SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY IN PATIENTS TREATED WITH HYDROXYCHLOROQUINE

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ABSTRACT:

Background: *The patients with early retinopathy can be asymptomatic with normal fundus before any signs of maculopathy appear; hence, screening for early detection in the premaculopathy stage is recommended. Spectral domain optical coherence tomography (SD-OCT) detects early structural damage to macula in patients on hydroxychloroquine (HCQ) therapy.*

Aim of the work: *To evaluate the role of spectral-domain optical coherence tomography (SD-OCT) in early detection of hydroxyl-chloroquine (HCQ) maculopathy.*

Patients and methods: *This cross-sectional observational study was conducted between November 2017 and November 2019 on 100 adult female patients taking HCQ referred from the ophthalmology and rheumatology outpatient clinics of Ain Shams University Hospital. The age of the participants ranged between 25 and 60 years. Fifty age and sex matched healthy subjects were assessed as a control group. The study was conducted in accordance with the ethical standards stated in the Faculty of Medicine - Ain Shams University, with informed consent obtained.*

Results: *The mean central foveal thickness was found to be thinner in the hydroxychloroquine group than the normal controls, which was statistically significant (p value = 0.042). The upper, lower, nasal and temporal parafoveal thickness were thinner in the hydroxychloroquine group in comparison to that of the control group (p value = 0.001, 0.020, 0.001 & 0.001 respectively). The upper, temporal and lower perifoveal thickness showed statistically significant thinning in the hydroxychloroquine group (p value = 0.002, < 0.001 & 0.041 respectively) in all quadrants except the nasal quadrant which was not statistically significant (p = 0.169). No significant difference was detected between the two groups regarding ganglion cell complex thickness.*

Conclusion: *Preclinical hydroxychloroquine toxicity can lead to early thinning in the central fovea as well as the parafoveal and perifoveal regions that is detected by SD-OCT.*

Keywords: *Spectral domain optical coherence tomography, hydroxychloroquine, maculopathy, retinopathy.*

INTRODUCTION:

Chloroquine (CQ) and hydroxyl-chloroquine (HCQ) are being used to treat rheumatoid arthritis, systemic lupus erythematosus, cutaneous lupus, other connective tissue and skin disorders. Both drugs have significant retinotoxicity with

HCQ being less retinotoxic [1] because it does not cross the blood-retinal barrier [2].

Early detection of CQ and HCQ maculopathy is important because toxicity can lead to progressive and permanent vision loss despite cessation of the drug intake [3]. Due to the slow clearance of medication from the body, the full effects of drug withdrawal may take from 3 months to even more than 1 year [4].

The aim of screening should be the detection of maculopathy in the "preclinical phase," which would allow an early cessation of the medication and prevent irreversible damage with severe visual loss. The American Academy of Ophthalmology (AAO) recommends using 10-2 automated fields together with at least one of the following procedures for routine screening: spectral domain optical coherence tomography (SD-OCT), multifocal electroretinogram (mfERG), or fundus autofluorescence (FAF). A baseline examination is advised for all patients starting these drugs to serve as a reference point and to rule out maculopathy, which might be a contraindication to their use. Annual screening should begin after 5 years of use or earlier in the presence of additional risk factors. Commonly accepted risk factors include receiving >5 mg/kg/day of HCQ (equivalent to 2.3 mg/kg/day of CQ), being on treatment for >5 years, having renal dysfunction, having pre-existing retinopathy and concomitant tamoxifen use [5].

AIM OF THE WORK

This study aims to evaluate the role of spectral-domain optical coherence tomography (SD-OCT) in early detection of hydroxychloroquine (HCQ) maculopathy.

PATIENTS AND METHODS

Patients:

This study was conducted between November 2017 and November 2019 on 100 adult female patients taking hydroxychloroquine (HCQ) referred from the ophthalmology and rheumatology outpatient clinics of Ain Shams University Hospital. The age of the participants ranged between 25 and 60 years. Fifty age and sex matched healthy subjects were assessed as a control group. The study was conducted in accordance with the ethical standards stated in the Faculty of Medicine - Ain Shams University, with informed consent obtained.

Selection criteria:

Inclusion criteria:

Patients treated with hydroxychloroquine for more than one year.

