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Application of SS-OCTA to evaluate the effects of long-term hydroxychloroquine treatment on retinal structure and microcirculation in patients with systemic lupus erythematosus

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Key message

Systemic lupus erythematosus, Hydroxychloroquine, retinal structure and microcirculation, SS-OCTA.

Abstract

Propose The application of swept-source optical coherence tomography angiography (SS-OCTA) technique is used to detect the effects of long-term use of hydroxychloroquine (HCQ) on retinal structure and microcirculation in patients with systemic lupus erythematosus (SLE) before visual dysfunction occurs.

Methods Retrospective case-control study. A total of 73 SLE patients (73 eyes) who had taken HCQ regularly for a long period of time were included as the SLE patient group, while 21 healthy individuals (21 eyes) were included as the control group. Based on the duration of HCQ use (HCQ course), the SLE patient group was divided into baseline group (6 months ≤ medication time < 1 year), low-risk group (1 year ≤ medication time < 5 years), and high-risk group (medication time ≥ 5 years). All participants underwent bilateral SS-OCTA macular imaging (6 mm*6 mm), slit-lamp examination, non-contact tonometry, computerized visual field (30 – 2) test, and fundus autofluorescence imaging (FAF).

Results Compared among the groups, the full-layer retinal thickness and superficial blood vessel density of the fovea, below the inner circle, temporal side of the outer circle and above the outer circle decreased in the macular area (6 mm*6 mm) in high-risk group of SLE patients, while the area and circumference of FAZ increased ($P < 0.0125$). Correlation analysis suggested that the duration of SLE disease and HCQ cumulative dose were negatively correlated with superficial retinal capillary plexus vessel density (SCP-VD) in the three regions of inner retina, full-layer retinal thickness in the fovea, fovea, temporal side of the inner circle, and above the inner circle ($r < 0, P < 0.05$), and positively correlated with the area and circumference of FAZ ($r > 0, P < 0.05$).

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Conclusion Analysis by SS-OCTA examination showed that long-term HCQ treatment had adverse effects on the inner retina, SCP-VD and FAZ parameters in subclinical SLE patients without visual impairment.

Keywords Systemic lupus erythematosus, Hydroxychloroquine, Retinal structure and microcirculation, SS-OCTA

Introduction

SLE is a chronic, diffuse connective tissue disease mediated by autoimmunity. Its main feature is the production of multiple monoclonal autoantibodies against self-antigens and the deposition of immune complexes, leading to systemic inflammation and damage to multiple organs. As a result, any part of the eye may be affected [1]. At present, the treatment of SLE mainly includes: glucocorticoids, immunosuppressants (such as methotrexate, azathioprine, cyclosporine and hydroxychloroquine sulfate, etc.) and biological agents. Hydroxychloroquine (HCQ) is currently a first-line medication for treating systemic lupus erythematosus, rheumatoid arthritis, and primary Sjögren's syndrome. Its structure involves the addition of a hydroxyl group to the side chain of chloroquine. While it is generally considered safe, prolonged use is associated with a variety of adverse reactions [2, 3]. With the increase of the application range of antimalarial drugs and the prolongation of drug administration, the toxicity of HCQ has increased, and the most severe retinal toxicity has become the focus of attention. The common clinical manifestations of retinal toxicity caused by HCQ are decreased vision, loss of central vision, decreased night vision, a few can be asymptomatic, fundus examination shows punctate, plaque-like pigmentation on the retina, typical "bull's eye" appearance in the late stage, visual field examination manifests as centripetal visual field defect [4, 5].Since the vision loss caused by HCQ-induced photoreceptor cell damage is irreversible [6], it is of great significance to detect the subtle changes of HCQ retinal toxicity before the visual function damage occurs. Currently, according to the 2016 revision of the American Academy of Ophthalmology (AAO) guidelines on hydroxychloroquine retinal toxicity screening, visual field examination, spectral-domain optical coherence tomography (SD-OCT), fundus autofluorescence (FAF), or multifocal electroretinogram (mfERG) serve as the primary diagnostic credentials [7]. However, there are no clear standards for the diagnosis of early hydroxychloroquine retinal changes.

In previous studies, the most commonly used methods to assess retinal and choroidal vascular lesions are fluorescein fundus angiography (FFA) and indocyanine green angiography (ICGA) [8]. OCTA (Optical Coherence Tomography Angiography) is a non-invasive imaging technique that involves rapidly scanning motion particles, such as blood cells, at the same location on the retina. This technology allows for the acquisition of retinal vascular images, enabling the analysis and visualization of retinal vascular perfusion intensity. OCTA is capable of detecting images with high depth resolution of superficial and deep capillary plexuses, as well as choriocapillaris microvasculature. It aids in quantitative measurements for clinical applications [9]. Compared with SD-OCT, SS-OCTA has a scanning speed of ≥100,000 A-scans/second, a scanning depth of ≥6 mm, and real-time eye tracking, resulting in clearer imaging. The retinal analysis system can manually measure the thickness of a specified area of the retina and can also automatically analyze the thickness of any two layers of the retina.; The blood flow analysis system supports blood flow density measurement of any scan size, supports grid partitions, Early treatment diabetic retinopathy study (ETDRs) and other partitions, and automatically recognizes FAZ, SCP-VD.

There are few studies on the detection of HCQ retinopathy by SS-OCTA. The study aimed to detect changes in retinal structure and microcirculation before visual impairment in patients treated with long-term HCQ for SLE by using SS-OCTA, and to explore the effect of SLE on the retina of patients with SLE and healthy people.

