

Optical Coherence Tomography Angiography (OCTA) to Detect Retinal Alterations in patients Taking Hydroxychloroquine (HCQ)

Ayman A. Hamed^a, Sahar S. Ganeb^b, Elham A. Gad^a,
Mohamed A. Elsayed^a, Hend O. Elbeshry^a

^aOphthalmology Department,
Faculty of Medicine Benha
University, Egypt.

^bRheumatology, Rehabilitation,
and Physical Medicine
Department, Faculty of
Medicine Benha University,
Egypt.

Corresponding to:

Dr. Hend O. Elbeshry.
Ophthalmology Department,
Faculty of Medicine Benha
University, Egypt.

Email:

hind.osama16@fmed.bu.edu.eg

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Abstract:

Background: Hydroxychloroquine (HCQ) was widely used in the treatment of rheumatoid arthritis. HCQ retinopathy, is a well-documented side effect of HCQ which could be investigated by Optical coherence tomography angiography (OCTA). **Purpose:** to detect retinal alterations in Rheumatoid arthritis patients taking hydroxychloroquine (HCQ) by OCTA and compare them with a control group. **Patients and methods:** This prospective cross-sectional study included a total of 80 eyes, 40 eyes of rheumatoid arthritis (RA) patients taking HCQ and 40 eyes of normal healthy individuals with completely normal ophthalmological examination. The patients were further divided into high risk and low risk retinopathy groups according to duration of HCQ use. OCTA imaging was performed via Angiovue software. **Results:** The patients' superior hemi, inferior hemi, and peri-fovea all showed noticeably decreased deep vascular density. ($p<0.05$). No significant differences were observed regarding vascular density in the fovea and para fovea. High risk patients demonstrated significantly lower superficial vascular density in whole image, superior hemi, para-fovea, and peri-fovea and also significantly lower deep vascular density in superior hemi and para fovea ($p<0.05$). Duration of drug use showed significant negative correlations with superficial vascular density in whole image, superior hemi, para fovea and peri fovea also with deep vascular density in whole image, superior hemi, and peri fovea ($p<0.05$). **Conclusion:** OCTA could be a tool of value to detect retinal alterations in RA patients taking HCQ at the level of deep vascular density parameters in all patients and in superficial and deep vascular density in high-risk patients.

Keywords: hydroxychloroquine (HCQ), optical coherence tomography angiography (OCTA), rheumatoid arthritis (RA)

Introduction

Hydroxychloroquine (HCQ) is widely used in the treatment of several rheumatic disorders, including rheumatoid arthritis and lupus erythematosus beside other diseases so this medication used by many patients (1).

HCQ-induced retinal toxicity, or HCQ retinopathy, is a well-documented side effect of HCQ and is characterized by bilateral bull's-eye maculopathy, which presents as a ring of parafoveal retinal pigment epithelium depigmentation that spares the fovea (2). The American Academy of Ophthalmology (AAO) revised the guidelines for screening, including visual field examination, fundus autofluorescence (FAF), multifocal electroretinogram (mfERG), and optical coherence tomography evaluation (1).

The most important risk factors for HCQ-induced retinal toxicity are high dose and long duration of use, dosage > 5.0 mg/kg dramatically increases both population risk and annual incremental risk, and extreme doses can be exceedingly dangerous, other major factors are concomitant renal disease or use of tamoxifen (3).

The pathogenesis of HCQ retinopathy is not completely understood. Prior studies have suggested that HCQ affects the metabolism of retinal cells, or that is involves breakdown of the blood-retinal barrier (4). However, these hypotheses have not been strongly supported. Although the inner retina is not damaged significantly in eyes with HCQ-induced toxicity, the photoreceptors and the retinal pigment epithelium (RPE) can show remarkable degeneration (5).