Exclusion criteria:

- Pre-existing retinal diseases whether congenital or acquired.
- Media opacity hindering fundus examination.
- Glaucoma.
- Previous history of uveitis.
- Previous eye trauma.
- Previous retinal surgery.
- Previous optic nerve disease as optic neuritis or ischemic optic neuropathy.
- Myopia more than six diopters.

Methods:

All patients underwent the following steps:

A: History taking as regard:

Demographic data including age, body weight, underlying disease, past medical history, duration, and dosage of drug.

B: Ophthalmological Examination:

- Visual acuity testing (best-corrected visual acuity) using Landolt's C chart.
- Anterior segment examination using slit lamp biomicroscope (Nidek, Gamagori, Japan).
- Fundus examination with indirect ophthalmoscopy (Riester, Jungingen, Germany) using 20 D lens and with 90 D magnifying lens (Volk, Mentor, USA).
- IOP measurement using Goldmann's applanation tonometry (Haag Streit, Bern, Switzerland).
- Amsler's grid.
- Color vision testing using Ishihara pseudoisochromatic plates (Optitech eye care): color vision was considered defective if the patient could not read correct numbers for the literates or follow the line for the illiterates in three plates or more.

C: Spectral domain optical coherence tomography (SD-OCT): using RS-3000 Advance OCT (Nidek, Gamagori, Japan). A macular thickness map, radial scan and horizontal high definition (HD) line scan centered on the fovea were obtained in each patient.

<u>The following parameters were assessed in each patient:</u>

- Photoreceptor inner segment/outer segment junction (IS/OS) inspection using a horizontal High Definition (HD) line scan centered on the fovea and radial scans.
- Numerical values of the central foveal thickness (CFT), parafoveal, perifoveal thickness and average ganglion cell complex (GCC) thickness in microns. These values were compared with those of control group and correlated with the duration of treatment in each patient.

Statistical Analysis:

We conducted statistical analysis using the statistical package for the social sciences (SPSS 20). Descriptive statistics were calculated, and the data were summarized as mean ± SD for numerical data and percentages for categorical data. Student's t-test was used to assess the statistical significance of differences between two groups. The results were considered statistically significant with a p value ≤ 0.05. Pearson's correlation coefficient (r) was used to assess the strength of association between two quantitative variables. The correlation coefficient denoted symbolically "r" defines the strength (magnitude) and direction (positive or negative) of the linear relationship between two variables.

RESULTS:

Demographics

All subjects included in the study were females. As regard the underlying disease, 63 patients had systemic lupus erythematosus (SLE), 36 had rheumatoid arthritis (RA) and 1 had scleroderma (Diagram 1).

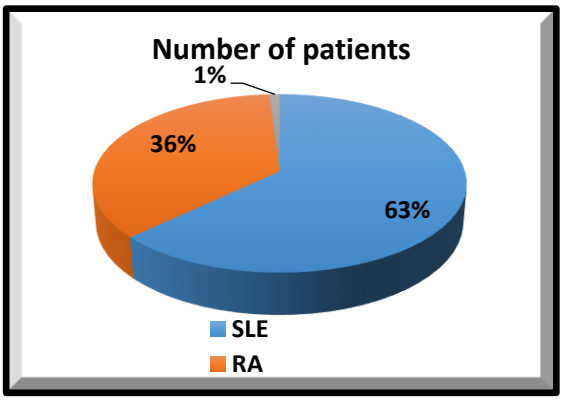

Diagram (1): Distribution of the underlying diseases.

The mean age of the patients was 40.8 ± 10 years (ranged from 25 to 60 years) while that of the controls was 38.7 ± 8.4 years. Regarding age, no statistically significant differences were observed between the patients and controls.

Based on the duration of treatment, the mean duration was 5.9 ± 4.6 years (ranged from 1 to 20 years). As regard the daily dosing, most patients were on standard dosages of 200 or 400 mg daily, but when body weight was taken into consideration, five of the 100 patients were on dosages higher than the recommended dose (5 mg/kg/day). As regard the cumulative dose, the mean cumulative dose was 430.7 ± 335.8 grams.