Materias and methods

Research object

The research process is in line with the Declaration of Helsinki, and the study has been approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University (approval number: IIT [2021] Linlun Review No. 104), and all patients were informed of the purpose and steps of the study and signed the informed consent form. Collecting data from 73 patients (73 eyes) diagnosed with Systemic Lupus Erythematosus (SLE) who have been receiving long-term regular hydroxychloroquine (HCQ) treatment at the Rheumatology and Immunology Department outpatient clinic of the First Affiliated Hospital of Nanchang University. These patients meet the ULAR/ACR 2019 classification criteria. The SLE group will be stratified based on the duration of HCQ usage: the baseline group includes those with HCQ usage duration of 6 months or more but less than 1 year, the low-risk group includes those with HCQ usage for 1 year or more but less than 5 years, and the high-risk group includes those with HCQ usage for 5 years or more. Data collection will span from March 1, 2022, to January 31, 2023. Among them, 72 (98.63%) patients were female and 1 (1.37%) were male, aged 21 ~ 57 years, and the patients were divided into baseline group 21 cases (21 eyes), 23 cases (23 eyes) in low-risk group and 29 cases (29 eyes) in high-risk group according to the length of HCQ taking

HCQ. At the same time, 21 cases (21 eyes) were collected as a healthy control group for eye health checkups in our hospital, including 18 (85.71%) cases of women and 3 (14.29%) cases of men, aged 21 ~ 53 years. All SLE patients are in a non-active state, while recording patient basic information, SLE course, Glucocorticoid (GC) medication, HCQ daily dose, HCQ treatment course, and calculating HCQ cumulative dose (HCQ daily dose * HCQ treatment course) 、 systemic lupus erythematosus disease activity index(SLEDAI).All enrolled SLE patients underwent the following ophthalmologic examinations: visual acuity, best corrected visual acuity (BCVA), intraocular pressure, slit-lamp examination, automated visual field examination (30 – 2), microscopic field test, fundus autofluorescence examination, macular area (6 mm*6 mm) SS-OCTA examination. All of the above tests are done by the same experienced ophthalmologist. According to the analysis of the results of the binocular examination of the research object, if there is no visual impairment in both eyes, the left eye examination data is selected for recording and analysis, otherwise the normal eye is selected for visual function detection.

Inclusion criteria for SLE patients: (1) Age ≥ 18 years old, < 60 years old Chinese residents, communication barrier-free; (2) All patients with SLE met the classification diagnostic criteria of the American College of Rheumatology (LAR/ACR2019) [1]; (3) Taking HCQ for ≥ 6 months, with a daily dosage of 100-400 mg and no recent interruption within 10 days; (4) Assess disease activity SLEDAI ≤ 4 and be in remission; (5) Best corrected visual acuity 1.0, diopter: +4.0D~-4.0D, no abnormalities in visual field examination, micro-visual field and FAF. Inclusion criteria for the control group: (1) Age ≥ 18 years old, < 60 years old Chinese residents, communication barrier-free; (2)There were no obvious symptoms of ocular discomfort, and no obvious abnormalities were found on the ocular surface and fundus examination under the slit lamp; (3) Diopter: +4.0D~-4.0D, no other eye diseases, no history of eye surgery or trauma; (4) No systemic serious disease and able to cooperate with all tests. Exclusion criteria: (1) Previous ocular diseases such as high myopia, glaucoma, eye surgery, retinopathy, optic neuritis, etc.; (2)Visual impairment (BCVA < 1.0 or repeated appearance of central parafoveal dark spots in visual field examination, or high spontaneous fluorescence around the central fovea in FAF); (3) At the same time, it is combined with another autoimmune disease, such as Sjogren's syndrome, autoimmune cirrhosis, Behcet's disease, undifferentiated connective tissue disease, etc.; (4) Combine other chronic diseases such as hypertension, diabetes, malignant tumors, hyperthyroidism, etc.; (5) Assess disease activity SLEDAI > 4, in a state of disease activity; (6) Recent use of chemotherapy drugs, biologics, or radiation therapy; (7) Poor compliance, unable to cooperate with the completion of examination and treatment.

SS-OCTA examination

All participants completed the SS-OCTA test from 2 to 5 p.m. and were asked to refrain from caffeinated foods and smoking for 12 h prior to the test. Before the examination, instill compound tropicamide eye drops for pupillary dilation in both eyes. Use SS-OCTA (YG-100 K Yalkaid, TowardPi Medical Technology, Beijing, China, with 100,000 A-scans/second and axial and lateral resolutions of 3.8 μm and 10 μm, respectively) for the examination. During the examination, the patient should maintain an upright seated position, with the lower jaw on the chin rest and the forehead firmly against the headrest. The head and eyeballs should not be moved randomly. Instruct the patient to fixate on the fixation light within the instrument. Choose the 6 mm*6 mm mode for scanning in the macular area, and the system will automatically capture images of the patient's macular region. If the image quality is ≥ 8, use that image and record the numerical values of its various indicators; otherwise, recapture the image. In each eye, three concentric circles are automatically inserted in the macular region based on the ETDRs grid. The central circle, with a diameter of 1 mm, is defined as the fovea. The inner circle (1–3 mm) is defined as the parafoveal region, and the outer circle (3–6 mm) is defined as the perifoveal region (As shown in Fig. 1a).And manually select the retinal layering boundary, the device automatically divides the retina into the inner retina (Inner boundary membrane (ILM) to the Outer part of the inner plexiform layer (IPL), as shown in Fig. 1d), the outer retina (the inner layer (INL) to the outside of the RPE layer, as shown in Fig. 1e) and the full-thickness retina (ILM to the outside of the RPE layer, as shown in Fig. 1f); Simultaneously, based on the ETDRs grid, automatically measure the SCP-VD in the macular region (6 mm*6 mm), including the central fovea, inner temporal, inner superior, inner nasal, inner inferior, outer temporal, outer superior, outer nasal, and outer inferior sectors.(As shown in Fig. 1b); Automatic measurement of FAZ area and FAZ circumference in the fovea of the macula (As shown in Fig. 1c).

