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RETINAL DISORDERS

Application of optical coherence tomography angiography for microvascular changes in patients treated with hydroxychloroquine: a systematic review and meta-analysis

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Abstract

Background Retinal toxicity with long-term hydroxychloroquine (HCQ) treatment is a major concern. This systematic review aims to assess the application of optical coherence tomography angiography (OCTA) to detect microvascular alterations in patients under HCQ.

Methods PubMed, Scopus, Web of Science, and Cochrane Library databases were systematically searched until January 14, 2023. Studies using OCTA as a primary diagnostic method to evaluate the macular microvasculature of HCQ users were included. Primary outcomes were macular vessel density (VD) and foveal avascular zone (FAZ) at the superficial (SCP) and deep (DCP) capillary plexus. Meta-analysis was performed using a random-effects model.

Results Of 211 screened abstracts, 13 were found eligible, enrolling 989 eyes from 778 patients. High-risk patients due to longer duration of treatment presented lower VD in the retinal microvasculature than those with low-risk in SCP ($P=0.02$ in fovea; $P=0.004$ in parafovea) and in DCP ($P=0.007$ in fovea; $P=0.01$ in parafovea). When compared with healthy controls, HCQ users had lower VD in both plexus—no quantitative synthesis was presented.

Conclusions Microvascular changes were found in autoimmune patients under HCQ treatment without any documented retinopathy. However, the evidence produced so far does not allow to draw conclusion concerning the effect of drug as studies were not controlled for disease duration.

Key messages

What is known

- Hydroxychloroquine may lead to irreversible retinal damage. The pathophysiology of this toxicity is not fully understood but some reports speculate that vasculopathy might participate in the process.

What this paper adds

- Patients under hydroxychloroquine, especially those with a longer duration of treatment, have a lower vascular density in both retinal plexuses in the absence of retinopathy.
- The evidence produced so far does not allow to draw conclusions on the effect of hydroxychloroquine on microvasculature as studies were not controlled for disease effect or duration.

Keywords Autoimmune diseases · Hydroxychloroquine · Macula lutea · Microvasculature · Optical coherence tomography angiography

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Introduction

Hydroxychloroquine (HCQ) is an antimalarial drug widely used by many specialties for the management of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and other autoimmune conditions. It is being considered for broader applications [1], including cancers, multiple sclerosis, primary antiphospholipid antibody syndrome, hypertension [2], and diabetes mellitus [3]. More recently, it was used in the first months of the COVID-19 pandemic [4, 5]. Despite the few systemic adverse effects, long-term use of HCQ may lead to irreversible and vision-threatening toxic retinopathy [1]. Although it is considered rare, it may occur in up to 7.5% of patients [6]. It is known that a long duration of exposure (> 5 years) confers a higher risk of retinal toxicity [6]. Additional risk factors include high dose (> 5 mg/kg/day), concomitant tamoxifen therapy, and renal failure [7]. Early detection of retinal toxicity is crucial to avoid irreversible damage and vision loss.

OCT angiography (OCTA) is a novel noninvasive imaging modality based on the variation in the signal caused by moving particles, such as red blood cells, allowing the assessment of retinal and choroidal microvasculature without the need of dye injection. Several recent studies detected microvascular changes in patients using HCQ without evident microangiopathy or retinopathy on ophthalmoscopy and complementary exams such as SD-OCT and fluorescein angiography [8–10]. In addition, OCTA may help elucidate the mechanisms of HCQ-induced retinal toxicity.

Several observational publications exist on this subject, but a systematic review and a meta-analysis are yet to be published to our best knowledge. We sought to conduct a systematic review and meta-analysis of the OCTA technique to detect microvascular alterations in patients under HCQ and further characterize them.

Methods

We conducted a systematic review with meta-analysis following the guidelines presented by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [11] and the Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) statement [12]. The protocol was not registered.

Search strategy

Two independent reviewers (A.F. and R.A.) searched PubMed, Web of Science, Cochrane Library, and Scopus databases for all relevant studies published from inception to January 14, 2023. Search terms used are detailed in Supplementary Table 1. References of relevant articles were hand-searched, and a forward citation search was performed.

Study selection

The following inclusion criteria were applied: (a) *type of studies*: Observational studies. Articles in English, Portuguese or Spanish were included; (b) *type of participants*: (i) studies with the primary focus on patients treated with HCQ; (ii) studies with a healthy control group or comparing patients with high-risk versus low-risk of HCQ-induced retinopathy; (iii) population > 18 years old; (c) *type of interventions*: studies where OCTA was performed; (d) *type of outcome*: studies including measurements performed in at least one of the following: (i) foveal avascular zone (FAZ); (ii) vessel density (VD) at the macular superficial capillary plexus (SCP); (iii) VD at the macular deep capillary plexus (DCP). No restrictions regarding time or country of origin were placed during the search process.

The exclusion criteria were as follows: (a) duplicate publications, conference presentations, summaries; (b) studies in patients with ocular diseases; (c) studies in patients with other relevant systemic co-morbidities and nonhuman studies; (d) qualitative studies; (e) review studies and meta-analysis were excluded although bibliographic references were manually reviewed.

