Original Article

Total and outer macular retinal thickness in hydroxychloroquine-treated women with rheumatoid arthritis: a descriptive cross-sectional study

Nouran Gamal Elzeiny [1], Ehab Mahmoud Ghoneim [1] and Raghda Shawky El-Gendy [1]

[1] *Department of Ophthalmology, Faculty of Medicine, Port Said University, Port Said, Egypt*

ABSTRACT

Background: Hydroxychloroquine (HCQ)-associated retinal toxicity may lead to irreversible visual loss, which highlights the importance of accurately characterizing retinal structural measurements in patients receiving long-term treatment. This study aimed to describe device-derived total retinal thickness (TRT) and outer retinal thickness (ORT) measurements obtained using spectral-domain optical coherence tomography (SD-OCT) in women with rheumatoid arthritis (RA) receiving HCQ and healthy female controls.

Methods: This descriptive, exploratory cross-sectional study included 64 eye records from 32 women with RA receiving HCQ and 64 eye records from 32 healthy control women. Spectral-domain optical coherence tomography was performed using the REVO FC 130 system (Optopol Technology, Poland). TRT and ORT were summarized for the central, parafoveal, and perifoveal regions of the Early Treatment Diabetic Retinopathy Study grid. The analysis was restricted to descriptive summaries, without inferential comparisons.

Results: Mean (SD) age was 46.66 (8.90) years in the HCQ-treated RA group and 46.84 (9.13) years in the control group. The corresponding mean (SD) best-corrected visual acuity was 0.04 (0.08) and 0.02 (0.06) logMAR, respectively. In the HCQ-treated RA group, the mean (SD) treatment duration, weight-adjusted daily dose, and cumulative dose were 8.22 (6.85) years, 3.74 (0.97) mg/kg/day, and 1,006.03 (977.80) g, respectively. Mean (SD) central, parafoveal-average, and perifoveal-average TRT measurements were 230.75 (19.41), 305.46 (14.16), and 268.44 (10.11) μm, respectively, in the HCQ-treated RA group and 235.81 (8.15), 314.68 (6.10), and 275.14 (6.78) μm, respectively, in the control group. The corresponding ORT measurements were 165.48 (13.51), 148.62 (8.56), and 128.21 (5.78) μm in the HCQ-treated RA group and 168.42 (6.77), 155.22 (2.68), and 133.00 (4.34) μm in the control group.

Conclusions: In this selected cross-sectional sample, descriptive eye-record summaries showed numerically lower mean TRT and ORT measurements in HCQ-treated women with RA than in healthy controls. These observations do not establish population-level differences, HCQ-specific toxicity, selective outer-retinal involvement, temporal progression, or diagnostic biomarker performance. Interpretation is limited by fellow-eye dependence, complete overlap between HCQ exposure and RA status, and the study's selection and measurement limitations. Future longitudinal studies incorporating an appropriate RA comparison group, accounting for fellow-eye correlation, and using independently defined toxicity outcomes are needed to determine whether ORT has value in detecting early HCQ-related retinal changes.

KEYWORDS

hydroxychloroquine, retinal diseases, optical coherence tomography, retina, cross-sectional studies

Correspondences: Nouran Gamal Elzeiny, Department of Ophthalmology, Faculty of Medicine, Port Said University, Port Said, Egypt. Email: nourangamalelzeiny@med.psu.edu.eg. ORCID iD: https://orcid.org/0000-0001-6603-3559

How to cite this article: Elzeiny NG, Ghoneim EM, El-Gendy RS. Total and outer macular retinal thickness in hydroxychloroquine-treated women with rheumatoid arthritis: a descriptive cross-sectional study. Med Hypothesis Discov Innov Optom. 2026 Fall; 7(3):116-122. DOI: https://doi.org/10.51329/mehdioptometry252

Received: 07 August 2026; Accepted: 05 October 2026

Copyright © Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/) which permits copy and redistribute the material just in noncommercial usages, provided the original work is properly cited.

INTRODUCTION

Hydroxychloroquine (HCQ) is widely used as a disease-modifying therapy for rheumatoid arthritis (RA), systemic lupus erythematosus, and other autoimmune disorders. Its principal ophthalmic safety concern is an irreversible toxic retinopathy whose risk is determined largely by daily dose and treatment duration. In a widely cited cohort of patients treated for at least five years, the overall prevalence was 7.5%; among those receiving 4.0–5.0 mg/kg/day, prevalence approached 20% after 20 years [1]. Subsequent cohort data have confirmed a strong dose-response relationship for incident retinopathy [2]. Current guidance recommends a daily dose not exceeding 5.0 mg/kg of real body weight [3, 4]. Renal impairment, concomitant tamoxifen use, and older age at HCQ initiation further increase risk [3, 5]. Advanced toxicity may produce parafoveal or pericentral photoreceptor and retinal pigment epithelium (RPE) loss, sometimes with classic bull's-eye maculopathy [3, 4, 6].