Statistical methods

SPSS 23.0 data analysis software was used for statistical analysis, and the classification data between groups were expressed by the number of cases and frequency, and the continuous correction of 2 tests was used for analysis; Firstly, the homogeneity of variance test was carried out for each group of measurement data, and the measurement data of uniform variance conforming to normal distribution were expressed as ($\bar{x} \pm s$), and the measurement data that did not conform to normal distribution

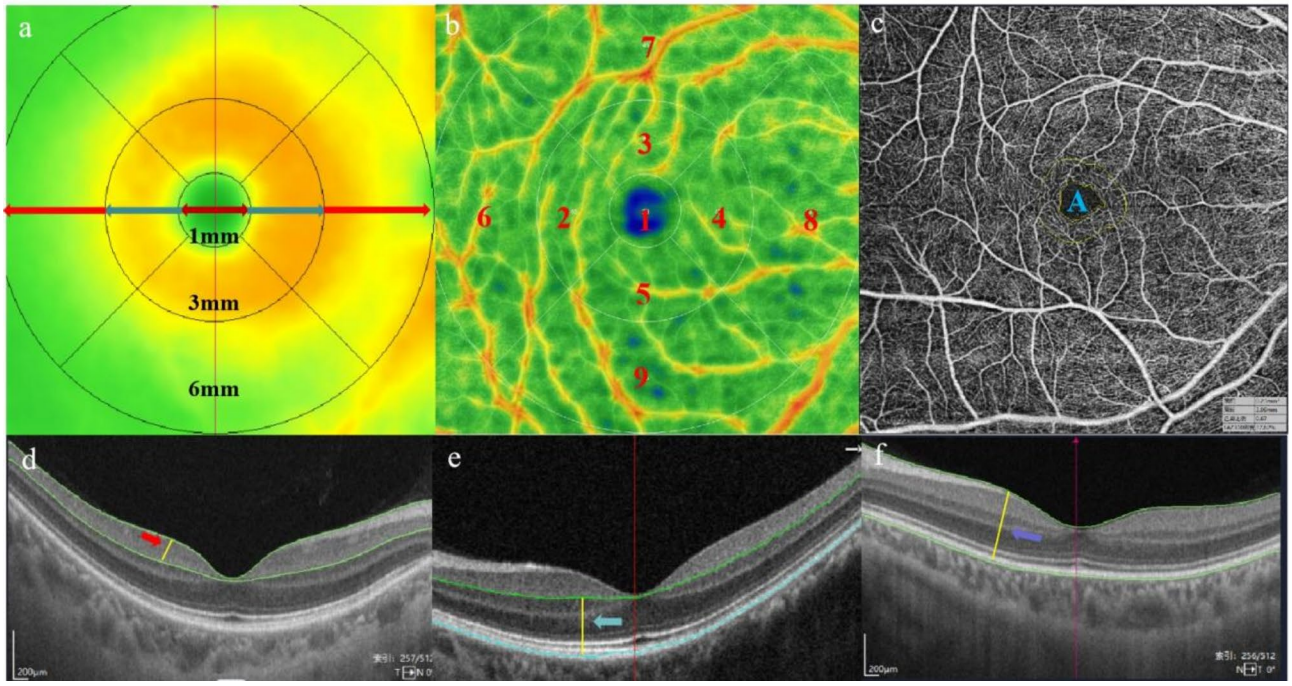

Fig. 1 SS-OCTA macular area 6 mm*6 mm retinal thickness and retinal blood flow parameter detection (Fig. 1a. According to the ETDRS grid device, three concentric circles are automatically inserted into the macular region; Fig. 1b. Superficial retinal capillary perfusion density according to ETDRs (numbers 1–9 in the figure represent the foveal area of the retina, the temporal side of the inner ring, the upper side of the inner circle, the nasal side of the inner circle, the lower part of the inner circle, the temporal side of the outer circle, the upper side of the outer circle, the nasal side of the outer circle and the lower part of the outer circle, respectively); Fig. 1c. Avascular area (FAZ) of the central fovea of the macula, as indicated in Fig. 1a and d. Inner retinal (ILM-IPL outside) structure, as indicated by the red arrow; Fig. 1e. Outer retinal (INL-RPE layer) structure, as indicated by the blue arrow; Fig. 1f. Full-thickness retinal (ILM to RPE layer) structure, as pointed by the purple arrow)

were represented by M(P25, P75). Anova analysis of variance was used to compare the measurement data of homogeneity of variance between multiple groups; otherwise Kruskal-WallisH non-parametric test was used; LSD-t test was used to compare the measurement data between two groups.If the measurement data are tested for normality, all conform to the normal distribution, Pearson correlation analysis is used, and Spearman correlation analysis is used for categorical variables and non-normal distribution measurement data. Multivariate analysis of continuous variables conforming to normal distribution uses multiple linear regression analysis. For intergroup comparisons, use the Bonferroni-corrected p-value as the criterion. Correlation analysis will be considered statistically significant if the p-value is less than 0.05 after correction.

Result

General information comparison

Among the 94 included subjects, the average height was 1.59 ± 0.06 m (1.49 m ~ 1.75 m) and the average weight was 54.84 ± 9.25 kg (38.00 kg ~ 85.00 kg). The data of BMI (kg/m^2) did not conform to the normal distribution, which was expressed by M(P25, P75), which was (19.51, 23.88), and the comparison of weight, height and mean BMI of each group was shown in Table 1, and there was no significant difference between the groups ($P > 0.0125$). The intraocular pressure and visual field examination of the right eye of the study subjects were recorded, and there were no significant differences in the results of intraocular pressure, MD and PSD between the groups ($P > 0.0125$).

Comparison of clinical data between groups of SLE patients

The clinical data of systemic examination in the baseline group, low-risk group and high-risk group of SLE patients were shown in Table 2, and there were statistical differences in SLE course, HCQ course, HCQ daily dose and HCQ cumulative dose between the groups ($P < 0.016$), among which there was a statistical difference between the baseline group and the high-risk group ($P < 0.016$), while there was no significant difference between the baseline group and the low-risk group, and between the low-risk group and the high-risk group ($P > 0.016$). There was no clear difference in the remaining results ($P > 0.016$).