Data collection process

Two authors (A.F. and R.A.) independently reviewed each title and study to exclude duplicates and irrelevant studies. The two authors performed a full-text review to assess study eligibility, and disagreements were resolved by consensus. Authors were contacted to acquire any missing information. Data was extracted using Microsoft® Word. Our primary outcomes were as follows: FAZ area and VD at the macular SCP and DCP. Whenever possible, the analysis of choriocapillaris was performed. OCTA parameters were only synthesized for analysis if they were reported in a minimum number of three papers. When data were reported in subgroups, combination onto a single group was performed using a methodology described elsewhere [13]. Data extracted included study setting (first author, publication, year); participant characteristics (age, gender, eyes included, daily doses, duration of disease, and duration of treatment); study design; OCTA characteristics (model, scan size, and scan definition); image analysis (software) and main outcomes.

Quantitative analysis

Meta-analyses of continuous outcomes were conducted with the Cochrane Collaboration's Review Manager software

(Version 5.3) using an inverse variance in the model. Two consecutive analyses were performed: (i) comparing patients with high-risk versus low-risk of HCQ-induced retinopathy, based on the duration of exposure using five years as cutoff; (ii) comparing patients using HCQ versus healthy controls. Random-effects models were chosen for both analyses.

Cochran's chi-squared test for homogeneity (Chi2) was used to assess heterogeneity between studies, and variation due to heterogeneity was estimated by calculating the I^2 and interpreted as recommended [14, 15]. Following Cochrane Guidelines [16], meta-regression was only performed for one OCTA parameter as there were fewer than ten studies for each one of the others parameters that was meta-analyzed. Funnel plots were used to assess publication bias.

Due to unacceptable heterogeneity (ranging from 79 to 96%) not solved with a sensitivity analysis, the quantitative analysis of HCQ patients versus healthy controls comparison was excluded.

Risk of bias in individual studies and sensitivity analysis

Two reviewers (AF and R.J.-V.) independently evaluated the risk of bias for each eligible study using a modified Moskalewicz and coworkers [17]. Seven-Question Newcastle–Ottawa Scale (NOS) questionnaire to our study-specific language as detailed in Supplementary Methods 1. A sensitivity analysis was conducted for analysis with an $I^2 > 60\%$.

Results

Literature search

The study selection process is shown in a flow diagram (shown in Fig. 1). The whole search process retrieved 211 original abstracts, of which 50 were duplicates. After full-text review, 13 met the inclusion criteria and were included in this systematic review [8–10, 18–27]. No previous systematic reviews with meta-analysis on this specific issue were found.

Study characteristics

Tables 1 and 2 summarize the characteristics of the thirteen studies included. All studies were cross-sectional and published between 2018 and 2022. A total of 989 eyes from 778 patients were enrolled, including 480 patients with autoimmune diseases. All studies but the one by Tarakcioglu et al. [27] used age- and sex-matched groups. The overall mean age varied between 38.4 and 57.5 years, and the proportions of women spanned between 64 and 100%. The OCTA

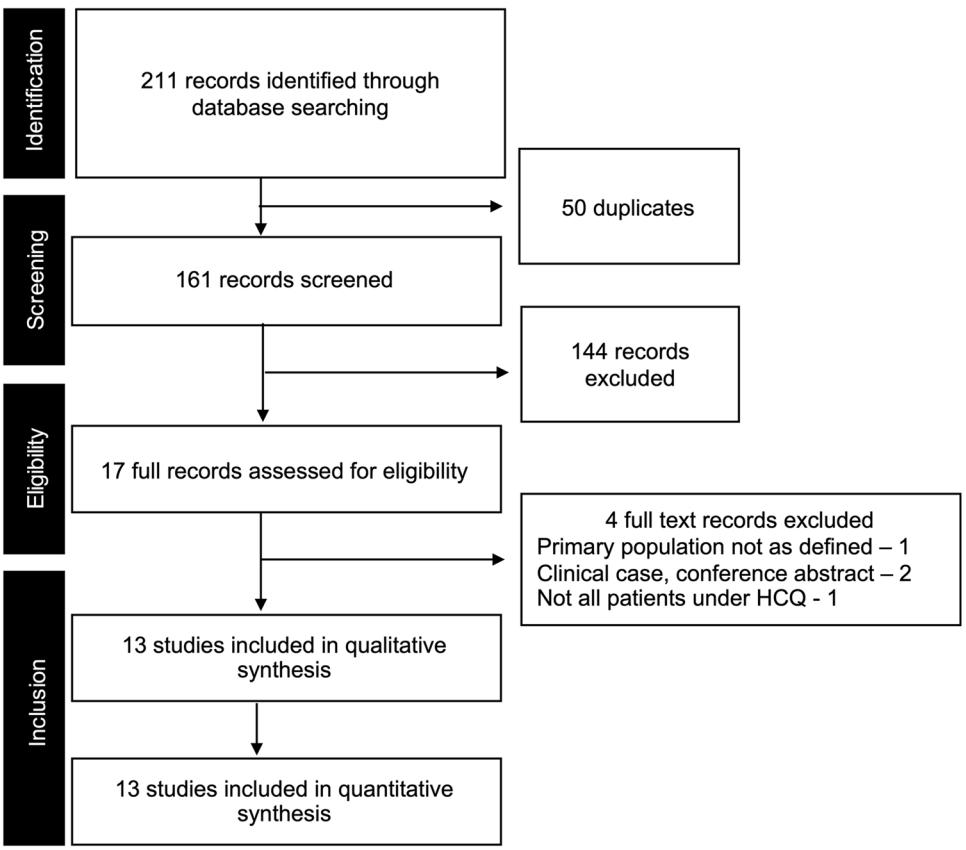

Fig. 1 Flowchart of the search strategy

Table 1 Study design and patient characteristics of included studies that compared high-risk vs low-risk HCQ patients

