.3	**p=0.04**	26	[14]
			Cumulative HCQ dose	r=−0.424	**p=0.005**	43	[15]
			Carotid intima media thickness	r=0.012	**p=0.027**	43	[24]
			Systolic blood pressure	r=0.131	**p=0.011**	43	[24]
			QRISK3 score	r=0.342	**p<0.001**	43	[24]
			SLICC-DI	β=1.432	**p=0.006**	43	[24]
			SLICC-DI	r=−0.6	**p<0.0001**	26	[14]
			SLEDAI	r=−0.491	**p=0.009**	29	[25]
			SLEDAI	r=−0.4	**p=0.01**	26	[14]
			SLEDAI	r=−0.383	**p=0.014**	41	[26]
			SLEDAI	r=−0.321	**p=0.028**	47	[20]
			SLEDAI	(not significant)	p>0.05	15	[21]
			SLEDAI	(not significant)	p>0.05	60	[17]
			Apolipoprotein B levels	r=0.072	**p=0.021**	43	[24]
			Anti-dsDNA antibodies	Lesser with antibodies	**p=0.012**	48	[23]
			Cumulative HCQ dose	r=0.74	**p=0.04**	10	[16]
		FAZ Area	Cumulative HCQ dose	r=0.72	**p=0.01**	10	[16]
CC	SSc	VAD	Qualitative nailfold capillaroscopy	r=0.456	**p=0.011**	22	[11]
			Mean capillary number in digits	r=0.23	**p=0.01**	32	[27]
			Mean digit perfusion	r=0.28	**p=0.01**	32	[27]
			dcSSc vs lcSSc	Lesser with dcSSc	**p=0.033**	32 (10 with dcSSc, 22 with lcSSc)	[27]
			Presence of ILD	(not significant)	p>0.05	20	[10]
	SLE	VAD	Cumulative HCQ dose	r=−0.76	**p=0.02**	10	[16]
			SLEDAI	r=−0.521	**p=0.005**	29	[25]
Haller's Layer (of choroid)	SSc	VAD	CSURI	r=−0.406	**p=0.026**	15	[28]

(*Continued*)

https://doi.org/10.2147/OARRR.S511810

Table 3 (Continued).

Plexus	Disease	OCTA Metrics	Systemic Marker/Feature	Strength of Correlation or Comparison	Statistical Significance	Number of Subjects	Reference
RPCP	SSc	VAD	Antinuclear antibody titer	r=−0.267	**p=0.037**	61	[29]
			Anti-Scl-70 antibody	Lesser with presence of antibody	**p=0.021**	61	[29]
			Hydroxychloriquine use	Greater with drug use	**p=0.021**	61	[29]
			Calcium channel blockers use	Greater with drug use	**p=0.027**	61	[29]
			Corticosteroid use	Greater with drug use	**p=0.043**	61	[29]
		VLD	lcSSc vs VEDOSS	Lesser with lcSSc	**p<0.001**	44 (25 with lcSSc, 19 with VEDOSS)	[30]
	SLE	VAD	Albumin:globulin ratio	r=0.375	**p=0.041**	77	[31]
			Anti-dsDNA antibodies	r=−0.462	**p=0.012**	77	[31]
			24-hour proteinuria	r=−0.524	**p=0.006**	77	[31]
	BD	VAD	Presence of SVI	Lesser with SVI	**p=0.006**	33 (6 with, 27 without)	[32]

Notes: Correlation coefficients are presented for statistically significant bivariate and multivariate correlations, while the direction of change is presented for statistically significant binary comparisons. The strength of correlations and comparisons is not reported where statistical significance was not reached. Statistically significant comparisons ($p<0.05$) are presented in boldface font.

https://doi.org/10.2147/OARRR.S511810

Table 4 Summary of Reported Findings Correlating Optical Coherence Tomography Angiography (OCTA) Foveal Avascular Zone (FAZ) Metrics with Systemic Markers or Features of Systemic Sclerosis (SSc) or Systemic Lupus Erythematosus (SLE)