Table 1 Comparison of general information between groups

Project	Health group (*n* = 21)	Baseline group (*n* = 21)	Low-risk group (*n* = 23)	High-risk group (*n* = 29)	χ^2/H/F	*P*-value
Gender (female/male)	18/3	20/1	23/0	29/0	7.408	0.060[a]
Age (year)	38.29 ± 9.65	37.57 ± 9.96	39.04 ± 11.28	37.27 ± 9.03	0.164	0.920
Height (m)	1.61 ± 0.07	1.60 ± 0.06	1.57 ± 0.04	1.59 ± 0.06	1.495	0.221
Weight (kg)	55.71 ± 7.89	56.57 ± 12.04	52.65 ± 7.57	54.67 ± 9.20	0.733	0.535
BMI (kg/m^2)	21.10(20.00,23.46)	20.82 (19.34,23.89)	20.57 (19.15,23.19)	21.44 (18.91,25.54)	1.065	0.786[b]
Intraocular pressure (mmHg)	15.17 ± 2.29	14.48 ± 2.29	15.00 ± 1.75	15.27 ± 2.54	0.549	0.650
MD (dB)	-0.90 ± 1.02	-0.99 ± 1.13	-1.11 ± 0.93	-0.93 ± 1.00	0.180	0.910
PSD (dB)	1.48 ± 0.41	1.53 ± 0.33	1.48 ± 0.38	1.43 ± 0.34	0.289	0.833

Note: *Bonferroni-corrected $P < 0.0125$ indicates statistically significant differences. **a** indictes that the analysis used the χ2 test; **b** indicates the use of the Kruskal-Wallis H non-parametric test, otherwise, Anova analysis was employed

Table 2 Comparison of clinical data results between groups of SLE patients

Project	Baseline group (*n* = 21)	Low-risk group (*n* = 23)	High-risk group (*n* = 29)	χ^2/H/F	*P*-value
SLE course of disease (months)	11.00 (8.00,12.00)	39.00 (29.00,48,00)	96.00 (73.00,120.00)	59.301	0.000[b*]
SLEDAI	3.43 ± 0.87	3.00 ± 0.95	3.34 ± 0.94	1.384	0.257
HCQ course of treatment (months)	10.00 (7.00,11.5)	37.00 (29.00,44.00)	96.00 (69.00,115.50)	63.611	0.000[b*]
HCQ daily dose(mg)	400.00 (300.00,400.00)	400.00 (200.00,400.00)	200.00 (200.00,350.00)	12.873	0.002[b*]
HCQ cumulative dose (g)	96.00 (72.00,138.00)	288.00 (216.00,468.00)	666.0 (414.00,792.00)	52.861	0.000[b*]
HCQ concentration (ng/ml)	504.45 ± 270.60	488.36 ± 244.62	416.82 ± 275.08	0.804	0.452
GC (used/ not used)	18/3	23/0	27/2	3.511	0.173[a]
GCdose (mg)	4.31 ± 2.61	5.11 ± 1.54	4.45 ± 1.84	1.036	0.360

Note: * Bonferroni-corrected $P < 0.016$ indicates statistically significant differences. **a** indictes that the analysis used the χ2 test; **b** indicates the use of the Kruskal-Wallis H non-parametric test, otherwise, Anova analysis was employed

Comparison of SS-OCTA regional parameters in the macular region

The comparison of retinal thickness parameters between the healthy group and SLE group showed that there were statistical differences in inner retinal thickness (foveal area, parafoveal area and surrounding area) and full retinal thickness in foveal area among all groups ($P < 0.0125$). There was no significant difference in the thickness of the outer omentum (fovea, parafovea and surrounding area) or the whole omentum (parafovea and surrounding area) ($P > 0.0125$). The comparison of foveal layer retinal thickness between the two groups showed that there was no statistical significance between the healthy group, baseline group and low-risk group ($P_1 > 0.0125$, $P_2 > 0.0125$, $P_4 > 0.0125$). There were statistically significant differences between healthy group, baseline group and low-risk group and high-risk group ($P_3 < 0.0125$, $P_5 < 0.0125$, $P_6 < 0.0125$). There was significant difference between healthy group and baseline group ($P_1 < 0.0125$), but there was no significant difference between healthy group and low-risk group and high-risk group, or between low-risk group and baseline group and high-risk group ($P_2 > 0.0125$, $P_3 > 0.0125$, $P_4 > 0.0125$, $P_5 > 0.0125$,$P_6 > 0.0125$). Health group compared with the baseline group surrounding area inner retinal thickness difference obvious ($P_1 < 0.0125$), while health groups with low risk and high risk groups and low-risk group and the compare between baseline and high-risk group had no statistical significance ($P_2 > 0.0125$, $P_3 > 0.0125$, $P_4 > 0.0125$, $P_5 > 0.0125$, $P_6 > 0.0125$). There were significant differences in mean shallow vascular density, foveal SCP-VD, FAZ area and FAZ circumference between high-risk group and healthy group, baseline group and low-risk group ($P_3 < 0.0125$, $P_5 < 0.0125$, $P_6 < 0.0125$). The results of SCP-VD on the temporal side and above the outer circle were statistically different between the high-risk group and the healthy group ($P_3 < 0.0125$). There was no statistical significance in the comparison of residual results between groups ($P > 0.0125$), and the specific results were shown in Table 3.