Author Year Country	Design	Study summary/ HCQ groups	*N* of subjects (eyes)		Mean age ± SD (years)		Female (%)		Mean dose ± SD - Daily (mg/day) - Daily (mg/kg) - Total (g)		Mean duration ± SD (years) - Disease - Treatment	
			High-risk	Low-risk	High-risk	Low-risk	High-risk	Low-risk	High-risk	Low-risk	High-risk	Low-risk
Bulut et al 2018 Turkey	CS	≥5 years vs < 5 years of HCQ use	T, 30 (30) RA, 10 SS, 12 SLE, 5 CTD, 3	T, 30 (30) RA, 11 SS, 11 SLE, 5 CTD, 3	54.60 ± 7.42	53.07 ± 5.59	100%	100%	268.97 ± 96.75 3.60 ± 1.03 746.73 ± 446.52	246.67 ± 86.04 3.50 ± 0.85 137.67 ± 104.56*	8.43 ± 3.29 7.74 ± 3.58	4.78 ± 2.89* 1.69 ± 1.37*
Cinar et al 2021 Turkey	CS	HCQ use > 12 months ≥5 years vs < 5 years of HCQ use	14 (14)	14 (14)	NR	NR	NR	NR	NR	NR	NR	NR
Esser et al 2022 Germany	CS	RA patients ≥5 years vs < 5 years of HCQ use	21 (21)	9 (9)	59.9 ± 12.9	51.7 ± 14.9*	90.5%	88.9%	NR NR 937 ± 599	NR NR 350 ± 242*	NR 113.10 ± 55.49	NR 38.44 ± 20.31*
Mihailovic et al 2020 Germany	CS	SLE patients > 5 years vs < 5 years of HCQ use	10 (10)	9 (9)	40.40 ± 10.50	39.70 ± 13.20	8 (80%)	6 (67%)	NR NR 1317 ± 754	NR NR 265 ± 218*	NR 9.46 ± 4.55	NR 2.71 ± 2.68
Mimier-Janczak et al 2022 Poland	CS	SLE patients > 5 years vs < 5 years of HCQ use	13 (NR)	17 (NR)	NR	NR	NR	NR	NR	NR	NR	NR
Ozek et al 2019 Turkey	CS	RA patients ≥5 years vs < 5 years of HCQ use	24 (24)	16 (16)	45.47 ± 12.4	38.38 ± 15.4	83.3%	87.5%	203.23 ± 55.32 NR 520.34 ± 112.71	218.34 ± 101.12 NR 330.12 ± 138.56*	NR 10.33 ± 1.79	NR 1.90 ± 0.88*
Sargues et al 2022 Spain	CS	SLE patients ≥5 years vs < 5 years of HCQ use	43 (22)	57 (29)	53.37 ± 12.57	53.51 ± 10.25	79.3%	81.8%	NR	NR	NR 12.00 ± 4.32	NR 2.57 ± 1.58*
Tarakcio-glu et al 2020 Turkey	CS	> 5 years vs ≤ 5 years of HCQ use	41 (41) AD—NR	29 (29) AD—NR	49.2 ± 10.5		NR	NR	228 ± 45 NR NR	221 ± 41 NR NR	NR 8.52 ± 2.69	NR 2.48 ± 1.19*

Abbreviations: *HCQ*, hydroxychloroquine; *CS*, cross-sectional; *NR*, not reported; *RA*, rheumatoid arthritis; *SS*, Sjögren's syndrome; *SLE*, systemic lupus erythematosus; *CTD*, connective tissue disease; *AD*, autoimmune disease

*Statistically significant compared with the high-risk group

Table 2 Study design and patient characteristics of included studies that compared HCQ patients vs controls