Optical coherence tomography angiography (OCTA) is a non-invasive imaging technique that employs motion

contrast imaging to high-resolution volumetric blood flow information generating angiographic images in a matter of seconds. OCTA compares the decorrelation signal (differences in the backscattered OCT signal intensity or amplitude) between sequential OCT b-scans taken at precisely the same cross-section in order to construct a map of blood flow (6).

Retinal and choroidal microvascular structures can be evaluated thoroughly with OCTA without a need for a contrast agent (7).

The aim of this study is to use optical coherence tomography angiography (OCTA) for evaluation of the effect of HCQ on the retina in patients with rheumatoid arthritis and to compare the retinal alterations between eyes with and without HCQ retinopathy.

Patients and methods:

This is a prospective cross sectional study included 80 eyes and divided into two groups: Group (1): 40 eyes of 21 rheumatoid arthritis patients taking HCQ, Group (2): 40 eyes of 21 normal healthy individuals with completely normal ophthalmological examination. The patient were further divided into high risk (5 years or longer) and low risk (lower than 5 years) retinopathy groups according to duration of HCQ use.

The patients were selected from Rheumatology, Rehabilitation and Physical medicine department in Banha university hospitals and Banha Educational hospital during the period between January and August 2022.

An informed written consent was obtained from each participant and approval from

the Ethical Board of Benha University committee was obtained (MS 9-4-2021).

Inclusion criteria were patients with rheumatoid arthritis who were treated with oral HCQ and visited Ophthalmology department, Banha University.

Exclusion criteria were history of ocular trauma, patients with high myopia, previous intraocular surgery other than cataract extraction, other coexistent macular or retinal diseases, history of other drug inducing retinal toxicity (tamoxifen, oral steroids), also poor-quality OCTA images. Patients with severe cardiovascular events or stroke and people who refuse to give consent.

All patients underwent examination through: History taking and complete ophthalmologic examination, including pupillary reaction, best corrected visual acuity (BCVA) using snellen's chart testin, anterior segment assessment by slit lamp, intraocular pressure measurement with an applanation tonometer and fundus examination using +20 D lens (to evaluate the periphery of the retina) and +90 D lens (biomicroscopy for evaluating the posterior pole).

Optical Coherence Tomography Angiography (OCTA) was done in Ophthalmology department, Banha university hospitals by using the OPTOVue OCT angiography (Fremont, CA 94538, USA) using RTVue software. 6 x 6 scan size was used for OCTA imaging. The tissue resolution is 5 mm axially and beam width is 15 mm. the device performed several repeated B-scans at the same retinal location and the obtained structural information are compared to detect signal changes secondary to flowing erythrocytes (motion contrast). This allows the operator to image the fundus and evaluate vessel density and retinal

thickness quantitatively via the built-in automated software of the device without dye injection but only by detection of the erythrocyte motion.

Statistical methods

Data management and statistical analysis were done using SPSS version 28 (IBM, Armonk, New York, United States). Quantitative data were assessed for normality using the Shapiro-Wilk test and direct data visualization methods. Quantitative data were summarized as means and standard deviations or medians and ranges. Categorical data were summarized as numbers and percentages. Quantitative data were compared between the studied groups or according to risk groups using the independent t-test. Categorical data were compared using the Chi-square test. Correlation analyses were done using Spearman's correlation. All statistical tests were two-sided. P values less than 0.05 were considered significant.

Results:

This case-control study included 80 eyes which were divided into two groups: group (1): forty eyes of rheumatoid arthritis patients taking HCQ and group (2): forty eyes of normal healthy individuals. The patients were further divided into high risk (5 years or longer) and low risk (lower than 5 years) retinopathy groups according to duration of HCQ use.

The patients showed significantly lower visual acuity than controls (0.8 ± 0.2 vs. 1 ± 0.1 , $P = 0.007$). No significant differences were observed regarding age ($P = 0.583$) and sex ($P = 0.488$).