Table (1): Showing the demographic data of both groups (Marked differences are significant at p <0.05):

	Control	Patients	t test	
	Mean ± SD	Mean ± SD	T	p value
Age	38.7 ± 8.4	40.8 ± 10.0	-1.2	0.218
Duration of treatment (in years)	N/A	5.9 ± 4.6	N/A	N/A
Cumulative dose (in grams)	N/A	430.7 ± 335.8	N/A	N/A

Clinical Examination

Of the 100 patients, only one patient showed fundoscopic findings suggestive of bull's eye maculopathy, decreased BCVA (6/36), scotoma in Amsler grid and defective colour vision in Ishihara testing. Otherwise, the remaining 99 patients showed normal clinical examination.

Spectral Domain OCT

- Photoreceptor inner segment/outer segment junction (IS/OS)

Of the 100 patients in the study, visual inspection of the SD-OCT images showed loss or disruption of the IS-OS junction in only three patients: P26, P94, and P100 (Diagram 2). All three showed parafoveal discontinuity or disruption of the IS-OS junction, and the ''flying saucer'' sign of HCQ retinopathy was evident for P94.

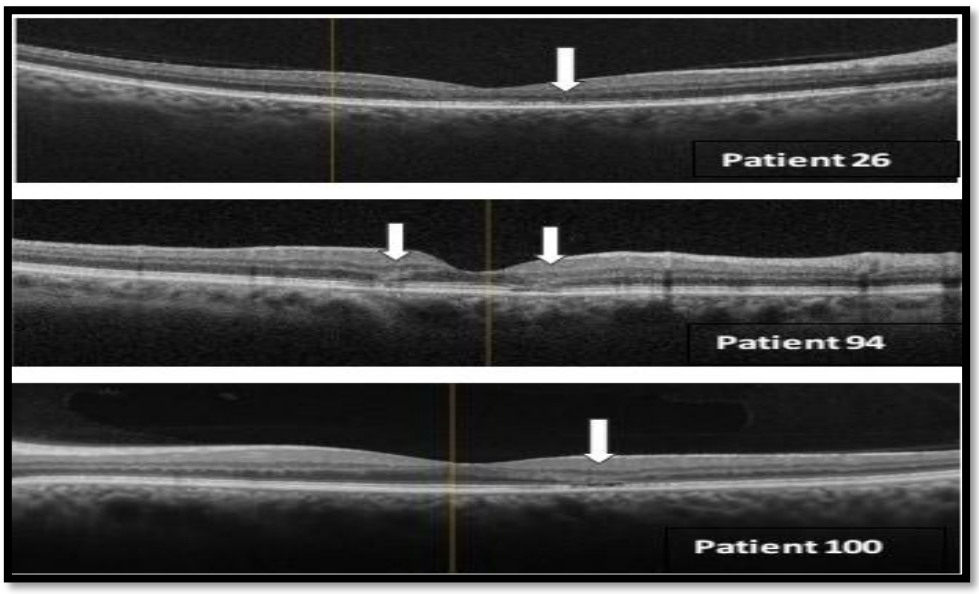

Figure (1): Parafoveal disruption of IS-OS junction (white arrow).

- Numerical values of the central foveal thickness (CFT), parafoveal, perifoveal thickness and average ganglion cell complex (GCC) thickness in microns.

Table (2): Showing the comparison between patients and controls regarding numerical thickness values (Marked differences are significant at p <0.05):

	Control	Patients	t test	
	Mean ± SD	Mean ± SD	T	p value
CFT	256.1 ± 18.7	249.1 ± 20.5	2.0	0.042
Upper parafoveal	338.3 ± 9.9	330.4 ± 18.6	3.4	0.001
Nasal parafoveal	337.7 ± 10.1	329.9 ± 17.9	3.4	0.001
Lower parafoveal	335.8 ± 10.4	330.5 ± 17.4	2.3	0.020
Temporal parafoveal	323.9 ± 9.6	316.1 ± 17.6	3.5	0.001
Upper perifoveal	305.0 ± 10.9	298.4 ± 14.0	3.2	0.002
Nasal perifoveal	313.3 ±10.2	310.0 ± 14.8	1.4	0.169
Lower perifoveal	292.7 ±18.3	287.0 ± 14.3	2.1	0.041
Temporal perifoveal	286.7 ±10.6	278.5 ± 13.8	3.7	< 0.001
GCC	98.2 ±7.0	98.9 ± 10.9	-0.4	0.679

Central foveal thickness (CFT) in the patient group showed statistically significant thinning as compared to the control group.