Author Year Country	Design	Study summary	*N* of patients (eyes)		Mean age ± SD (years)		Female (%)		Mean dose ± SD - Daily (mg/day) - Daily (mg/kg) -Total (g)		Mean duration ± SD (years) - Disease - Treatment	
			HCQ	Control	HCQ	Control	HCQ	Control	HCQ	Control	HCQ	Control
Cinar et al 2021 Turkey	CS	HCQ use > 12 months vs healthy controls	T, 28 (28) RA, 5 SS, 5 SLE, 10 CTD, 8	28 (28)	45.5 ± 11.1	44.5 ± 13.9	85.7%	85.7%	292.857 ± 85 NR 593.714 ± 450	-	NR 5.25 ± 0.93	-
Ermurat et al 2022 Turkey	CS	SLE patients under HCQ vs healthy controls	T, 47 (47) All SLE	41 (41)	Median (range): 39 (21–55)	Median (range): 36 (18–55)	43 (92%)	36 (88%)	Median (range): NR 255.5 (73–1606) NR	-	4.19 ± 3.35 -	
Esser et al 2022 Germany	CS	RA patients under HCQ vs healthy controls	T, 30 (30) All RA	30 (30)	57.5 ± 14.2	53.4 ± 9.9	90%	90%	760 ± 581 NR NR	-	NR 90.70 ± 58.72	-
Forte et al 2019 Spain	CS	HCQ use > 5 years vs healthy controls	T, 10 (20) All SLE	9 (18)	38.87 ± 8.6	41.11 ± 8.12	80%	77.8%	NR 4.46 ± 1.47 937.59 ± 332.37	-	10.25 ± 3.28 10.0 ± 3.25	-
Goker et al 2019 Turkey	CS	HCQ ≤ 5 mg/kg/day for ≥ 5 years vs healthy controls	T, 20 (40) SLE, NR RA, NR	20 (40)	55.58 ± 8.33	54.61 ± 8.62	90%	90%	3.08 mg/kg/day	-	NR 5.85 ± 0.85	-
Lopes et al 2020 Portugal	CS	HCQ users vs healthy controls	T, 15 (30) RA, 4 SS, 4 SLE, 7	15 (30)	54.3 ± 19.5	52.4 ± 1.0	100%	100%	5.81 ± 1.37 mg/kg/day 1231 ± 619.3 (cumulative)	-	NR 8.9 ± 4.0	-
Mihailovic et al 2020 Germany	CS	SLE patients under HCQ vs healthy controls	T, 19 (19) All SLE	19 (19)	40.10 ± 11.50	38.20 ± 12.60	14 (74%)	14 (74%)	NR NR 819 ± 773	-	NR 5.76 ± 5.18	-
Mimier-Janczak et al 2022 Poland	CS	SLE patients under HCQ vs healthy controls	T, 30 (53) All SLE	31 (56)	46.07 ± 14.09	44.55 ± 14.11	25 (83%)	27 (87%)	NR NR 391.23 ± 425.52	-	8.48 ± 7.50 NR	-
Ozek et al 2019 Turkey	CS	HCQ users vs healthy controls	T, 40 (40) All RA	20 (20)	Vide Table 1	42.06 ± 8.31	85%	80%	Vide Table 1	-	Vide Table 1	-
Sargues et al 2022 Spain	CS	SLE patients with > 5 years vs < 5 years of HCQ use	T, 51 (100) SLE, 21 RA, 17 SS, 3 CTD, 10	25 (50)	Vide Table 1	55.05 ± 13.60	vide Table 1	16 (64%)	NR		NR Vide Table 1	-

Table 2 (continued)

Author Year Country	Design	Study summary	*N* of patients (eyes)		Mean age ± SD (years)		Female (%)		Mean dose ± SD - Daily (mg/day) - Daily (mg/kg) -Total (g)		Mean duration ± SD (years) - Disease - Treatment	
			HCQ	Control	HCQ	Control	HCQ	Control	HCQ	Control	HCQ	Control
Subasi et al 2022 Turkey	CS	SLE patients under HCQ vs healthy controls	T, 60 (60) All SLE	60 (60)	43.36 ± 12.05	39.73 ± 7.74	NR	NR	759.14 ± 459.12	-	11.63 ± 6.94 NR	-

Abbreviations: *HCQ*, hydroxychloroquine; *AD*, autoimmune disease; *CS*, cross-sectional; *T*, total; *NR*, not reported; *RA*, rheumatoid arthritis; *SS*, Sjögren's syndrome; *SLE*, systemic lupus erythematosus; *CTD*, connective tissue disease

devices used were Optovue (Optovue Inc., Fremont, CA, USA) in nine studies [8, 9, 18–20, 22, 24, 26, 27], DRI-OCT Triton Plus (Topcon, Tokyo, Japan) [10, 23, 25] in three studies and Cirrus HD-OCT 5000 (Carl Zeiss Meditec, Jena, Germany) [21] and in one study each. All devices are spectral domain OCTA with the exception of the Triton Plus, which uses the Swept Source technology. The OCTA parameters analyzed in each study are depicted in Supplementary Table 2.

Eight studies [8, 9, 19, 22–25, 27] compared patients with high-risk versus low-risk of HCQ-induced retinopathy taking 5 years as the cutoff. No differences were found in the mean daily doses of HCQ between groups in the three studies [8, 24, 27] reporting this parameter. However, four studies [8, 19, 22, 24] reported significant differences between groups in the cumulative dose of HCQ. Only one study [8] reported the disease duration, and it was significantly different between groups.

Eleven studies [9, 10, 18–26] compared HCQ patients versus healthy controls. The mean duration of treatment or disease was superior to 5 years in all reports.

Quantitative analysis of high-risk versus low-risk HCQ patients

High-risk versus low-risk HCQ patients' analysis is shown in the forest plot of Fig. 2. Two studies [18, 26] reported the results for this comparison but the raw data was not available. Thus, those studies were not included in the meta-analysis. Subasi et al. [26] found statistically significant decreases in the VD of SCP of high-risk patients in the whole image ($P = 0.015$) and perifovea ($P = 0.008$). Ermurat et al. [18] did not find significant differences.

Superficial capillary plexus (shown in Fig. 2A)

A signification reduction of VD was found in fovea ($P = 0.02$) and parafovea ($P = 0.02$) in high-risk HCQ patients with moderate and low heterogeneity ($I^2 = 38\%$ and 17%, respectively). In the whole scan analysis, the difference was not significant ($P = 0.05$) and displayed substantial heterogeneity ($I^2 = 67\%$). In the sensitivity analysis of the whole scan, excluding the paper by Sargues and coworkers [25], led to a reduction of heterogeneity ($I^2 = 43\%$) and to a significant effect (SMD − 0.60 [− 1.01, − 0.19], $P = 0.004$).