Correlation analysis of OCTA retinal thickness and blood flow parameters with systemic clinical data

Table 4 records the course of SLE (length of SLE disease), HCQ daily dose, HCQ cumulative dose and HCQ concentration and the thickness of the macular meadin, outer retina, and full-thickness retina, as well as SCP-VD in the fovea of the macula region, SCP-VD in the inner temporal side, SCP-VD above the inner ring, SCP-VD on the nasal side of the inner circle, SCP-VD below the inner circle, SCP-VD on the outer temporal side, SCP-VD above the outer ring, SCP-VD on the nasal side of the outer ring, SCP-VD, FAZ area, and FAZ perimeter below the outer ring are correlated results.It can be seen that the course of SLE and the cumulative dose of HCQ are negatively correlated with the thickness of the inner

Table 3 Comparison of retinal thickness and blood flow parameters in macular area between healthy group and SLE group

OCT parameter	Health group ($n=21$)	Baseline group ($n=21$)	Low-risk group ($n=23$)	High-risk group ($n=29$)	F	*P*-value	P_1	P_2	P_3	P_4	P_5	P_6
Inner retinal membrane thickness(μm)												
Central fovea	61.33 ± 1.40	59.43 ± 5.79	57.96 ± 8.20	45.93 ± 7.15	26.994	0.000*	0.372	0.107	0.000*	0.480	0.000*	0.000*
Paracentral fovea	119.45 ± 1.09	118.21 ± 4.37	118.02 ± 6.19	111.42 ± 4.50	13.135	0.000*	0.438	0.359	0.000*	0.902	0.000*	0.000*
Surrounding area	113.04 ± 0.99	113.49 ± 4.55	112.01 ± 5.44	108.06 ± 4.49	7.360	0.000*	0.754	0.468	0.000 *	0.296	0.000*	0.003*
Outer omentum thickness(μm)												
Central fovea	218.71 ± 9.05	212.95 ± 6.16	214.74 ± 8.24	215.41 ± 7.85	1.958	0.126	0.020	0.099	0.148	0.455	0.280	0.760
Paracentral fovea	225.96 ± 9.68	217.68 ± 8.96	219.28 ± 10.13	221.50 ± 7.03	3.468	0.019	0.003*	0.015	0.083	0.552	0.137	0.374
Surrounding area	199.74 ± 7.95	191.35 ± 8.31	195.30 ± 8.53	195.54 ± 6.12	4.198	0.008*	0.001*	0.059	0.059	0.091	0.059	0.911
Full thickness of omentum(μm)												
Central fovea	254.38 ± 8.16	255.29 ± 6.97	254.04 ± 9.75	247.34 ± 9.63	4.550	0.005*	0.740	0.899	0.006*	0.642	0.002*	0.008*
Paracentral fovea	334.45 ± 10.08	335.60 ± 9.40	331.61 ± 11.38	332.97 ± 7.39	0.738	0.532	0.677	0.326	0.590	0.169	0.340	0.609
Surrounding area	296.57 ± 7.68	298.87 ± 8.96	296.37 ± 7.02	298.50 ± 5.56	0.724	0.540	0.307	0.927	0.356	0.257	0.859	0.296
SCP-VD (%)												
Central fovea	31.00 (29.00,32.50)	28.00 (27.00,30.00)	28.00 (27.00,31.00)	21.00 (15.00,23.00)	37.517	0.000b*	0.203	0.045	0.000*	0.470	0.000*	0.000*
temporal side of the inner circle	42.62 ± 2.52	41.57 ± 3.49	42.43 ± 2.68	40.41 ± 3.22	2.870	0.041	0.263	0.840	0.012*	0.345	0.184	0.018
above the inner ring	44.05 ± 2.31	43.19 ± 4.08	43.57 ± 2.19	41.72 ± 2.71	3.126	0.030	0.339	0.582	0.006*	0.668	0.080	0.025
nasal side of the inner ring	42.33 ± 2.58	43.19 ± 2.32	42.83 ± 2.35	41.97 ± 2.67	1.137	0.339	0.269	0.515	0.608	0.630	0.090	0.220
below the inner ring	44.48 ± 2.54	42.19 ± 4.59	43.78 ± 2.76	41.83 ± 4.12	2.849	0.042	0.045	0.530	0.013	0.151	0.729	0.058
temporal side of the outer ring	44.14 ± 2.78	42.67 ± 2.63	42.96 ± 2.88	41.03 ± 2.80	5.349	0.002*	0.089	0.161	0.000*	0.730	0.043	0.015
above the outer ring	45.81 ± 1.83	44.90 ± 2.77	44.74 ± 2.49	43.24 ± 2.64	4.691	0.004*	0.240	0.156	0.000*	0.825	0.021	0.033
nasal side of the outer ring	45.43 ± 1.91	43.71 ± 2.61	44.52 ± 2.04	43.31 ± 3.19	3.172	0.028	0.032	0.242	0.005*	0.297	0.582	0.092
below the outer ring	44.76 ± 2.34	42.43 ± 4.43	43.52 ± 3.31	42.41 ± 4.16	2.050	0.113	0.044	0.269	0.029	0.330	0.989	0.286
FAZ area(mm^2)	0.24 ± 0.07	0.25 ± 0.07	0.30 ± 0.09	0.47 ± 0.08	50.255	0.000*	0.705	0.013	0.000*	0.034	0.000*	0.000*
FAZ circumference(mm)	1.93 ± 0.34	1.95 ± 0.25	2.04 ± 0.48	2.85 ± 0.49	30.130	0.000*	0.900	0.396	0.000*	0.472	0.000*	0.000*

Note: P represents the comparison among three groups.; P_1 represents the comparison between the healthy group and the baseline group. P_2 represents the comparison between healthy group and low-risk group. P_3 represents the comparison between healthy group and high-risk group. P_4 represents the comparison between baseline group and low-risk group. P_5 represents the comparison between baseline group and high-risk group. P_6 represents the comparison between low-risk group and high-risk group. *Using Bonferroni correction, $P<0.0125$ indicates statistically significant differences. In comparisons between groups, b indicates the use of the Kruskal-Wallis H non-parametric test; otherwise, Anova analysis was applied. LSD-t test was used for comparison between the two groups