Early recognition is important because retinal injury is irreversible and severe retinopathy may continue to progress after HCQ discontinuation. The 2025 American Academy of Ophthalmology recommendations identify optical coherence tomography (OCT), together with wide-pattern fundus autofluorescence, as the primary screening approach; automated visual-field testing and multifocal electroretinography are positioned as secondary confirmatory tests. The recommendations also emphasize assessment for both parafoveal and pericentral patterns of toxicity [3].

Spectral-domain OCT (SD-OCT) permits cross-sectional visualization and quantitative assessment of retinal layers. In established HCQ retinopathy, the predominant structural abnormalities involve the outer retina, particularly the photoreceptors, and include attenuation or disruption of the ellipsoid zone and thinning of the outer nuclear layer (ONL) [6, 7]. Whether quantitative retinal thinning is consistently detectable before manifest retinopathy, however, remains uncertain. Consistent with this uncertainty, Mimier-Janczak et al. found no significant differences in total retinal, retinal nerve fiber layer, or ganglion-cell measurements between HCQ-treated patients with systemic lupus erythematosus and healthy controls, and no association with HCQ treatment duration or cumulative exposure [8]. One study found no consistent inner- or outer-retinal thinning with longer HCQ exposure among patients without retinopathy [9], whereas other investigations reported thinner ONL measurements or abnormal outer-retinal thickness maps in HCQ users without overt toxicity [10–12]. Differences in study populations, OCT platforms, segmentation boundaries, outcome definitions, and analytical methods limit direct comparison of these findings and preclude assuming that a thickness difference alone represents HCQ toxicity.

Against this background, device-derived total retinal thickness (TRT) and outer retinal thickness (ORT) measurements may provide a descriptive account of macular structure, but their diagnostic or prognostic significance requires independent validation. The present exploratory cross-sectional study therefore describes TRT and ORT measurements across the central, parafoveal, and perifoveal Early Treatment Diabetic Retinopathy Study regions in women with RA receiving HCQ and in healthy control women. The analysis is intended to characterize the observed measurements in this selected sample, not to establish HCQ-specific toxicity, selective outer-retinal involvement, temporal progression, or diagnostic performance.

METHODS

This descriptive, exploratory cross-sectional study was conducted in the Department of Ophthalmology, Port Said University Hospital, Port Said, Egypt, between April 2025 and January 2026. The study protocol was approved by the Institutional Review Board and the Research Ethics Committee of Port Said University. The study was conducted in accordance with the tenets of the Declaration of Helsinki. All participants provided written informed consent before enrolment and study examinations.

The study included women with RA receiving HCQ therapy who were recruited from the outpatient ophthalmology clinic and healthy women volunteers with no previous HCQ exposure or history of systemic autoimmune disease. Both eligible eyes were included. Recruitment was convenience-based. Participants were excluded if they had pre-existing retinal disease, including diabetic retinopathy or age-related macular degeneration, or refractive error more myopic than −6.00 diopters. Additional exclusion criteria were diabetes mellitus, uncontrolled hypertension, renal or hepatic failure, cardiovascular disease, previous stroke, concurrent use of another retinotoxic medication such as tamoxifen, and current pregnancy or lactation. Eyes with media opacities that precluded adequate imaging were excluded. Participants who could not perform reliable automated perimetry were also excluded.

All participants underwent a detailed clinical assessment. For the HCQ-treated RA group, rheumatological indication, treatment duration, body weight, absolute daily dose, daily weight-adjusted dose, and cumulative HCQ dose were recorded; dose, duration, renal disease, and tamoxifen use are established considerations in HCQ retinopathy assessment [3, 4]. Best-corrected distance visual acuity (BCDVA) was measured with a Snellen chart and converted to logarithm of the minimum angle of resolution (logMAR) units for descriptive reporting [13]. The anterior segment was examined by slit-lamp biomicroscopy (SL-3G; Topcon Corporation, Tokyo, Japan). After pharmacological pupil dilation, fundus biomicroscopy was performed at the slit lamp using a +90-diopter non-contact lens (Volk Optical Inc., Mentor, OH, USA).