Disease	OCTA FAZ Metrics	Systemic Marker/Feature	Strength of Correlation or Comparison	Statistical Significance	Number of Subjects	Reference
SSc	Area	Vasodilator Use	Lesser with use	**p=0.04**	40 (11 using vasodilators)	[33]
	Circularity	Vasodilator Use	Greater with use	**p=0.035**	40 (11 using vasodilators)	[33]
	Perimeter	lcSSc vs VEDOSS	Greater with lcSSc	**p=0.017**	44 (25 with lcSSc, 19 with VEDOSS)	[30]
SLE	Area	Cumulative HCQ dose	r=0.784	**p<0.001**	135	[34]
		Cumulative HCQ dose	r=0.445	**p=0.003**	43	[15]
		SLEDAI	r=0.451	**p=0.018**	29	[25]
		SLEDAI	(not significant)	p>0.05	15	[21]
		SLEDAI	(not significant)	p>0.05	60	[17]
		SLEDAI	(not significant)	p=0.7	78	[35]
		SLICC-DI	Increased with SLICC>1	**p=0.023**	78	[35]
	Circularity	SLEDAI	(not significant)	p=0.8	78	[35]
		SLICC-DI	Decreased with SLICC>1	**p=0.03**	78	[35]
		Neuropsychiatric SLE	Greater with presence	**p=0.004**	78 (26 with, 52 without)	[18]
	Perimeter	Cumulative HCQ dose	r=0.734	**p<0.001**	135	[34]
		Cumulative HCQ dose	r=0.434	**p=0.004**	43	[15]
		ESR	r=0.276	**p=0.015**	78	[18]
		ESR	(not significant)	p>0.05	35	[36]
		SLEDAI	(not significant)	p>0.05	60	[17]
		SLEDAI	(not significant)	p=0.8	78	[35]
		SLICC-DI	Increased with SLICC>1	**p=0.02**	78	[35]

Notes: No such results were identified for Behçet disease (BD) by this review. Note that these studies treated the FAZ as a single entity, as has been determined by histopathologic studies, rather than as an entity existing in multiple capillary plexuses. Studies examining an FAZ in each of the superficial, intermediate, and deep capillary plexuses (SCP, ICP, and DCP) are reported in Table 3. Correlation coefficients are presented for statistically significant bivariate and multivariate correlations, while the direction of change is presented for statistically significant binary comparisons. The strength of correlations and comparisons is not reported where statistical significance was not reached. Statistically significant comparisons (p<0.05) are presented in boldface font.

Abbreviations: BD, Behçet disease; CC, Choriocapillaris; CSF, cerebrospinal fluid; CSURI, Capillaroscopic skin ulcer risk index; DCP, Deep capillary plexus; dcSSc, Diffuse cutaneous systemic sclerosis; ESR, erythrocyte sedimentation rate; FAZ, Foveal avascular zone; HCQ, Hydroxychloroquine; ICP, Intermediate capillary plexus; IMT, intima media thickness; ILD, Interstitial lung disease; lcSSc, Limited cutaneous systemic sclerosis; NSIP, Non-specific interstitial pneumonia; OCTA, optical coherence tomography angiography; RPCP, radial peripapillary capillary plexus; SCP, Superficial capillary plexus; SLE, Systemic lupus erythematosus; SLEDAI, Systemic lupus erythematosus disease activity index; SLICC-DI, Systemic Lupus International Collaborating Clinics damage index; SSc, Systemic sclerosis; SVI, Systemic vascular involvement; UIP, Usual interstitial pneumonia; VAD, Vessel area density; VEDOSS, Very early diagnosis of systemic sclerosis; VLD, Vessel length density.

DCP FAZ area compared to patients with active or late SSc videocapillaroscopy patterns (n = 26; 5 with early SSc, 12 with active SSc, 9 with late SSc; p = 0.0104 and p = 0.0076, respectively).[12] Such changes in eye OCTA metrics between earlier and later SSc suggest ophthalmic OCTA might both provide additional information relevant to staging this disease and play a role in early detection of SSc.