The median duration of drug use was 5 years, ranging from 1 – 20 years. The mean daily dose was 352 ± 87 mg/day, while the median cumulative dose was 584 g, ranging from 219 – 2920 g. The median

disease duration was 7 years, ranging from 2 – 25 years.

As regards OCTA parameters no significant differences were observed between the studied groups regarding all superficial vessel density parameters, including whole image ($P = 0.192$), superior hemi ($P = 0.859$), inferior hemi ($P = 0.586$), fovea ($P = 0.627$), para fovea ($P = 0.405$), peri-fovea ($P = 0.218$).

Regarding deep vascular density, the patients demonstrated significantly lower density in the whole image, superior hemi, inferior hemi and peri-fovea. No

significant differences were observed regarding density in the fovea and para fovea (table 1).

As regards thickness, no significant differences were observed between the studied groups regarding all superficial and deep thickness parameters.

High risk patients demonstrated significantly lower superficial density in whole image, superior hemi, para-fovea, and peri-fovea. No significant differences were observed regarding vascular density in inferior hemi and fovea (table 2).

Table 1: Deep vascular density in the studied groups

Deep vascular density (%)	Cases (40 eyes)	Controls (40 eyes)	P-value
Whole image	49.2 ±5.6	53.2 ±5.2	0.001
Superior hemi	50.2 ±7	53.8 ±5.3	0.012
Inferior hemi	47.5 ±5.9	51.8 ±5.3	<0.001
Fovea	34.8 ±7.1	37.4 ±7.3	0.111
Para fovea	55.6 ±5.7	56.8 ±4.3	0.299
Peri fovea	49.9 ±6.2	53.9 ±5.7	0.004

Data are presented as mean ±SD; Significant P-values are marked in bold.

Table 2: Superficial vascular density according to patients' risk

Superficial vascular density (%)	Low risk (n = 17 eyes)	High risk (n = 23 eyes)	P-value
Whole image	50.3 ±2.1	47.6 ±3.5	0.004
Superior hemi	51 ±3.4	47.6 ±4.1	0.009
Inferior hemi	49.7 ±1.8	48 ±3.6	0.073
Fovea	22.8 ±6.6	21.2 ±5.2	0.399
Para fovea	53.6 ±3.1	48.4 ±5.6	<0.001
Peri fovea	51.8 ±2.9	48.6 ±3.9	0.007

Data are presented as mean ±SD; Significant P-values are marked in bold.

High risk patients demonstrated significantly lower deep vascular density in superior hemi and para fovea. No significant differences were observed regarding deep density in whole image, inferior hemi, fovea and peri-fovea (table 3). Duration of drug use showed significant negative correlations with

superficial vascular density in whole image, superior hemi, para fovea and peri fovea.

Additionally, duration of drug use showed significant negative correlations with deep vascular density in whole image, superior hemi, and peri fovea (table 4).

Table 3: Deep vascular density according to patients' risk

Deep vascular density (%)	Low risk (n = 17 eyes)	High risk (n = 23 eyes)	P-value
Whole image	51.1 ±4	47.8 ±6.3	0.063
Superior hemi	53.1 ±6	48.1 ±7	0.023
Inferior hemi	48.1 ±4.6	47.1 ±6.8	0.629
Fovea	34.1 ±6.3	35.3 ±7.8	0.621
Para fovea	57.8 ±4.5	54.1 ±6.1	0.04
Peri fovea	51.9 ±4.3	48.4 ±7	0.077

Data are presented as mean ±SD; Significant P-values are marked in bold.

Table 4: Correlation between drug use duration and OCT parameters

	Drug use duration (yrs.)	
	R	P
Superficial vascular density (%)		
Whole image	-0.461	0.003
Superior hemi	-0.482	0.002
Inferior hemi	-0.286	0.073
Fovea	-0.299	0.061
Para fovea	-0.602	<.001
Peri fovea	-0.494	0.001
Deep vascular density (%)		
Whole image	-0.374	0.018
Superior hemi	-0.352	0.026
Inferior hemi	-0.017	0.918
Fovea	0.076	0.643
Para fovea	-0.265	0.098
Peri fovea	-0.348	0.028

r: Correlation coefficient; Significant P-values are marked in bold.