Spectral-domain optical coherence tomography (SD-OCT) was performed in all participants using the REVO FC 130 system (Optopol Technology Sp. z o.o., Zawiercie, Poland), a device with published use for retinal-thickness measurements organized by Early Treatment Diabetic Retinopathy Study (ETDRS) sectors [14]. A single experienced examiner obtained 3D and radial macular scans centered on the fovea under standardized pupillary dilation and ambient illumination conditions. Only scans with a device-reported Quality Index of at least 9 were retained. Scans with motion artefact, decentration, or

evident segmentation-boundary failure were rejected and repeated where possible. The available study documentation did not record software version, exact scan dimensions, or A-scan and B-scan sampling density.

Retinal layers were segmented automatically using the device's integrated software. No manual segmentation-correction protocol was documented; scans with evident boundary failures were rejected and repeated where possible. Retinal thickness was summarized using the ETDRS grid, comprising the central subfield and the superior, inferior, nasal, and temporal sectors of the parafoveal and perifoveal rings. The structural outcomes were device-derived total retinal thickness (TRT) and outer retinal thickness (ORT). According to the study documentation, TRT was measured from the internal limiting membrane to the RPE/Bruch's membrane (BM) line, and ORT was measured from the inner nuclear layer/outer plexiform layer (INL/OPL) line to the RPE/BM line. In the manufacturer's nomenclature, the INL/OPL line represents the outer boundary of the inner nuclear layer and the RPE/BM line represents the outer boundary of the RPE. These definitions are device- and software-specific and should not be considered interchangeable with outer-retinal measurements defined using other anatomical boundaries [9, 15].

Central visual-field sensitivity was assessed by automated static perimetry using the Humphrey Field Analyzer 3 (HFA3; Carl Zeiss Meditec, Inc., Dublin, CA, USA), with the 10-2 test pattern and the Swedish Interactive Threshold Algorithm (SITA)-Standard strategy. White-target 10-2 automated perimetry has been used in HCQ retinopathy assessment [4, 16, 17]. The HFA reliability indices of fixation losses, false-positive responses, and false-negative responses were evaluated [18]. The study-specific acceptability criteria were fixation losses < 20% and false-positive and false-negative response rates < 15%. Tests that failed these criteria were repeated or excluded. Perimetry formed part of the original clinical assessment and eligibility process; visual-field indices were not outcomes in this report.

Data were coded and entered into IBM SPSS Statistics, version 28.0 (IBM Corp., Armonk, NY, USA). This report presents descriptive summaries only. Continuous variables are reported as mean and standard deviation (SD), and, where already available, median with ranges reported as minimum and maximum values. Categorical variables are reported as counts and percentages. Participant-level characteristics and HCQ exposure variables are distinguished from eye-level measurements. Both eyes contributed to the ocular summaries, therefore the eye records within each participant are correlated observations. Because the available analyses did not account for fellow-eye correlation, no hypothesis tests, P-values, inferential confidence intervals, or statistical-significance claims are presented. The descriptive group summaries are not interpreted as demonstrating population-level differences, HCQ-specific effects, causality, temporal ordering, or diagnostic performance. No prospective sample-size calculation was documented. The focus on TRT and ORT was adopted post hoc during manuscript revision and was not prespecified.

RESULTS

The study included 32 women with RA receiving HCQ and 32 healthy women, contributing 64 eye records per group (Table 1). Mean (SD) age was 46.66 (8.90) years in the HCQ-treated RA group and 46.84 (9.13) years in the control group. These characteristics are presented descriptively and do not establish group equivalence.

Among participants receiving HCQ, mean (SD) treatment duration was 8.22 (6.85) years, mean (SD) weight-adjusted dose was 3.74 (0.97) mg/kg/day, and mean (SD) reported cumulative dose was 1,006.03 (977.80) g (Table 1). No additional systemic comorbidities specified in the exclusion criteria were recorded in either group.

Mean (SD) BCDVA was 0.04 (0.08) logMAR in the HCQ-treated RA group and 0.02 (0.06) logMAR in the control group (Table 1). BCDVA was summarized across 64 eye records per group. Dilated fundus examination was unremarkable in all 128 included eyes.

Table 1. Participant and ocular characteristics

Characteristic	HCQ-Treated RA Group (n = 32)	Healthy Control Group (n = 32)
Age (y), Mean ± SD	46.66 ± 8.90	46.84 ± 9.13
Sex (Female), n (%)	32 (100)	32 (100)
Weight (kg), Mean ± SD, Median (Range)	90.55 ± 13.64, 90.00 (60.00–135.00)	—
RA duration (y), Mean ± SD	8.41 ± 7.03	—
HCQ treatment duration (y), Mean ± SD	8.22 ± 6.85	—
HCQ absolute daily dose (mg/day), Mean ± SD	337.50 ± 93.44	—
HCQ weight-adjusted dose (mg/kg/day), Mean ± SD	3.74 ± 0.97	—
HCQ cumulative dose (g), Mean ± SD, Median (Range)	1,006.03 ± 977.80, 584.00 (146.00–3,650.00)	—
BCDVA (logMAR), Mean ± SD, Median (Range)	0.04 ± 0.08, 0.00 (0.00–0.30)	0.02 ± 0.06, 0.00 (0.00–0.20)