In summary, ophthalmic OCTA metrics have been found to differ between individuals with SSc according to systemic organ involvement, medical therapy status, autoantibody presence, and stage of disease. Thus, OCTA may eventually assist with early diagnosis, staging, monitoring, and prognosis of systemic involvement in SSc, as well as assessment of

effectiveness of drug therapy for SSc. However, these preliminary results would benefit from further investigation of their potential clinical utility.

Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus (SLE) is a rheumatologic disorder that frequently involves multiple organ systems including the renal, dermatologic, musculoskeletal, and pulmonary systems, amongst others. Disease onset typically occurs in young adulthood and occurs more frequently in women than in men. Ocular complications of SLE are typically related to keratoconjunctivitis sicca, but retinal involvement can also occur and can lead to vision loss. Ophthalmic OCTA studies generally have found decreased VAD and increased FAZ area in those with SLE relative to healthy controls, indicating decreased microvascular perfusion. Here, we focus on studies correlating OCTA metrics with features of systemic, non-ocular involvement in SLE, including medication use; renal, cardiac, and neurologic involvement; serum markers; and damage indices.

OCTA studies of medication use in SLE focus on hydroxychloroquine (HCQ). In patients treated with HCQ for over 5 years, no significant correlation was identified between SCP VAD and HCQ dosage, while a positive correlation was observed in those using HCQ for less than 5 years ($n = 9$, $r=-0.462$, $p = 0.211$ and $n = 10$, $r = 0.700$, $p = 0.035$, respectively),[13] potentially suggesting the identification of an early vascular-protective effect of HCQ use followed by HCQ toxicity. That the effect of HCQ treatment on OCTA metrics may depend on duration of HCQ use may explain that cumulative dose of HCQ has been found to correlate both positively ($n = 26$, $r = 0.4$, $p = 0.009$)[14] and negatively ($n = 43$, $r = -0.383$, $p = 0.011$),[15] ($n = 10$, $r = -0.78$, $p = 0.01$),[16] ($n = 60$, $r = -0.332$, $p = 0.010$)[17] with SCP VAD in other studies, especially in light of an identified negative correlation between SCP VAD and duration of HCQ treatment ($n = 10$, $r = -0.85$, $p = 0.007$).[16] At the same time, another study did not find any correlation between duration of HCQ use and SCP VAD ($n = 102$, $p = 0.14$).[18] Other capillary plexus and FAZ OCTA parameters have also been correlated to cumulative dose of HCQ, with inverse correlations typically identified for DCP VAD ($n = 26$, $r = 0.3$, 0.04),[14] ($n = 43$, $r = -0.424$, $p = 0.005$),[15] ICP VAD ($n = 10$, $r = -0.83$, $p = 0.02$),[16] and CC VAD ($n = 10$, $r = -0.76$, $p=0.02$),[16] and direct correlations typically identified for FAZ parameters including FAZ perimeter ($n = 43$, $r = 0.434$, $p = 0.004$),[15] ($n = 135$, $r = 0.734$, $p < 0.001$),[34] and FAZ area ($n = 43$, $r = 0.445$, $p = 0.003$),[15] (SCP FAZ, $n = 10$, $r = 0.71$, $p = 0.03$; ICP FAZ, $n = 10$, $r = 0.74$, $p = 0.04$; DCP FAZ, $n = 10$, $r = 0.72$, $p = 0.01$),[16] ($n = 135$, $r = 0.784$, $p < 0.001$).[34] Notably, significant positive and negative correlations were identified between DCP VAD and cumulative dose of HCQ, slightly complicating interpretation, but the overall results suggest widespread vascular depletion with increasing cumulative dose of HCQ. Overall, these findings suggest OCTA may both capture early vascular-protective effects of HCQ use and potentially inform monitoring of HCQ toxicity.