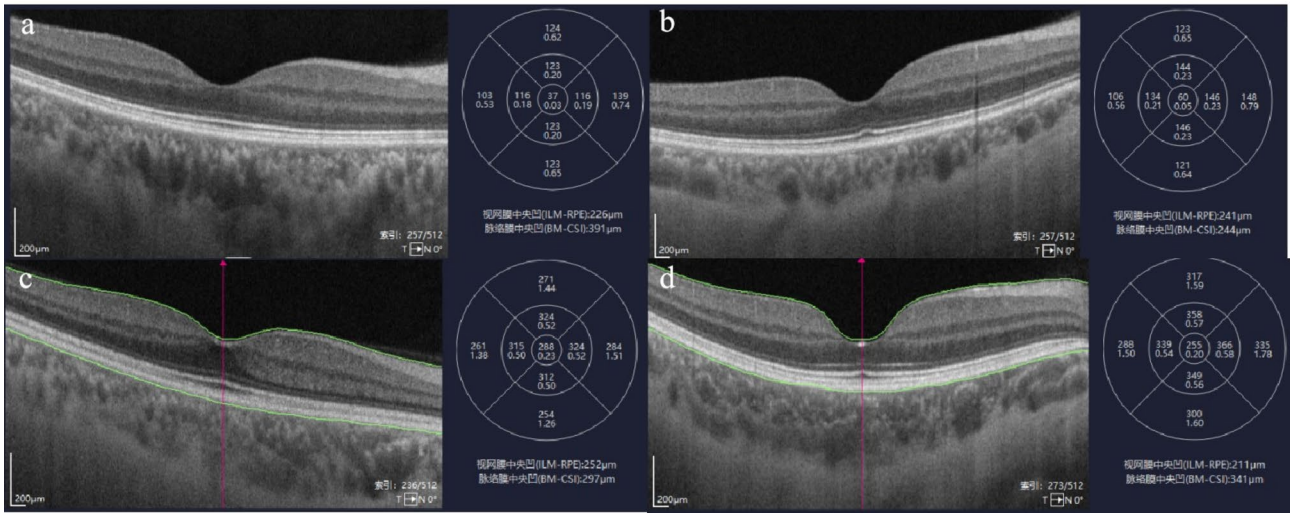

Fig. 2 Comparison of 6 mm*6 mm inner retinal and full-thickness retinal thickness in macular area between high-risk group and low-risk group (Fig. 2a. HCQ treatment > Inner retinal thickness (ILM-IPL) thickness in SLE patients with 5 years of treatment; Fig. 2b Inner retinal (ILM-IPL) thickness in SLE patients after 24 months of HCQ treatment; Fig. 2c. Thickness of full-thickness retinal (ILM-RPE) in patients with SLE treated > HCQ for 5 years; Fig. 2d. Full-thickness retinal (ILM-RPE) thickness in SLE patients after 36 months of HCQ treatment)

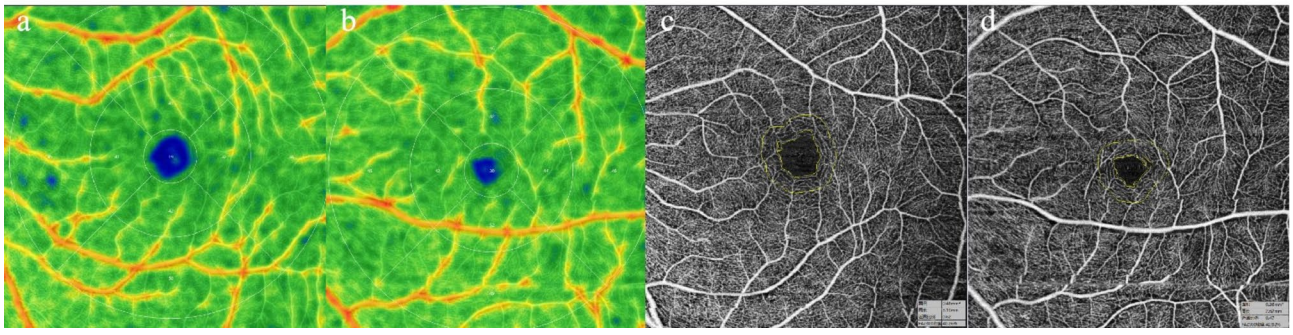

Fig. 3 Comparison of superficial retinal blood flow density, FAZ area and circumference in macular area between high-risk group and low-risk group (Fig. 3a. HCQ treatment > 5 years of SLE superficial retinal vascular density (%); Fig. 3b. Superficial vascular density of macular retina in SLE patients < 5 years after HCQ treatment; Fig. 3c. HCQ treatment > 5 years SLE patients with macular fovea vascular area; Fig. 3d. HCQ treatment < 5 years after SLE patients with macular foveal vascular area)

retina and the thickness of the fovea full-thickness retina in various regions ($r<0$,$P<0.05$). The correlation P value between the course of SLE and the cumulative dose of HCQ and the thickness of the outer retina and the thickness of the parafovea and the full-thickness retina in the surrounding area was greater than 0.05, and the above indicators were not correlated with the course of SLE, HCQ course and HCQ cumulative dose. There was no correlation between the daily dose and HCQ concentration of HCQ and the thickness of the inner retina, outer retina and full thickness of the retina in each region ($P>0.05$).The P values of SCP-VD in the fovea area, SCP-VD on the temporal side of the inner ring, SCP-VD above the inner ring, and SCP-VD above the outer circle were less than 0.001, and were negatively correlated with SCP-VD in the fovea area, SCP-VD on the temporal side of the inner ring, SCP-VD above the inner ring, and SCP-VD above the outer circle ($r<0$,$P<0.05$).The course of SLE and the cumulative dose of HCQ were positively correlated with FAZ circumference and FAZ area ($r>0$, $P<0.05$). Lateral temporal SCP-VD in the outer ring was inversely correlated with the course of SLE ($r<0$, $P<0.05$), but not associated with cumulative HCQ dose ($P>0.05$). The correlation P value between the daily dose of HCQ and HCQ concentration and SCP-VD, FAZ area and FAZ circumference in various regions of the macular area was greater than 0.05, so the above indicators were not correlated with the daily dose of HCQ and HCQ concentration.