Abbreviations: HCQ, hydroxychloroquine; RA, rheumatoid arthritis; n, number; y, years; SD, standard deviation; %, percentage; kg, kilogram; mg, milligram; g, gram; BCDVA, best-corrected distance visual acuity; logMAR, logarithm of the minimum angle of resolution. Note: Participant-level summaries are based on 32 participants per group. BCDVA summaries are based on 64 eye records from 32 participants per group. Both eyes contributed, and no inferential comparisons are presented.

Table 2. Total retinal thickness by ETDRS subfield

ETDRS subfield	HCQ-treated RA group (n = 64 eyes), Mean ± SD	Healthy control group (n = 64 eyes), Mean ± SD
Central Macular (μm)	230.75 ± 19.41	235.81 ± 8.15
Superior Parafoveal (μm)	310.22 ± 16.84	318.34 ± 7.39
Nasal Parafoveal (μm)	307.63 ± 14.19	315.27 ± 6.84
Inferior Parafoveal (μm)	308.00 ± 14.19	315.30 ± 6.97
Temporal Parafoveal (μm)	296.02 ± 15.47	309.81 ± 6.49
Parafoveal average (μm)	305.46 ± 14.16	314.68 ± 6.10
Superior Perifoveal (μm)	271.17 ± 10.57	275.91 ± 8.34
Nasal Perifoveal (μm)	284.52 ± 16.06	287.30 ± 11.89
Inferior Perifoveal (μm)	260.81 ± 11.64	268.53 ± 6.39
Temporal Perifoveal (μm)	257.27 ± 14.47	268.81 ± 8.41
Perifoveal average (μm)	268.44 ± 10.11	275.14 ± 6.78

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; HCQ, hydroxychloroquine; RA, rheumatoid arthritis; n, number of eyes; SD, standard deviation; μm, micrometers. Note: Data are based on 64 eye records from 32 participants per group. Both eyes contributed, and no inferential comparisons are presented.

Table 3. Outer retinal thickness by ETDRS subfield

ETDRS subfield	HCQ-treated RA group (n = 64 eyes), Mean ± SD	Healthy control group (n = 64 eyes), Mean ± SD
Central Macular (μm)	165.48 ± 13.51	168.42 ± 6.77
Superior Parafoveal (μm)	148.09 ± 8.67	154.27 ± 2.67
Nasal Parafoveal (μm)	151.17 ± 9.72	156.38 ± 4.39
Inferior Parafoveal (μm)	145.70 ± 7.78	153.92 ± 2.82
Temporal Parafoveal (μm)	149.50 ± 9.71	156.33 ± 2.98
Parafoveal average (μm)	148.62 ± 8.56	155.22 ± 2.68
Superior Perifoveal (μm)	130.97 ± 6.24	134.17 ± 2.65
Nasal Perifoveal (μm)	129.94 ± 6.84	131.81 ± 12.96
Inferior Perifoveal (μm)	123.36 ± 6.22	131.03 ± 5.22
Temporal Perifoveal (μm)	128.58 ± 5.91	135.00 ± 2.98
Perifoveal average (μm)	128.21 ± 5.78	133.00 ± 4.34

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; HCQ, hydroxychloroquine; RA, rheumatoid arthritis; n, number of eyes; SD, standard deviation; μm, micrometers. Note: Data are based on 64 eye records from 32 participants per group. Both eyes contributed, and no inferential comparisons are presented.

Table 2 presents TRT measurements across the included eye records. Mean (SD) central TRT was 230.75 (19.41) μm in the HCQ-treated RA group and 235.81 (8.15) μm in the control group. Mean (SD) parafoveal TRT was 305.46 (14.16) μm and 314.68 (6.10) μm, respectively, and mean (SD) perifoveal TRT was 268.44 (10.11) μm and 275.14 (6.78) μm, respectively. Across all reported TRT subfields, the mean values were numerically lower in the HCQ-treated RA group. These summaries are descriptive; no inferential between-group comparisons are presented.

Table 3 displays ORT measurements across the included eye records. Mean (SD) central ORT was 165.48 (13.51) μm in the HCQ-treated RA group and 168.42 (6.77) μm in the control group. Mean (SD) parafoveal ORT was 148.62 (8.56) μm and 155.22 (2.68) μm, respectively, and mean (SD) perifoveal ORT was 128.21 (5.78) μm and 133.00 (4.34) μm, respectively. Across all reported ORT subfields, the mean values were numerically lower in the HCQ-treated RA group. These summaries are descriptive and do not establish population-level differences or an HCQ-specific effect.