Differences in OCTA metrics have been found between SLE patients with and without renal involvement, suggesting these metrics may be useful in identification of SLE patients with or at risk for this complication, though some studies have been insignificant.[18,36,41] Patients with SLE with nephritis ($n = 26$, $p = 0.02$)[14] or with renal involvement ($n = 33$, $p = 0.004$)[22] displayed reduced SCP VAD compared with those of patients without, and DCP VAD was found to have slight ability to discriminate between SLE patients with and without nephritis ($n = 60$; 33 with nephritis, 27 without; area under curve (AUC)=0.671, $p = 0.016$).[17] Thus, detection of early retinal microvascular changes with OCTA might potentially serve as a screening modality to decrease renal morbidity in SLE, with negative findings potentially a result of differences in SLE duration or HCQ cumulative dose.

OCTA metrics have also been correlated to cardiac risk and involvement in SLE. Negative correlations were identified between DCP VAD and carotid intima media thickness (IMT), systolic blood pressure, QRISK3 score (a predictive score for the development of cardiovascular disease within ten years based on twenty risk factors), Systemic Lupus International Collaborating Clinics Damage Index (SLICC-DI), and apolipoprotein B levels in patients with SLE ($n = 43$, $r = 0.012$, $p = 0.027$; $n = 43$, $r = 0.131$, $p = 0.011$; $n = 43$, $r = 0.342$, $p < 0.001$; $n = 43$, $\beta = 1.432$, $p = 0.006$; $n = 43$, $r = 0.072$, $p = 0.021$; respectively).[24] The reductions in DCP VAD with increased IMT and QRISK3 score were still significant after statistical adjustment for age and sex ($n = 43$, $r = 0.007$, $p = 0.039$ and $n = 43$, $r = 0.199$, $p = 0.049$),[24] though of relatively low magnitude and statistical significance. In addition, SCP VAD was significantly higher in SLE

patients with cardiac involvement than in SLE patients without cardiac involvement (n = 78, 13 with, 65 without; p = 0.02).[18] Thus, OCTA metrics may assist in identifying those with SLE at risk of or experiencing cardiac involvement.

A single study found increased FAZ circularity in those with neuropsychiatric SLE relative to those without, suggesting OCTA metrics may identify those at risk of neurologic involvement (n = 78, 26 with, 52 without; p = 0.004).[18]

Studies have also correlated OCTA metrics to serum biomarkers in SLE, including to erythrocyte sedimentation rate (ESR), C3, C4, albumin:globulin ratio, anti-dsDNA antibodies, and anti-phospholipid antibodies, as well as to 24-hour proteinuria. ESR levels correlated positively with FAZ perimeter in one study (n = 78, r = 0.276, p = 0.015),[18] but another study found no significant correlation (n = 35, p > 0.05).[36] A different study found C4 levels in SLE patients were negatively correlated with SCP VAD (n = 102, r = −0.28, p = 0.013), though C3 levels did not significantly correlate (n = 102, p = 0.07).[18] RPCP VAD in SLE positively correlated with albumin:globulin ratio (n = 77, r = 0.375, p = 0.041).[31] SLE patients with anti-dsDNA antibodies had significantly lower SCP VAD (n = 48; p = 0.023),[23] DCP VAD (n = 48, p = 0.012),[23] and RPCP VAD (n = 77, r = −0.462, p = 0.012),[31] relative to those without. Further, SLE patients with anti-phospholipid antibodies were found to have reduced VAD and VLD relative to those without (n = 78, p = 0.02; plexus not reported by study authors),[35] and these alterations were independent of disease activity,[35] though a separate study found no significant differences in SCP VAD between these groups.[18] 24-hour proteinuria was negatively correlated with RPCP VAD (n = 77, r = −0.524, p = 0.006).[31] Thus, laboratory measures of SLE severity, subtype, and systemic involvement have been correlated to changes in ocular OCTA metrics.