Dissusion

Due to the presence of antiendothelial antibodies in systemic lupus erythematosus, complement-mediated cytotoxicity causes vascular endothelial cell damage, resulting

Table 4 Correlation analysis of SLE course, cumulative HCQ dose and HCQ concentration with retinal thickness and blood flow in macular areas

Project	SLE course of disease (months)		HCQ daily dose (mg)		HCQ cumulative dose(g)		HCQ concentration(ng/ml)	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value	*r*	*P*-value
Inner retinal membrane thickness (μm)								
Central fovea	-0.574	0.000*	-0.169	0.154	-0.740	0.000*	-0.230	0.051#
Paracentral fovea	-0.486	0.000*	0.040	0.736	-0.493	0.000*	-0.068	0.566#
Surrounding area	-0.440	0.000*	-0.080	0.500	-0.496	0.000*	-0.170	0.151#
Outer omentum thickness (μm)								
Central fovea	0.033	0.781	-0.131	0.270	0.063	0.598	-0.084	0.481#
Paracentral fovea	0.120	0.312	-0.097	0.414	0.095	0.422	0.061	0.607#
Surrounding area	0.047	0.693	-0.084	0.478	0.067	0.571	-0.095	0.426#
Full thickness of omentum (μm)								
Central fovea	-0.374	0.001*	-0.039	0.741	-0.386	0.001*	-0.093	0.434#
Paracentral fovea	-0.099	0.404	-0.142	0.230	-0.186	0.116	-0.176	0.136#
Surrounding area	0.038	0.750	-0.184	0.100	-0.120	0.314	-0.021	0.860#
SCP-VD (%)								
Central fovea	-0.643	0.000*	0.186	0.114	-0.637	0.000*	-0.013	0.912#
temporal side of the inner circle	-0.251	0.032*	-0.047	0.691	-0.258	0.028*	-0.090	0.447#
above the inner ring	-0.283	0.015*	0.015	0.898	-0.350	0.002*	-0.169	0.154#
nasal side of the inner ring	-0.220	0.061	0.012	0.918	-0.253	0.031*	-0.121	0.308#
below the inner ring	-0.136	0.250	0.109	0.360	-0.107	0.366	0.161	0.175#
temporal side of the outer ring	-0.343	0.003*	0.064	0.589	-0.219	0.063	-0.070	0.553#
above the outer ring	-0.264	0.024*	-0.040	0.737	-0.317	0.006*	0.023	0.845#
nasal side of the outer ring	-0.108	0.362	0.081	0.495	-0.036	0.760	0.198	0.093#
below the outer ring	-0.109	0.358	0.181	0.126	0.032	0.786	0.063	0.597#
FAZ area(mm^2)	0.661	0.000*	-0.140	0.237	0.730	0.000*	-0.076	0.522#
FAZ circumference(mm)	0.575	0.000*	-0.185	0.118	0.598	0.000*	-0.163	0.168#

Note: # indicates that the analysis method used is Pearson correlation analysis; otherwise, it is Spearman correlation analysis. * $P<0.05$ indicates a significant correlation between the two factors

in microvascular dysfunction that can affect blood vessels anywhere in the body [10]. Although HCQ has a favorable safety profile as a first-line agent for SLE at present, current studies have shown that 7.5% of all patients taking the drug long-term have retinopathy, and its prevalence increases with the duration of treatment and the increase in the dose per kilogram of body weight [11, 12]. Therefore, early detection of the emergence and progression of HCQ retinopathy is essential. In recent years, according to the 2016 American Academy of Ophthalmology (AAO) revised screening guidelines, different imaging techniques have been used to explore detection methods for HCQ-associated retinopathy with high sensitivity and specificity [7]. However, imaging for this period has been of interest due to the slight and lack of specificity of the previous retinopathy. As the eye can directly observe tissue structure and microcirculation through living organisms, this study aims to use SS-OCTA to observe the changes in retinal structure and microcirculation in SLE patients taking HCQ for a long time without abnormal vision, visual field and visual acuity.

In this study, the retinal thickness in each area of SLE patients was compared with that of healthy control group, and it was found that the inner retinal thickness in each area of the macular area with a diameter of 6 mm and the full retinal thickness in the fovea in high-risk group were significantly thinner than those in the lower risk group, baseline group and healthy group. Similarly, the superficial retinal blood density of SLE patients in high-risk group was lower than that in low-risk group, baseline group, and healthy group. SCP-VD in different areas was found to decrease more significantly in fovea, temporal and upper part of inner circle, temporal part of outer circle, temporal part of upper part, and nasal part by comparison. The FAZ area and FAZ circumference were larger than those in low-risk, baseline and healthy groups. Further analysis of the correlation between duration of SLE, cumulative HCQ dose and peripheral blood HCQ concentration in patients with retinal thickness and SCP-VD in each region showed that SLE course and cumulative HCQ dose were negatively correlated with inner retinal thickness, foveal SCP-VD, temporal SCP-VD and upper SCP-VD. It is positively correlated with FAZ area and FAZ perimeter. However, there was no significant correlation between HCQ concentration

in peripheral blood and retinal thickness, SCP-VD, FAZ area and FAZ perimeter.