Cumulative dose of HCQ showed significant negative correlations with superficial vascular density in whole image ($r = -0.362$, $P = 0.022$), superior hemi ($r = -0.405$, $P = 0.01$), fovea ($r = -0.396$, $P = 0.011$), para fovea ($r = -0.491$, $P = 0.001$), and peri fovea ($r = -0.360$, $P = 0.023$).

As regards disease duration, it was significant negative correlations with superficial density in para fovea ($r = -0.472$, $P = 0.002$) and peri fovea ($r = -0.323$, $P = 0.042$).

Discussion:

OCT angiography (OCTA) is an imaging modality developed to study retinal and

choroidal vascular perfusion by detecting capillary blood cell flow without the need for contrast injection (8). This noninvasive tool can assess retinal vascular system quantitatively, and the efficacy of OCTA in HCQ retinopathy was previously evaluated by several authors (7,9,10).

Although rare, HCQ retinopathy is potentially irreversible, and cellular damage may continue even after the medication is discontinued; thus, early detection is essential to prevent serious retinal damage (11,12).

In this study optical coherence tomography angiography (OCTA) was used for evaluation of the effect of HCQ on the

retina in patients with rheumatoid arthritis and to compare the retinal alterations between eyes with and without HCQ retinopathy.

Our results showed that the patients demonstrated significantly lower deep vascular density in the whole image, superior hemi, inferior hemi and peri-fovea. No significant differences were observed regarding deep vascular density in the fovea and parafovea. No significant differences were observed between the studied groups regarding all superficial vessel density OCTA findings.

This was consistent with (13) who compared the OCTA findings between the patients who were under HCQ treatment for > 5 years and a control group. They reported that the vascular density in deep capillary plexus and choriocapillaris were decreased.

The authors in (10) evaluated the OCTA findings in rheumatoid arthritis patients receiving HCQ treatment. The vessel density research revealed that in patients who had been receiving HCQ medication for more than five years, deep temporal and hemi-inferior vascular density had decreased. This was consistent with our findings, according to which there was no change in the study groups' fovea vascular density. Additionally, the perifoveal deep plexus had a decrease in vascular density. These alterations were noticeable in the groups receiving HCQ treatment, but they were more pronounced as the duration exceeded five years.

Some researchers reported that vascular density values were similar between the control and treatment groups, the vascular density were reduced in patients who receiving HCQ treatment for > 5 years, these changes did not occur centrally at the fovea; instead, they occurred at both

parafoveal and perifoveal areas (14). However, the fovea was reported to be mainly affected in the study done in 2019 where it showed that the vascular density in fovea was significantly lower in patients who were under HCQ treatment than the patients who were not (9).

In contrast to our study, both superficial and deep vascular density were reduced in patients undergoing daily use of HCQ when compared with healthy individuals (9,15,16).

The pathophysiology of retinopathy secondary to HCQ is still unclear. A possible mechanism is the inhibition of uptake of all-trans-retinol leading to a negative effect on the visual cycle (17). Some studies suggest that retinal toxicity could be detected at an earlier stage through the measurement of the inner layer thickness using *SD-OCT* (7,18). However, other studies that use *SD-OCT* show a distinctive loss of the perifoveal inner segment/outer segment photoreceptor junction, suggesting that HCQ retinal toxicity mainly affects the external retina/photoreceptor layer, particularly in the parafoveal and perifoveal regions, before causing structural damage involving the retinal pigment epithelium and the inner retinal layers (19–23).

In this study superficial and deep retinal thickness parameters showed no significant differences between the studied groups including whole image, superior hemi, inferior hemi, fovea, parafovea and peri-fovea.