Disease severity scores for SLE include the SLE Disease Activity Index (SLEDAI) and the Systemic Lupus International Collaboration Clinics/American College of Rheumatology damage index (SLICC/ACR DI).[42] These scoring systems include clinical and immunological findings across many organ systems.[42] Scores from both systems correlated negatively with SCP and DCP VAD (SLEDAI-DCP VAD; n = 26, r = −0.4, p = 0.01; SLICC-SCP VAD; n = 26, r = −0.5, p = 0.0001; SLICC-DCP VAD; n = 26, r = −0.6, p < 0.0001),[14] (SLEDAI-DCP VAD; n = 29, r = −0.491, p = 0.009),[25] (SLEDAI-DCP VAD; n = 41, r = −0.383, p = 0.014),[26] (SLEDAI-SCP VAD, n = 47, r = −0.353, p = 0.015; SLEDAI-DCP VAD, n = 47, r = −0.321, p = 0.028),[20] (SLICC-SCP VAD in certain subfields, n = 20, r = −0.456 to −0.593, p = 0.006 to 0.043; SLICC-DCP VAD in central middle sector, n = 20, r = −0.484, p = 0.031),[19] with some insignificant results (n = 60, p > 0.05),[17] (n = 10, p = 0.4),[35] (n = 15, p > 0.5).[21] Additionally, one study found a positive correlation between SCP VAD and SLEDAI scores (SLEDAI-SCP VAD, n = 48, r = 0.263, p = 0.020),[18] which the authors attributed to the included patients having greater SLEDAI scores than patients in other studies. SLEDAI score also correlated negatively with CC VAD (n = 29, r = −0.521, p = 0.005)[25] and positively with FAZ area (SLEDAI-FAZ area, n = 29, r = 0.451, p = 0.018).[25] In those with a high SLICC/ACR DI score relative to those with a low score, FAZ area and perimeter were greater (n = 78, p = 0.023 and p = 0.02, respectively)[35] and FAZ circularity was lower (n = 78, p = 0.03).[35] Such findings suggest that ophthalmic microvascular OCTA metrics may provide information valuable in scoring of overall systemic severity of SLE.

In summary, changes in quantitative OCTA metrics have been identified in SLE patients according to medication use, renal and cardiac involvement, serum markers, and damage indices. Thus, OCTA might one day contribute to assessment of the effectiveness of medical therapy for SLE and the extent of systemic involvement in this condition, and further study of these possibilities should be pursued.

Behçet Disease (BD)

Behçet disease (BD) is a rheumatologic disease associated with symptoms spanning the dermatologic, musculoskeletal, gastrointestinal, and neurologic systems, among others. BD is thought to be a chronic autoimmune vasculitis. The most common ocular finding involves bilateral uveitis that often presents during systemic symptom flares. Studies have identified consistent OCTA metric changes demonstrating reduced retinal blood flow in both ocular and non-ocular BD by meta-analysis,[43,44] thus identifying subclinical ocular involvement in this disease. One study identified in our literature review correlated OCTA metrics to non-ocular findings in BD. RPCP inside-disk VAD was lower in non-ocular BD with systemic vascular involvement (SVI) than in non-ocular BD without SVI (n = 33, n = 6 with SVI, n = 27 without SVI; p = 0.006).[32] This finding suggests a potential role for OCTA in screening for and possibly predicting clinical systemic involvement in BD. Future efforts should determine the potential clinical relevance of this preliminary result.

Discussion

Overall then, in three different rheumatologic conditions, systemic sclerosis, systemic lupus erythematosus, and Behçet disease, ophthalmic posterior segment OCTA metrics have been correlated to non-ocular features including systemic complications and organ involvement, disease severity, serum markers, imaging findings, and medication use. OCTA metrics may provide value in diagnosis and prognosis of these conditions and their complications, as well as in disease stratification and treatment monitoring. Limitations of our review include that it examined only the PubMed database and dealt with only those articles published in English. It is therefore likely limited in the diversity of participants. It is also likely that some insignificant results have not been reported in the literature, leading to reporting bias. Furthermore, most of the reported analyses were cross sectional rather than longitudinal, limiting their potential to identify causal relationships between the correlated variables. There may also be different evaluation criteria for rheumatologic disease progression as well as differing OCTA metric calculations due to alternative methods for measuring OCTA metrics and the use of different OCTA machines. Finally, many of the reported studies did not attempt to correct for confounders, for example for the effect of hydroxychloroquine use on OCTA metrics when examining factors like serum markers, complicating interpretation of some of the correlations presented in this review.