DISCUSSION

This descriptive, exploratory cross-sectional study presents device-derived TRT and ORT measurements obtained by SD-OCT in women with RA receiving HCQ and in healthy control women. Mean TRT and ORT values were numerically lower across most parafoveal and perifoveal sectors in the HCQ-treated RA eye records, whereas the central-subfield values were more similar between groups. These observations are descriptive. Because both eyes from each participant contributed correlated eye records and no cluster-adjusted inferential analysis was undertaken, the reported numerical differences do not establish population-level differences between the groups.

Established HCQ retinopathy predominantly affects the outer retina, particularly the photoreceptors, and may show parafoveal or pericentral patterns of involvement [3, 7, 19]. Quantitative studies have also evaluated outer-retinal thickness maps and outer nuclear layer (ONL) measurements as potential markers of structural damage [11, 12, 20]. This literature provides a clinical rationale for describing TRT and ORT, yet does not establish that numerical differences in the present sample represent HCQ toxicity. The treated group was defined simultaneously by HCQ exposure and RA, whereas the

comparison group consisted of healthy women. The study therefore cannot separate HCQ-associated differences from those related to RA, concomitant therapies, or other between-group characteristics [21].

The biological mechanisms of HCQ retinopathy remain incompletely defined [22]. Experimental work with chloroquine has demonstrated altered lysosomal function in retinal neurons and the RPE, including increased lysosomal pH and impaired degradation of phagocytosed photoreceptor outer segments [23]. These findings provide mechanistic plausibility but cannot be assumed to explain cross-sectional retinal-thickness measurements in people receiving HCQ. In a clinical SD-OCT study, Uslu et al. reported lower photoreceptor outer-segment and combined inner- and outer-segment thicknesses, greater RPE-Bruch's membrane complex thickness, and selected ganglion cell-inner plexiform layer differences in HCQ users compared with controls [24]. As with the present study, such cross-sectional observations cannot establish the temporal sequence or cause of the measured differences.

The relatively similar central-subfield measurements and numerically lower values in surrounding sectors may resemble the foveal-sparing distribution described in some cases of established parafoveal HCQ retinopathy [3, 7]. Nevertheless, the central, parafoveal, and perifoveal regions of an Early Treatment Diabetic Retinopathy Study grid are measurement regions rather than diagnostic categories. The observed pattern should therefore not be interpreted as evidence of a particular disease stage, a precursor lesion, or an outer-retina-first sequence. Such inferences require longitudinal measurements and independently adjudicated toxicity outcomes.

A post hoc analysis by Montesel et al. reported inverse associations between cumulative HCQ dose and outer-retinal thickness in the foveal, parafoveal, and perifoveal regions [25]. However, that study defined outer-retinal thickness from the outer plexiform layer to the external limiting membrane, whereas the present device-derived ORT extended from the INL/OPL line to the RPE/BM line. These measurements therefore encompass different anatomical compartments, and their absolute values are not directly comparable. The findings of Montesel et al. provide contextual evidence regarding retinal structural measurements in HCQ-treated patients but do not validate the ORT definition or numerical values used in the present study. An OCTA study of HCQ-treated patients with connective-tissue diseases also reported associations of cumulative treatment duration and dose with foveal avascular-zone and vessel-density measurements, although these microvascular outcomes are not directly comparable with TRT or ORT [26]. The present study describes treatment duration, daily dose, and cumulative exposure but does not evaluate their relationships with TRT or ORT. Consequently, the exposure summaries cannot explain the reported thickness measurements or support a dose-response interpretation in this sample.

Published findings on inner-retinal involvement are not uniform. Pasadhika et al. reported selective perifoveal thinning of the combined inner plexiform and ganglion cell layers in a small cohort of HCQ users without clinically evident toxicity [27], and Uslu et al. reported selected ganglion cell-inner plexiform layer differences [24]. In contrast, de Sisternes et al. found no meaningful inner-retinal involvement in established retinopathy and no consistent inner- or outer-retinal thinning with longer exposure before retinopathy developed [7, 9]. Casado et al. found no significant ganglion-cell-layer difference between groups either [20]. Similarly, Jung et al. found no significant difference in macular ganglion-cell-complex thickness between HCQ-treated patients with systemic lupus erythematosus and healthy controls, although selected mfERG ring ratios differed [28]. Differences in study populations, OCT platforms, segmentation definitions, disease classification, and analytical methods may contribute to these discrepant findings. Inner retinal thickness data were not retained in the revised report because the available summaries could not be reconciled reliably with the stated segmentation and ring-averaging definitions. Their omission does not demonstrate inner-retinal preservation, and the present study neither confirms nor refutes the published findings on inner-retinal involvement.