These results were in accordance with others who found that none of the retinal thickness outcomes differed between the study groups except for inferior superficial plexus and hemi-inferior deep capillary plexus thickness values which were lower

in the group of patients who were receiving HCQ treatment for > 5 years (10).

In contrary to our study, other scientists found that the retinal thickness values of the treatment group were statistically lower than the control group (14).

In this present study, high risk patients demonstrated significantly lower vascular superficial density in whole image, superior hemi, para-fovea and peri-fovea. No significant differences were observed in inferior hemi and fovea areas. But as regarding deep vascular density superior hemi and para fovea were significantly decreased in comparison with the control group.

Scientist in 2018 conducted a study to evaluate the additional benefit of OCTA in the screening of HCQ-induced retinal alterations. They divided the patients into two groups as low risk (receiving HCQ for < 5 years) and high risk (receiving HCQ for > 5 years). All of the vascular density parameters (whole, superficial, deep foveal, parafoveal and perifoveal) were found to be decreased in the high-risk group of patients which was consistent partially with our results which is consistent with the possible presence of vasculopathy in the pathogenesis of retinopathy induced by HCQ treatment (7). When the OCTA findings in rheumatoid arthritis patients receiving HCQ treatment were evaluated, the vessel density analysis showed some positive outcomes as regarding deep vascular area only in temporal and hemi-inferior zone which was decreased in patients who were receiving HCQ treatment for > 5 years (10).

Our study was consistent with others who found that in patients receiving HCQ treatment for > 5 years, the changes did

not occur centrally at the fovea, The first changes in HCQ toxicity begin from the perifoveal and parafoveal regions; therefore, if some change is expected in vascular density, it should be in this area. Foveal affection is generally affected late (14).

In this study, duration of drug use showed significant negative correlations with superficial vascular density in whole image, superior hemi, para fovea and peri fovea. Additionally, duration of drug use showed significant negative correlations with deep vascular density in whole image, superior hemi and peri fovea.

Cumulative dose showed significant negative correlations with superficial density in whole image, superior hemi, fovea, para fovea, and peri fovea.

In accordance with our results, a negative correlation between both superficial and deep vascular density and duration of drug and cumulative dose of HCQ, was proved (7).

In disagreement to our results, it was revealed that there was no significant correlation between vascular density in the different plexuses and cumulative dose of HCQ or duration of treatment ($P > .05$) (15).

In summary, only some OCTA studies were able to detect retinal alterations in patients receiving HCQ treatment (7,9,10,13). It seems that retinal thickness decreases both topographically and topographically after HCQ treatment. Retinal circulation might also be affected by some means. In our study, we found that, after HCQ use, the retinal thickness was not affected, additionally, superficial parafoveal vascular density, whole image and superior hemi vascular density were decreased in patients who were under HCQ treatment for (5 years or more as

compared to those who were under HCQ treatment for less 5 years). On the other hand, deep vascular density was affected in the patient group as a whole and in high-risk patients.

The superficial retinal circulation provides the blood for the inner retinal layers (24). Our study's OCTA results could be used to identify a potential pathologic mechanism underlying early HCQ toxicity in the inner retinal circulation. Some data indicate that the earliest changes following HCQ exposure occur in the cytoplasm of ganglion cells and photoreceptors, which is consistent with our findings revealing superficial retinal circulation impairment in the patients who were receiving HCQ medication for 5 years or more. After the medication binds to melanin, the RPE appears to be impacted. Moreover, hydroxychloroquine may affect the metabolism of retinal cells and slowly produce chronic harmful consequences (25,26).

Conclusion

Using OCTA, some retinal changes occurred at the deep retinal vascular density due to HCQ use in Rheumatoid arthritis patients, these changes seen in superficial and deep vessel density with increase the risk (when the duration of drug use was more than 5 years).

So, OCTA could be a useful technique for screening of HCQ retinal alterations, these findings needed to be reinforced by further work with larger sample sizes

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