Conclusion

These results warrant further investigation of ophthalmic posterior segment OCTA as a potential means to assess prognosis, presence, and severity of systemic involvement in rheumatologic conditions, especially longitudinal and prospective studies with potential to clarify temporality and predictive value of changes in OCTA metrics in these conditions.

Funding

Unrestricted department grant from Research to Prevent Blindness.

Disclosure

The authors declare no competing interests in this work.

References

1. Dias-Santos A, Tavares Ferreira J, Pinheiro S, et al. Ocular involvement in systemic lupus erythematosus patients: a paradigm shift based on the experience of a tertiary referral center. *Lupus*. 2020;29(3):283–289. doi:10.1177/0961203320903080
2. Dammacco R, Procaccio P, Racanelli V, Vacca A, Dammacco F. Ocular involvement in systemic lupus erythematosus: the experience of two tertiary referral centers. *Ocul Immunol Inflamm*. 2018;26(8):1154–1165. doi:10.1080/09273948.2018.1501495
3. Guan Y, Li F, Li N, Yang P. Decoding Behcet's uveitis: an in-depth review of pathogenesis and therapeutic advances. *J Neuroinflammation*. 2024;21(1):133. doi:10.1186/s12974-024-03123-6
4. Kreps EO, Carton C, Cutolo M, et al. Ocular involvement in systemic sclerosis: a systematic literature review, it's not all scleroderma that meets the eye. *Semin Arthritis Rheum*. 2019;49(1):119–125. doi:10.1016/j.semarthrit.2018.12.007
5. Carlà MM, Gambini G, Caporossi T, et al. Ocular involvement in systemic sclerosis: updated review and new insights on microvascular impairment. *Ocul Immunol Inflamm*. 2024;32(9):2209–2216. doi:10.1080/09273948.2024.2308030
6. Ferreira A, Vieira RJ, Furtado MJ, Lume M, Andrade JP, Menéres P. Detection of subclinical microvascular changes in systemic lupus erythematous using optical coherence tomography angiography: a systematic review and meta-analysis. *Surv Ophthalmol*. 2023;68(6):1115–1128. doi:10.1016/j.survophthal.2023.07.008
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(13):2887. doi:10.3390/jcm10132887
8. Koca S, Onan D, Kalaycı D, Allı N. Comparison of optical coherence tomography angiography findings in patients with Behçet's disease and healthy controls. *Ocul Immunol Inflamm*. 2020;28(5):806–813. doi:10.1080/09273948.2019.1635167
9. Yilmaz PT, Ozdemir EY, Alp MN. Optical coherence tomography angiography findings in patients with ocular and non-ocular Behçet disease. *Arq Bras Oftalmol*. 2021;84(3):235–240. doi:10.5935/0004-2749.20210031
10. Carnevali A, Giannaccare G, Gatti V, et al. Retinal microcirculation abnormalities in patients with systemic sclerosis: an explorative optical coherence tomography angiography study. *Rheumatol Oxf Engl*. 2021;60(12):5827–5832. doi:10.1093/rheumatology/keab258
11. Mihailovic N, Lahme L, Braasch S, et al. Altered ocular microvasculature in patients with systemic sclerosis and very early disease of systemic sclerosis using optical coherence tomography angiography. *Sci Rep*. 2022;12(1):10990. doi:10.1038/s41598-022-14377-6
12. Paczwa K, Rerych M, Romanowska-Próchnicka K, Olesińska M, Różycki R, Gołębiewska J. Retinal microvasculature in systemic sclerosis patients and the correlation between nailfold capillaroscopic findings and optical coherence angiography results. *J Clin Med*. 2024;13(7):2025. doi:10.3390/jcm13072025