Studies have reported associations between OCT-derived structural measurements and functional findings in cohorts with established or suspected HCQ retinopathy. For example, Kim et al. reported associations between the topographic extent of parafoveal and pericentral photoreceptor damage on OCT and corresponding automated perimetry parameters [19], while Casado et al. described spatial correspondence between regional ONL thinning and visual-field defects [20]. These findings cannot be extrapolated directly to the present sample. Although 10-2 perimetry formed part of the original clinical assessment, visual-field indices are not reported in this descriptive analysis. Consequently, no conclusions about functional preservation or associations between retinal thickness and visual-field performance can be drawn.

The 2025 American Academy of Ophthalmology recommendations identify OCT together with wide-pattern fundus autofluorescence as the primary screening approach for HCQ retinopathy, with automated visual fields and multifocal electroretinography serving as secondary confirmatory tests [3]. The present comparison does not evaluate screening accuracy because it lacks an independent reference standard, prespecified diagnostic thresholds, and validation. Future studies should include an appropriate RA comparison group without HCQ exposure or longitudinal assessment beginning before treatment, use prespecified structural outcomes, account for fellow-eye correlation, document measurement reproducibility, and classify toxicity independently of the thickness measure being evaluated.

Strengths of the present study are the use of a uniform SD-OCT platform; anatomically defined ETDRS subfields encompassing the central, parafoveal, and perifoveal macula; and descriptive assessment of both TRT and ORT in age-similar, all-female groups. These features reduce measurement and demographic heterogeneity, and permit transparent topographic characterization of the retinal thickness measurements within the included sample. Several limitations constrain interpretation. First, both eyes of each participant were included as separate eye records. Because the available analyses did

not account for within-participant correlation, the revised report is restricted to descriptive summaries and presents no *P*-values, inferential confidence intervals, or statistical-significance claims. The observed numerical differences should not be interpreted as estimates of population-level group effects. Second, HCQ exposure overlapped completely with RA status. The study therefore compares HCQ-treated women with RA against healthy control women and cannot isolate an HCQ-specific effect. Potential differences related to RA, other antirheumatic treatments, ocular biometry, or unmeasured systemic and ocular characteristics may also have influenced the measurements. Third, the available documentation does not permit complete reconstruction of participant recruitment, exclusions, or missing observations, and selection bias cannot be ruled out. The cohort was recruited at a single center and included only women with RA, limiting generalizability to men, patients treated for other indications, and populations with different demographic or ocular characteristics. Fourth, the measurements were device- and segmentation-dependent. The available records did not fully document segmentation correction, grader masking, or measurement repeatability. Inner retinal thickness summaries were excluded because their internal consistency could not be verified. These measurement limitations restrict comparisons with studies using different OCT platforms or retinal-layer boundaries. Finally, reconstruction of cumulative HCQ exposure, including historical dose changes and body-weight adjustments, was incompletely documented. The cross-sectional design provides no information about within-eye change, temporal ordering, or subsequent toxicity. Accordingly, the reported findings are hypothesis-generating descriptions of this selected sample and should not be interpreted as evidence of disease progression, selective retinal vulnerability, or diagnostic biomarker performance.

CONCLUSIONS

In this selected cross-sectional sample, mean device-derived TRT and ORT measurements were numerically lower in eye records from HCQ-treated women with RA than in those from healthy controls. These descriptive findings should be regarded as hypothesis-generating and do not establish population-level differences, HCQ-specific retinal toxicity, selective outer-retinal involvement, temporal progression, or diagnostic biomarker performance. Interpretation is constrained by the inclusion of two correlated eyes per participant without cluster-adjusted inference, complete overlap between HCQ exposure and RA status, and the study's selection and measurement limitations. Prospective longitudinal studies incorporating an appropriate RA comparison group, accounting for fellow-eye correlation, and using independently defined toxicity outcomes are needed to determine whether ORT has value in detecting early HCQ-related retinal changes.

ETHICAL DECLARATIONS

Ethical approval: The study protocol was approved by the Institutional Review Board and the Research Ethics Committee of Port Said University. The study was conducted in accordance with the tenets of the Declaration of Helsinki. All participants provided written informed consent before enrolment and study examinations.

Conflict of interests: None.

FUNDING

None.

ACKNOWLEDGMENTS

None.