Deep capillary plexus (shown in Fig. 2B)

A significant reduction of VD was only found in the fovea of high-risk patients ($P = 0.007$) with moderate heterogeneity ($I^2 = 36\%$). After excluding the paper by Cinar et al. [9] in the sensitivity analysis, the heterogeneity of parafovea analysis was greatly reduced (I^2 from 75 to 17%) and led

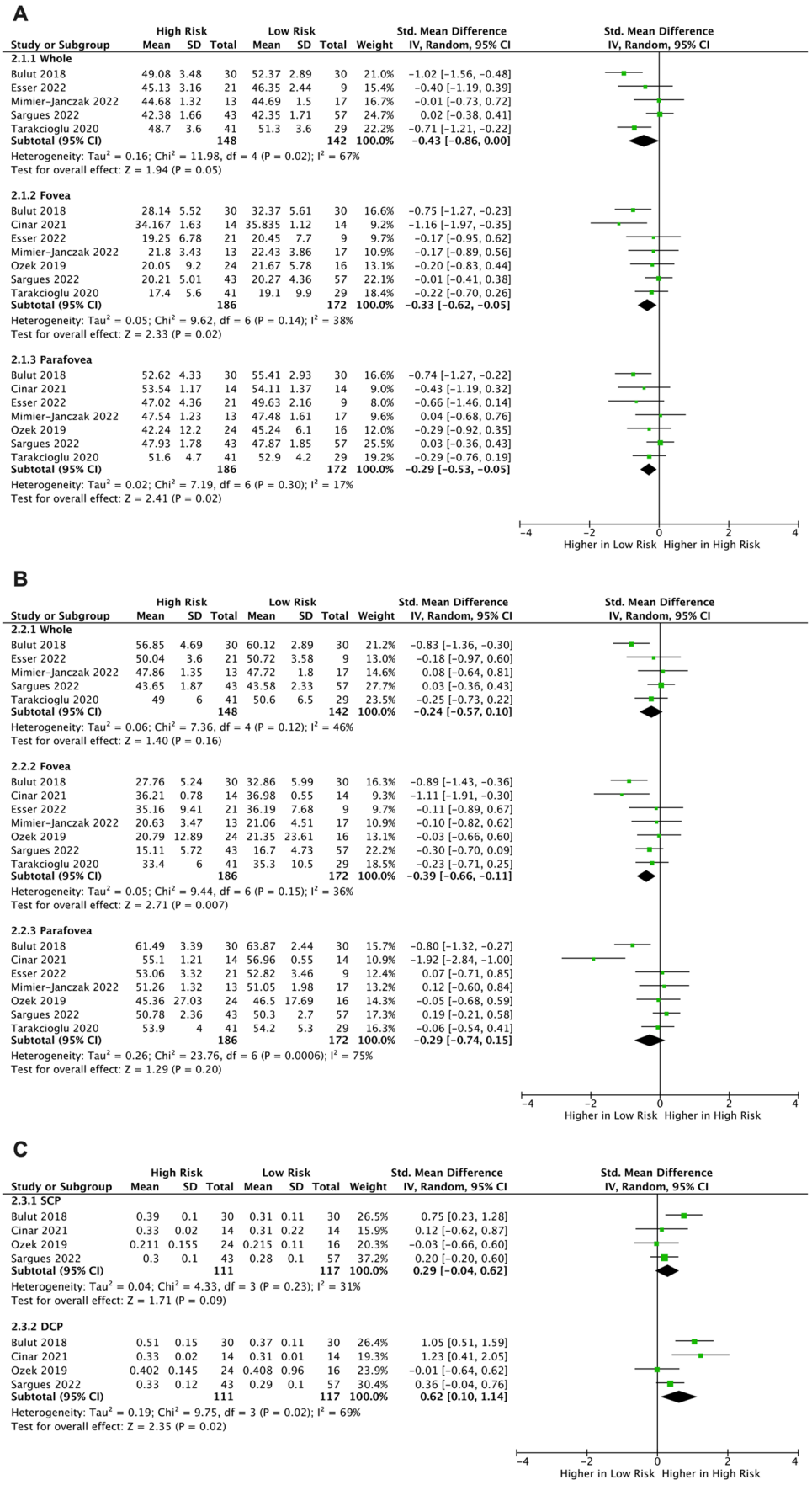

Fig. 2 Forest plot of vessel density at **A** superficial capillary plexus, **B** deep capillary plexus, and **C** foveal avascular area for the comparison between patients at high-risk versus low-risk of HCQ-induced retinopathy. Mean and standard deviation (SD) are included, with 95% confidence intervals (CIs), heterogeneity scores, and overall effect in an inverse variance (IV) random-effects model. The green square size represents the weight attributed to each study based on relative sample size

to a significant overall effect (SMD − 0.32 [− 0.57, − 0.07], $P = 0.01$).