At present, there are limited studies at home and abroad [13] on the use of SS-OCTA to evaluate retinal structural changes in HCQ retinopathy, and the results of the study are also different due to the different populations and groups included between the studies [14]. Most previous reports indicate that HCQ primarily affects the outer layer of the retina, namely [15] photoreceptor cells and RPE. Recently, some scholars have used OCT to evaluate the effect of HCQ on the choroids of patients, and found that choroidal thickness is negatively correlated with the cumulative accumulation of HCQ [16–19]. However, in the seminal paper published in 1978 by Rosenthal et al. [20, 21], chloroquine has effects on retinal ganglion cells in animal models. Meanwhile, studies such as Lee and Uslu have shown that Macular GCL and IPL are inversely correlated with cumulative HCQ doses. Through the results of this study, it is also shown that the damage to the retina caused by long-term HCQ is not limited to the outer retina, in this study, we regarded the thickness of the inner boundary membrane to the outer part of the inner plexiform layer as the inner retina, and this regional structure is mainly composed of RNFL (ganglion cell axon), GCL (ganglion cell somatosis) and IPL (bipolar cell axons and ganglion cell dendrites), and it was found that the effect of inner retinal thickness is more obvious. At the same time, combined with previous studies, patients with SLE have thinned RNFL and ganglion cell complexes than healthy patients [22–24]. It is considered that the results of this study may be caused by the combination of SLE and long-term HCQ use. This means that patients in the high-risk group have already experienced changes in the thickness of the inner retina before the patient's vision, visual field, and visual acuity are abnormal.

The pathogenesis of HCQ-induced retinopathy is unclear, and research on whether HCQ causes changes in retinal microcirculation is limited. Goker et al. [25] found a decrease in mean superficial vascular density and an increase in FAZ area and FAZ circumference in a study of 20 patients treated with HCQ for more than 5 years. Ozek et al. [26] reported a reduction in temporal side deep retinal blood flow density in rheumatoid arthritis patients who received hydroxychloroquine (HCQ) treatment for more than 5 years. Forte et at [27, 28]. observed a significant correlation between changes in retinal thickness and retinal blood flow density in patients undergoing long-term hydroxychloroquine treatment. They also found that patients receiving this treatment for more than five years exhibited a reduction in both retinal thickness and blood flow density. Currently, most studies suggest a correlation between the duration of HCQ use and the cumulative dose associated with microcirculation changes in hydroxychloroquine retinopathy. The impact of HCQ on retinal blood flow density in patients who have taken it early is not significant. However, in patients who have taken HCQ for over 5 years or in high doses (≥ 5 mg/kg), the impact on retinal blood vessel density is apparent. Therefore, the sensitivity of OCTA detection for early HCQ-induced retinal damage is low [29]. In the past, Comcali et al. [30] evaluated the effect of SLE on macular and optic disc vascular density through OCTA and found that the shallow, deep and chorioidal capillary densities in the fovea, parafovea and surrounding areas were similar in the healthy group and SLE group, while the medial optic disc blood density was significantly reduced in the SLE group. It may be related to early neurovascular damage in SLE patients.However, in this study, with the extension of HCQ treatment time and the increase of cumulative dose between SLE patients and healthy groups, significant differences were found in FAZ area, FAZ perimeter, foveal SCP-VD, temporal SCP-VD and superior SCP-VD in SLE patients. It is speculated that the changes of retinal microcirculation may be aggravated with the prolonged HCQ treatment and the increase of cumulative dose before the appearance of visual impairment and obvious microvascular lesions in SLE patients. There were statistical differences between the high-risk group and the low-risk group and the baseline group, and combined with theanalysis of previous studies, it may be that long-term use led to the accumulation of HCQ in the retina, and long-term action led to microcirculation changes.

In this study, we not only analyzed the association between the duration of HCQ use, the cumulative dose of HCQ and OCTA parameters, but also measured the peripheral blood HCQ concentration of each enrolled patient, and recorded and analyzed whether the HCQ concentration affected the patient's retina. The results showed that there was no significant correlation between the concentration of HCQ in peripheral blood and the thickness of each layer of the retina, SCP-VD, FAZ area and FAZ circumference. It may be due to the fact that HCQ retinopathy is caused by long-term accumulation of drugs, rather than an increase in drug concentrations in a short period of time, but it may also be related to the selection of stable SLE patients without visual impairment and the daily dose of HCQ is 100–400 mg, and the peripheral blood HCQ concentration is low.

There were some limitations to this study. The study was divided into four groups: baseline, low-risk, high-risk and healthy, each with a small cohort, small sample size, and lack of longitudinal studies. The lack of data on patients newly diagnosed with SLE could not be compared with healthy groups in patients who were newly diagnosed with SLE, and it was impossible to determine whether retinal damage was caused by the onset of SLE.

Generally, the normal control group had fewer eye cases, resulting in less data related to the macular area of the normal control group. And in our study, no more detailed layered analysis of the inner retina was carried out, and it was impossible to further determine which layer of the inner retina HCQ specifically affected, and failed to analyze the factors related to retinal changes from multiple aspects. In future studies, we can increase the sample size and set up a group of newly diagnosed SLE patients for more detailed studies, so as to more comprehensively analyze the effects of SLE disease itself and HCQ on the microcirculation changes in the optic disc area and retina of patients.On the basis of existing research, the inner retina was layered and compared. Through regular eye screening of patients, the occurrence and development of changes in the microstructure of hydroxychloroquine retinopathy were studied longitudinally.

Optical coherence tomography is an objective, rapid, non-invasive examination that can not only assess changes in retinal structure, but also understand changes in retinal microvessels through optical coherence tomography angiography. This study found that SS-OCTA can detect the subclinical changes of HCQ on the retina of SLE patients before visual impairment in SLE patients, which provides an objective basis for the early change of HCQ retinal toxicity.

Author contributions

HL and RW contributed to the study conception and design. Material preparation, data collection, and analysis were performed by XL, CX and SL. XL and CX wrote the manuscript's first draft. YC, ML, SW, YW and ZW offered feedback on earlier drafts. The final manuscript was reviewed and approved by all writers.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The current study was approved by the First Affiliated Hospital of Nanchang University Ethics Committee (Approval number: AF-SG-04-2.0). Written informed consent was obtained from all patients after receiving an explanation of the investigative nature and intent of the study and tenets of the Helsinki Declaration were followed.

Consent for publication

The patients were informed about the study and signed the informed consent forms.

Competing interests

The authors declare no competing interests.

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