REFERENCES

1. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol. 2014;132(12):1453-1460. doi:10.1001/jamaophthalmol.2014.3459. PMID: 25275721.
2. Melles RB, Jorge AM, Marmor MF, Zhou B, Conell C, Niu J, McCormick N, Zhang Y, Choi HK. Hydroxychloroquine dose and risk for incident retinopathy: a cohort study. Ann Intern Med. 2023;176(2):166-173. doi:10.7326/M22-2453. PMID: 36645889.
3. Marmor MF, Ahn SJ, Ehlers JP, Melles RB, Mieler WF, Sarraf D, Yusuf IH; American Academy of Ophthalmology. Special AAO report: recommendations on screening for hydroxychloroquine retinopathy (2025 revision). Ophthalmology. 2026;133(4):439-450. doi:10.1016/j.ophtha.2025.11.001. PMID: 41232611.
4. Marmor MF, Kellner U, Lai TYY, Melles RB, Mieler WF. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). Ophthalmology. 2016;123(6):1386-1394. doi:10.1016/j.ophtha.2016.01.058. PMID: 26992838.
5. Jorge AM, Melles RB, Marmor MF, Zhou B, Zhang Y, Choi HK. Risk Factors for Hydroxychloroquine Retinopathy and Its Subtypes. JAMA Netw Open. 2024 May 1;7(5):e2410677. doi: 10.1001/jamanetworkopen.2024.10677. PMID: 38722628; PMCID: PMC11082687.
6. Cheong KX, Ong CJT, Chandrasekaran PR, Zhao J, Teo KYC, Mathur R. Review of Retinal Imaging Modalities for Hydroxychloroquine Retinopathy. Diagnostics (Basel). 2023 May 16;13(10):1752. doi: 10.3390/diagnostics13101752. PMID: 37238236; PMCID: PMC10217485.
7. de Sisternes L, Hu J, Rubin DL, Marmor MF. Localization of damage in progressive hydroxychloroquine retinopathy on and off the drug: inner versus outer retina, parafovea versus peripheral fovea. Invest Ophthalmol Vis Sci. 2015 May;56(5):3415-26. doi: 10.1167/iovs.14-16345. PMID: 26024126; PMCID: PMC4455312.