FAZ area (shown in Fig. 2C)

Regarding the SCP, no difference was found between groups ($P = 0.09$). In the DCP, high-risk HCQ patients presented a larger FAZ with substantial heterogeneity ($I^2 = 69\%$) that could not be greatly reduced in the sensitivity analysis.

Results of HCQ patients versus healthy controls comparison (Table 3)

Superficial capillary plexus

The analysis performed for this plexus had substantial heterogeneity. In the sensitivity analysis, after excluding the studies by Sargues et al. [25] (whole scan) and Lopes et al. [21] (perifovea), a significant reduction of VD in HCQ patients was found in the whole scan (SMD − 0.53 [− 0.80, − 0.25], $P < 0.001$) and perifovea (SMD − 0.36 [− 0.60, − 0.13], $P = 0.002$) with moderate and low heterogeneity ($I^2 = 53\%$ and 0%, respectively).

Deep capillary plexus

The analysis of all zones but the perifovea presented substantial heterogeneity. In the perifovea, a significant reduction of VD in HCQ patients was found (SMD − 0.46 [− 0.76, − 0.15], $P = 0.003$) with moderate heterogeneity ($I^2 = 49\%$). In the sensitivity analysis, after excluding the study by Sargues et al. [25], a significant reduction of VD in HCQ patients was found in the whole scan (SMD − 0.41 [− 0.64, − 0.18], $P < 0.001$) with moderate heterogeneity ($I^2 = 33\%$). A meta-regression was performed to assess the effect of year of publication, OCTA device and inclusion of multiple vs single autoimmune diseases on the foveal VD of both plexus; no significant effect was found.

FAZ area

The analysis of both plexuses presented substantial heterogeneity. The sensitivity analysis was only able to decrease the heterogeneity in DCP ($I^2 = 45\%$, moderate) with the exclusion of the study by Cinar et al. [9], but no significant difference was found (SMD 0.08 [− 0.26, 0.42], $P = 0.65$).

Choriocapillaris

This analysis presented substantial heterogeneity that was reduced in the sensitivity analysis ($I^2 = 0\%$, low), after excluding the study by Forte et al. [10], and led to a significant effect (SMD − 0.38 [− 0.62, − 0.15], $P = 0.001$).

Bias assessment

Publication biases were investigated by plotting funnel plots (shown in Supplementary Fig. 1), which revealed a symmetrical distribution of studies about the SMD, suggesting little to none publication bias or small study bias. Bias analysis was performed in all seven studies that were considered eligible and are shown in Supplementary Table 3, Supplementary Fig. 2, and Supplementary Graph 1.

Discussion

OCTA is a noninvasive method that allows for visualization and quantification of the microvascular structure of the retina and choroid. In this systematic review with meta-analysis, we summarized the evidence on the use of OCTA to assess microvascular retinal changes in patients under HCQ. Patients with a high-risk of HCQ-induced retinopathy due to the longer duration of treatment (> 5 years) presented lower VD in the retinal microvasculature in both plexuses and a wider FAZ in DCP compared with those of low risk. HCQ users had lower VD in both retinal plexuses but not differences in FAZ compared with healthy controls. This work summarized studies enrolling only patients without any retinopathy.

The reductions in VD and enlargement of FAZ observed can result from either structural (absence of capillaries) or functional (nonperfusion) changes. As OCTA relies on comparing consecutive scans, flow is only detected above a minimum threshold, leaving the impression of non-perfusion for regions with flow below the detectable threshold [28]. Coupling OCTA with adaptive optics may help to elucidate further the status of retinal microvasculature as this technology provides in vivo ultra-high-resolution imaging of retinal vessel morphology [29].

Comparison of high-risk versus low-risk HCQ patients

The subjects enrolled in this comparison presented significant differences in mean treatment duration and cumulative dose, as expected, but not in the mean daily dose, which suggests that the potential microvascular changes induced by the drug depend on exposure time. In fact, in two studies [8, 9], the cumulative dose and duration of exposure had a significant negative correlation with VD and a significant positive correlation with FAZ parameters. Forte et al. [10] reported the VD had a negative correlation with HCQ duration of treatment and cumulative dose. A recent noncomparative

Table 3 Optical coherence tomography angiography parameters for hydroxychloroquine patients vs. healthy controls. When necessary, data from high-risk and low-risk HCQ patients were combined into a single group as described in the Methods and compared using an independent samples *t*-test using Stata software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP)