13. 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 Albrecht Von Graefes Arch Klin Exp Ophthalmol*. 2020;258(10):2263–2269. doi:10.1007/s00417-020-04788-4
14. Conigliaro P, Cesareo M, Chimenti MS, et al. Evaluation of retinal microvascular density in patients affected by systemic lupus erythematosus: an optical coherence tomography angiography study. *Ann Rheum Dis*. 2019;78(2):287–289. doi:10.1136/annrheumdis-2018-214235
15. Zhao H, Pan M, Liu Y, Cheng F, Shuai Z. Evaluation of early retinal changes in patients on long-term hydroxychloroquine using optical coherence tomography angiography. *Ther Adv Drug Saf*. 2024;15. doi:10.1177/20420986231225851
16. 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(9):1297–1301. doi:10.1136/bjophthalmol-2018-313679
17. Subasi S, Kucuk KD, San S, et al. Macular and peripapillary vessel density alterations in a large series of patients with systemic lupus erythematosus without ocular involvement. *Graefes Arch Clin Exp Ophthalmol*. 2022;260(11):3543–3552. doi:10.1007/s00417-022-05742-2
18. Meng L, Chen L, Zhang C, et al. Quantitative assessment of retinal vasculature changes in systemic lupus erythematosus using wide-field OCTA and the correlation with disease activity. *Front Immunol*. 2024;15. doi:10.3389/fimmu.2024.1340224
19. Arfeen SA, Bahgat N, Adel N, Eissa M, Khafagy MM. 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(6):1261–1268. doi:10.1007/s00417-020-04626-7
20. Ermurat S, Koyuncu K. Evaluation of subclinical retinal microvascular changes in systemic lupus erythematosus patients using optical coherence tomography angiography and its relationship with disease activity. *Lupus*. 2022;31(5):541–554. doi:10.1177/09612033221084222
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(8):2111–2118. doi:10.1007/s10792-020-01388-3
22. Mimier-Janczak M, Kaczmarek D, Proc K, Misiuk-Hojło M, Kaczmarek R. 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(24):7417. doi:10.3390/jcm11247417
23. Guo T, Jin Y, Zhou M, et al. Quantitative evaluation of retinal and choroidal vascularity in systemic lupus erythematosus by SS-OCT/OCTA. *Graefes Arch Clin Exp Ophthalmol*. 2023;261(12):3385–3393. doi:10.1007/s00417-023-06155-5
24. Ferrigno S, Conigliaro P, Rizza S, et al. Relationship between retinal microvascular impairment and subclinical atherosclerosis in SLE. *Lupus Sci Med*. 2023;10(2):e000977. doi:10.1136/lupus-2023-000977
25. Liu J, Zhang H, Yu H, et al. Changes in retinal and choroidal thickness and vascular density in patients with systemic lupus erythematosus: assessed by optical coherence tomography angiography. *Lupus*. 2024;33(2):129–136. doi:10.1177/09612033231224771
26. 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 Inflammation*. 2021;29(7–8):1392–1397. doi:10.1080/09273948.2020.1735452
27. Cutolo CA, Cere A, Toma P, et al. Peripheral and ocular microvascular alterations in systemic sclerosis: observations from capillaroscopic assessments, perfusion peripheral analysis, and optical coherence tomography angiography. *Rheumatol Int*. 2024;44(1):107–118. doi:10.1007/s00296-023-05495-z
28. Rommel F, Prangel D, Prasuhn M, Grisanti S, Ranjbar M. Correlation of retinal and choroidal microvascular impairment in systemic sclerosis. *Orphanet J Rare Dis*. 2021;16(1):27. doi:10.1186/s13023-020-01649-5
29. Zirtiloglu S, Alikma MS, Acar OPA, Güven F, Icacan OC, Yigit FU. Evaluation of the optic nerve head using optical coherence tomography angiography in systemic sclerosis patients. *Klin Monatsbl Augenheilkd*. 2023;240(11):1277–1283. doi:10.1055/a-1975-2222