8. Mimier-Janczak MK, Kaczmarek D, Proc K, Misiuk-Hojło M, Kaczmarek R. Subclinical retinopathy in systemic lupus erythematosus patients - optical coherence tomography study. Reumatologia. 2023;61(3):161-168. doi: 10.5114/reum/166296. Epub 2023 Jun 12. PMID: 37522138; PMCID: PMC10373166.
9. de Sisternes L, Hu J, Rubin DL, Marmor MF. Analysis of Inner and Outer Retinal Thickness in Patients Using Hydroxychloroquine Prior to Development of Retinopathy. JAMA Ophthalmol. 2016 May 1;134(5):511-519. doi: 10.1001/jamaophthalmol.2016.0155. PMID: 26986043.
10. Borrelli E, Battista M, Cascavilla ML, Viganò C, Borghesan F, Nicolini N, Clemente L, Sacconi R, Barresi C, Marchese A, Miserocchi E, Modorati G, Bandello F, Querques G. Impact of Structural Changes on Multifocal Electroretinography in Patients With Use of Hydroxychloroquine. Invest Ophthalmol Vis Sci. 2021 Sep 2;62(12):28. doi: 10.1167/iovs.62.12.28. PMID: 34581725; PMCID: PMC8479571.
11. Tarassoly K, Miraftabi A, Sedaghat A, Parvaresh MM. Analysis of the outer retinal thickness pixel maps for the screening of hydroxychloroquine retinopathy. Int Ophthalmol. 2023 May;43(5):1737-1743. doi: 10.1007/s10792-022-02573-2. Epub 2022 Nov 21. PMID: 36414851.
12. Salameh N, Abi Doumit C, Jalkh E, Nehme J. Association between hydroxychloroquine intake and damage to the outer nuclear layer in eyes without manifest retinal toxicity. BMC Ophthalmol. 2024;24(1):414. doi:10.1186/s12886-024-03684-3. PMID: 39334015.
13. Holladay JT. Proper method for calculating average visual acuity. J Refract Surg. 1997;13(4):388-391. doi:10.3928/1081-597X-19970701-16. PMID: 9268940.
14. Sikorski BL. Ultra-widefield retinal optical coherence tomography (OCT) and angio-OCT using an add-on lens. Diagnostics (Basel). 2025;15(13):1697. doi:10.3390/diagnostics15131697. PMID: 40647696.
15. Ugwuegbu O, Uchida A, Singh RP, Beven L, Hu M, Kaiser S, Srivastava SK, Ehlers JP. Quantitative assessment of outer retinal layers and ellipsoid zone mapping in hydroxychloroquine retinopathy. Br J Ophthalmol. 2019;103(1):3-7. doi:10.1136/bjophthalmol-2018-312363. PMID: 30190364.
16. Marmor MF, Chien FY, Johnson MW. Value of red targets and pattern deviation plots in visual field screening for hydroxychloroquine retinopathy. JAMA Ophthalmol. 2013;131(4):476-480. doi:10.1001/jamaophthalmol.2013.1404. PMID: 23710501.
17. Kim KE, Ryu SJ, Kim YH, Seo Y, Ahn SJ. Visual field examinations using different strategies in Asian patients taking hydroxychloroquine. Sci Rep. 2022 Aug 30;12(1):14778. doi: 10.1038/s41598-022-19048-0. PMID: 36042337; PMCID: PMC9427842.
18. Birt CM, Shin DH, Samudrala V, Hughes BA, Kim C, Lee D. Analysis of reliability indices from Humphrey visual field tests in an urban glaucoma population. Ophthalmology. 1997;104(7):1126-1130. doi:10.1016/S0161-6420(97)30173-0. PMID: 9224465.
19. Kim KE, Kim JH, Kim YH, Ahn SJ. Clock-hour topography and extent of outer retinal damage in hydroxychloroquine retinopathy. Sci Rep. 2022 Jul 12;12(1):11809. doi: 10.1038/s41598-022-15217-3. PMID: 35821509; PMCID: PMC9276819.
20. Casado A, López-de-Eguileta A, Fonseca S, Muñoz P, Demetrio R, Gordo-Vega MA, Cerveró A. Outer Nuclear Layer Damage for Detection of Early Retinal Toxicity of Hydroxychloroquine. Biomedicines. 2020 Mar 4;8(3):54. doi: 10.3390/biomedicines8030054. PMID: 32143497; PMCID: PMC7148510.
21. Ferreira A, Anjos R, José-Vieira R, Afonso M, Abreu AC, Monteiro S, Macedo M, Andrade JP, Furtado MJ, Lume M. Application of optical coherence tomography angiography for microvascular changes in patients treated with hydroxychloroquine: a systematic review and meta-analysis. Graefes Arch Clin Exp Ophthalmol. 2023 Aug;261(8):2221-2233. doi: 10.1007/s00417-023-06023-2. Epub 2023 Mar 8. PMID: 36884062; PMCID: PMC9993382.
22. Yusuf IH, Charbel Issa P, Ahn SJ. Hydroxychloroquine-induced retinal toxicity. Front Pharmacol. 2023;14:1196783. doi:10.3389/fphar.2023.1196783. PMID: 37324471.
23. Mahon GJ, Anderson HR, Gardiner TA, McFarlane S, Archer DB, Stitt AW. Chloroquine causes lysosomal dysfunction in neural retina and RPE: implications for retinopathy. Curr Eye Res. 2004 Apr;28(4):277-84. doi: 10.1076/ceyr.28.4.277.27835. PMID: 15259297.
24. Uslu H, Gurler B, Yildirim A, Tatar MG, Kantarci FA, Goker H, Pehlevan HS, Colak HN. Effect of Hydroxychloroquine on the Retinal Layers: A Quantitative Evaluation with Spectral-Domain Optical Coherence Tomography. J Ophthalmol. 2016;2016:8643174. doi: 10.1155/2016/8643174. Epub 2016 Aug 30. PMID: 27656292; PMCID: PMC5021475.
25. Montesel A, Sacconi R, La Rubia P, Querques G. Impact of cumulative dose of hydroxychloroquine on retinal structures. Graefes Arch Clin Exp Ophthalmol. 2025 Jan;263(1):235-237. doi: 10.1007/s00417-024-06602-x. Epub 2024 Aug 19. PMID: 39160441.
26. 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 Jan 27;15:20420986231225851. doi: 10.1177/20420986231225851. PMID: 38300766; PMCID: PMC10823852.
27. Pasadhika S, Fishman GA, Choi D, Shahidi M. Selective thinning of the perifoveal inner retina as an early sign of hydroxychloroquine retinal toxicity. Eye (Lond). 2010 May;24(5):756-62; quiz 763. doi: 10.1038/eye.2010.21. Epub 2010 Apr 16. PMID: 20395978; PMCID: PMC3711255.
28. Jung SH, Park YH, Park YG. Subclinical Detection of Hydroxychloroquine-Induced Retinopathy in Patients with Systemic Lupus Erythematous Using Multifocal Electroretinography and Optical Coherence Tomography. J Clin Med. 2024 Dec 16;13(24):7663. doi: 10.3390/jcm13247663. PMID: 39768585; PMCID: PMC11678038.