Author Year Country	Region for VD	HCQ	VD at SCP Controls	*P* value	HCQ	VD at SCP Controls	*P* value	Plexus for FAZ	HCQ	FAZ area Controls	*P* value
Cinar et al 2021 Turkey	Fovea	34.053 ± 1.83	36.635 ± 1.22	**0.013**	36.157 ± 0.71	37.978 ± 0.55	**0.032**	Superficial	0.331 ± 0.014	0.310 ± 0.018	**0.034**
	Parafovea	53.520 ± 1.27	55.771 ± 1.28	**0.011**	55.446 ± 1.01	57.285 ± 0.56	**0.030**	Deep	0.357 ± 0.010	0.309 ± 0.018	**0.013**
Ermurat et al 2022 Turkey	Whole	50.73 ± 2.82	51.82 ± 2.92	0.082	51.63 ± 5.74	55.51 ± 6.33	**0.003**	Not specified	0.28 ± 0.10	0.26 ± 0.07	0.271
	Fovea	19.43 ± 7.44	23.59 ± 7.32	**0.006**	36.16 ± 7.24	40.46 ± 6.26	**0.006**				
	Parafovea	52.84 ± 3.72	54.11 ± 3.24	0.129	56.07 ± 4.48	57.85 ± 5.11	**0.003**				
	Perifovea	51.37 ± 2.81	52.41 ± 3.13	0.075	53.06 ± 6.25	57.35 ± 6.53	**0.002**				
Esser et al 2022 Germany	Whole	45.5 ± 2.98	45.39 ± 2.66	0.887	50.25 ± 3.55	49.84 ± 3.89	0.676	Not specified	0.24 ± 0.11	0.23 ± 0.10	0.924
	Fovea	19.61 ± 6.95	20.72 ± 5.61	0.498	35.47 ± 8.80	36.66 ± 7.00	0.562				
	Parafovea	47.80 ± 3.99	47.94 ± 2.76	0.879	52.99 ± 3.31	51.23 ± 5.05	0.116				
	CC*	114.29 ± 5.6	115.97 ± 4.91	0.221							
Forte et al 2019 Spain	Fovea	22.65 ± 4.97	23.66 ± 3.78	0.2	19.89 ± 4.45	22.06 ± 6.03	**0.03**	Superficial	250.25 ± 134.36	213.65 ± 76.92	**0.03**
	CC*	53.72 ± 3.34	50.23 ± 7.06	**0.04**				Deep	295.4 ± 139.9	236.84 ± 91.76	**0.04**
Goker et al 2019 Turkey	Fovea	18.02 ± 6.15	23.43 ± 6.80	**0.012**	36.02 ± 6.75	40.28 ± 8.63	**0.022**	Superficial	0.578 ± 0.152	0.450 ± 0.121	**0.007**
	Parafovea	53.04 ± 3.86	53.53 ± 2.94	0.685	56.30 ± 4.74	56.25 ± 4.44	0.968	Deep	-	-	-
Lopes et al 2020 Portugal	Fovea	8.1 ± 6.2	12.3 ± 4.8	**< 0.001**	12.6 ± 6.0	15.6 ± 4.6	**0.001**	Not reported			
	Parafovea	16.8 ± 6.7	22.4 ± 6.7	**0.001**	34.0 ± 7.4	36.7 ± 6.8	0.061				
	CC*	37.3 ± 5.6	40.2 ± 5.8	0.052							
Mihailovic et al 2020 Germany	Whole	46.85 ± 2.18	50.62 ± 1.80	**< 0.001**		Not reported		Not specified	0.279 ± 0.085	0.218 ± 0.067	**0.019**
	CC*	117.34 ± 6.78	121.51 ± 5.37	**0.042**							
Mimier-Janczak et al 2022 Poland	Whole	44.69 ± 1.40	45.36 ± 1.32	0.13	47.78 ± 1.59	48.20 ± 1.52	0.39	Not specified	0.16 ± 0.07	0.2 ± 0.08	**0.03**
	Fovea	22.16 ± 3.63	20.14 ± 3.76	0.08	20.88 ± 4.03	18.94 ± 3.89	0.16				
	Parafovea	47.51 ± 1.43	48.51 ± 1.5	**0.02**	51.14 ± 1.7	51.85 ± 1.73	0.10				
Ozek et al 2019 Turkey	Fovea	20.70 ± 7.96	20.43 ± 8.23	0.902	21.01 ± 17.68	21.77 ± 5.43	0.852	Superficial	0.213 ± 0.137	0.227 ± 0.141	0.713
	Parafovea	43.44 ± 10.21	47.40 ± 14.2	0.220	45.82 ± 23.49	59.53 ± 18.54	**0.026**	Deep	0.404 ± 0.606	0.400 ± 0.88	0.983
Sargues et al 2022 Spain	Whole	42.36 ± 1.68	41.74 ± 1.29	**0.011**	43.91 ± 1.64	42.87 ± 1.79	**0.018**	Not specified	0.34 ± 0.13	0.33 ± 0.11	0.346
	Fovea	20.24 ± 4.63	20.08 ± 3.75	0.41	16.00 ± 5.45	14.04 ± 4.46	**0.011**				
	Parafovea	47.90 ± 1.81	47.16 ± 1.42	**0.006**	50.51 ± 2.56	49.85 ± 1.95	0.055				
	CC*	53.24 ± 1.39	53.61 ± 1.05	**0.049**							
Subasi et al 2022 Turkey	Whole	51.38 ± 2.96	52.55 ± 2.02	**0.040**	54.23 ± 6.41	57.39 ± 5.72	**0.001**	Not specified	0.32 ± 0.12	0.29 ± 0.11	0.155
	Fovea	18.90 ± 8.24	21.62 ± 6.94	0.053	36.40 ± 9.55	40.05 ± 8.41	**0.028**				
	Parafovea	53.71 ± 3.39	55.00 ± 2.49	**0.035**	57.93 ± 4.55	59.58 ± 3.77	**0.016**				
	Perifovea	52.00 ± 2.98	53.27 ± 2.38	**0.042**	55.77 ± 6.81	59.03 ± 6.39	**0.001**				

Abbreviations: *CC*, choriocapillaris, *HCQ*, hydroxychloroquine; *FAZ*, foveal avascular zone; *(S/D)CP*, superficial/deep capillary plexus; *VD*, vessel density

*Data of choriocapillaris is presented in the SCP for purposes of organization; CC does not have plexus

longitudinal study found no significant change in VD among RA patients during the first year of HCQ treatment, suggesting that a long exposure period is required to elicit microvascular alterations [30]. Another central point deserving consideration is the effect of disease duration on the microvasculature, primarily when considering immunologic diseases. Indeed, some authors detected an early reduction in the VD of SCP among naïve patients with recent onset of RA symptoms [30]. Only one study [8] reported that the mean disease duration was significantly different between groups, but no correlation was found between disease duration and OCTA parameters.