30. Erturk A, Erogul O, Kasikci M. Optical coherence tomography angiography is a useful tool for distinguishing primary raynaud's phenomenon from systemic sclerosis and/or very early disease of systemic sclerosis. *Diagn Basel Switz*. 2023;13(15):2607.
31. Rong X, Sun X, Hao Y, Sun X, Li J, Nie H. Assessment of peripapillary retinal nerve fiber layer thickness and vessel density in newly diagnosed SLE patients without ocular symptoms. *Graefes Arch Clin Exp Ophthalmol*. 2023;261(12):3599–3606. doi:10.1007/s00417-023-06091-4
32. Küçük MF, Yaprak L, Erol MK, Ayan A, Kök M. Quantitative changes in peripapillary, macular, and choriocapillaris microvasculature of patients with non-ocular Behcet's disease and relationship with systemic vascular involvement, an optical coherence tomography angiography study. *Photodiagnosis Photodyn Ther*. 2022;38:102749. doi:10.1016/j.pdpdt.2022.102749
33. Güven YZ, Akay F, Akmaz B, Solmaz D, Gercik Ö, Akar S. Evaluation of retinal microvascular network in patients with systemic sclerosis: an optical cohorence tomography angiography study. *Photodiagnosis Photodyn Ther*. 2023;44:103774. doi:10.1016/j.pdpdt.2023.103774
34. Liu PC, Luo SL, Lv MN, et al. Effect of hydroxychloroquine blood concentration on the efficacy and ocular toxicity of systemic lupus erythematosus. *Sci Rep*. 2024;14(1):7674. doi:10.1038/s41598-024-58391-2
35. Pelegrín L, Morató M, Araújo O, et al. Preclinical ocular changes in systemic lupus erythematosus patients by optical coherence tomography. *Rheumatol Oxf Engl*. 2023;62(7):2475–2482. doi:10.1093/rheumatology/keac626
36. 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(1):143–150. doi:10.1007/s10792-020-01561-8
37. Hesselstrand R, Scheja A, Shen GQ, Wiik A, Akesson A. The association of antinuclear antibodies with organ involvement and survival in systemic sclerosis. *Rheumatol Oxf Engl*. 2003;42(4):534–540. doi:10.1093/rheumatology/keg170
38. Höppner J, Tabeling C, Casteleyn V, et al. Comprehensive autoantibody profiles in systemic sclerosis: clinical cluster analysis. *Front Immunol*. 2023;13. doi:10.3389/fimmu.2022.1045523
39. Kılınç Hekimsoy H, Şekeroğlu MA, Koçer AM, Akdoğan A. Analysis of retinal and choroidal microvasculature in systemic sclerosis: an optical coherence tomography angiography study. *Eye Lond Engl*. 2020;34(4):763–770.
40. Cutolo M, Sulli A, Pizzorni C, Accardo S. Nailfold videocapillaroscopy assessment of microvascular damage in systemic sclerosis. *J Rheumatol*. 2000;27(1):155–160.
41. Wang X, Xie H, Yi Y, Zhou J, Yang H, Li J. Clinical research of lupus retinopathy: quantitative analysis of retinal vessels by optical coherence tomography angiography in patients with systemic lupus erythematosus. *Diagn Basel Switz*. 2023;13(20):3222.
42. Gladman DD, Goldsmith CH, Urowitz MB, et al. The systemic lupus international collaborating clinics/American college of rheumatology (SLICC/ACR) damage index for systemic lupus erythematosus international comparison. *J Rheumatol*. 2000;27(2):373–376.

43. Fan S, Shi X, Chen Z, Li X, Yu S, Li J. Retinal and choroidal microvascular alterations in Behcet's disease without ocular manifestations: a systematic review and meta-analysis. *Front Med*. 2022;9. doi:10.3389/fmed.2022.911990
44. Ji KB, Hu Z, Zhang QL, Mei HF, Xing YQ. Retinal microvasculature features in patients with Behcet's disease: a systematic review and meta-analysis. *Sci Rep*. 2022;12(1):752. doi:10.1038/s41598-021-04730-6