High-risk patients presented a trend for FAZ enlargement in the DCP but not in the SCP. However, the results of the studies analyzed were not in agreement, with one study [8] demonstrating FAZ enlargement in both plexuses and two in none [24, 25]. Among the three studies [19, 23, 27] that were not included as the FAZ area was not reported by plexus, none found a significant difference between groups. The reason for these differences is unclear. A considerable variation in the FAZ size among healthy individuals has been previously observed [31]. These facts prevent us from recommending FAZ as a parameter for assessing microvascular changes.

Comparison of HCQ patients versus healthy controls

In this comparison, patients under HCQ presented a mean treatment duration superior to 5 years, conferring these patients a high-risk of HCQ-induced retinopathy. Two studies [9, 24] presented a sub-analysis of low-risk patients versus controls, but the parameters reported were not coincident among them to permit a quantitative synthesis. These studies reported a reduction of VD in both plexuses of retinal [9, 24], and choriocapillaris [9] microvasculature but not in the FAZ zone.

The quantitative synthesis of the comparison between HCQ patients and healthy controls displayed considerable heterogeneity that could not be solved with a sensitivity analysis for most parameters. For this reason, this analysis was excluded. This high heterogeneity may be related to the utilization of three devices of different technologies, in-built and external software to perform the analysis, and the inclusion criteria for the treatment group.

Choriocapillaris

The choriocapillaris quantitative analysis was not performed for high-risk versus low-risk patients due to an insufficient number of studies reporting this parameter. Bulut and coworkers [8] described that choroidal flow rate and thickness were reduced in high-risk patients versus low-risk ones. In addition, other two reports [9, 27] found a decreased choroidal flow area in the same group. One study [21] reported a reduction of VD in choriocapillaris in HCQ patients compared with healthy subjects. Likewise, a significant reduction in choroidal thickness was described for HCQ patients, both high-risk and low-risk, compared with healthy subjects [9]. Other studies [19, 25] could not find any difference in choriocapillaris VD between high-risk versus low-risk patients or HCQ patients versus healthy subjects. Further studies are needed to draw conclusions on this subject.

Critical appraisal and recommendations for future research

One major limitation the studies hereby reviewed is the lack of control for the disease. Considering the immunologic diseases, one cannot exclude the effect of the disease on the retinal microvasculature either directly or synergistically with the drug. In fact, the comparison of high-risk versus low-risk HCQ patients applied treatment duration as a unique criterion, ignoring disease duration. The other analysis compared healthy subjects with patients whose microvascular alterations could be due to two potential sources: the drug and the disease. In addition, the retinal capillary changes hereby described do not adequately explain the typical alterations in outer retinal and RPE of HCQ-induced retinopathy and do not correlate with any inner retinal change. As choroidal vasculature supplies the outer retina, changes in that sector may be an essential element for that occurrence. Thus, future research must focus on comparing (1) autoimmune patients with low to no-risk of drug toxicity versus healthy subjects, to clarify the disease effect; (2) autoimmune patients under vs no HCQ treatment, adjusted for disease duration and comorbidities, aiming to clarify a potential effect of the drug. In addition, the choroidal vasculature beyond choriocapillaris must also be studied. Some authors have already shown changes in choroidal thickness between healthy subjects and autoimmune patients, with opposite effects for different autoimmune diseases [32–34]. Thus, future studies should also focus on one disease instead of considering several autoimmune diseases as a unique entity.

Strengths and limitations

This review presents several limitations. Albeit all studies enrolled age- and sex-matched groups, the difference in the mean age among different studies spanned 15 years. This fact prevented us from conducting a fixed effect analysis for the first comparison where all studies used the same device. On the other hand, this age range is representative of most patients with these diseases, increasing the generability of our results. Different devices, image analysis software, and other parameters make direct comparisons difficult, but the

methodology was similar to some degree. We preferred a standardized mean difference in the meta-analysis to minimize this problem. The difference in segmentation of retinal capillary plexuses may include the intermediate capillary plexus in the measurement of DCP in some OCTA devices. However, all studies used the same device for all patients, excluding a differential bias.

This systematic review presents several strengths. A significant number of papers that encompassed a representative number of patients were summarized. Our analysis was comprehensive and approached several OCTA parameters.

Conclusion

In summary, microvascular retinal and choroidal changes were found in patients under HCQ treatment without any documented retinopathy. Given the limitations in study design of the evidence produced so far, one cannot conclude if those alterations are a consequence of the drug or the disease. Thus, further studies controlling for disease duration and severity and drug exposure are warranted.

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

Data availability All data gathered for this review is presented in the manuscript or as supplementary files.

Declarations

Ethics approval An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of interest The authors declare no competing interests.

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