Parafoveal thickness in the patient group showed statistically significant thinning as compared to the control group in all quadrants.

Perifoveal thickness in the patient group showed statistically significant thinning in all quadrants except the nasal quadrant which was not statistically significant when compared to the control group.

No significant difference was found between the control and patient groups included in the study regarding ganglion cell complex (GCC) thickness.

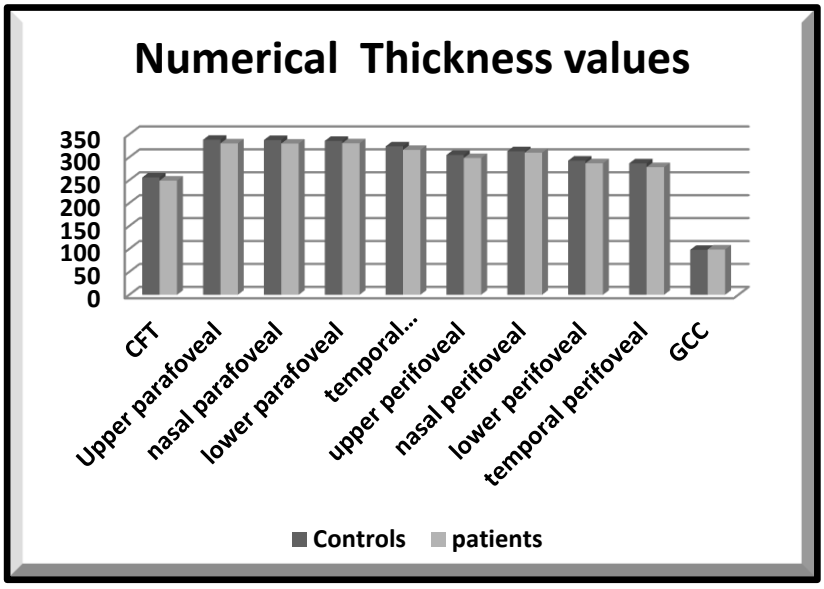

Diagram (2): Comparison between patients and controls regarding numerical thickness values.

Table (3): Showing the correlation between the numerical thickness values and the duration of treatment in years:

	Duration (in years)	
	Total patients (100)	
	r	p value
CFT	-0.085	0.399
Upper parafoveal	0.018	0.857
Nasal parafoveal	-0.098	0.331
Lower parafoveal	0.052	0.610
Temporal parafoveal	-0.030	0.770
Upper perifoveal	0.094	0.353
Nasal perifoveal	0.139	0.169
Lower perifoveal	0.094	0.353
Temporal perifoveal	-0.027	0.793
GCC	0.188	0.062

No statistically significant correlation was detected between the duration of the treatment with any of the parameters measured by OCT in the patient group.

Table (4): Showing the correlation between the numerical thickness values and the cumulative dose in grams:

	Cumulative dose (in grams)	
	Total patients (100)	
	r	p value
CFT	-0.081	0.423
Upper parafoveal	0.019	0.851
Nasal parafoveal	-0.096	0.342
Lower parafoveal	0.054	0.594
Temporal parafoveal	-0.031	0.759
Upper perifoveal	0.095	0.347
Nasal perifoveal	0.141	0.162
Lower perifoveal	0.095	0.347
Temporal perifoveal	-0.024	0.813
GCC	0.191	0.057

No statistically significant correlation was detected between the cumulative dose with any of the parameters measured by OCT in the patient group.

DISCUSSION:

The literature and clinical experience have proven without any doubt that exposure to systemic use of HCQ is a risk factor for toxic retinopathy, which is irreversible, and when advanced, can lead to permanent loss of central visual acuity. The screening for retinopathy will detect the earliest abnormalities associated with HCQ retinopathy and provide us with a fair idea about- 'if to stop', 'when to stop'.

The ideal screening test should be quick and easy to perform and moreover should have a high sensitivity and specificity for early detection of toxicity. This study documented that SD-OCT was sensitive, easy to perform and gave reliable results.

In this study, interrupted IS-OS junction was observed in 3 out of 100 patients. The IS/OS junction loss is considered a confirmed sign of damage in early retinopathy [(6)(7)]. They explained this finding by preferential loss of cone photoreceptors [(6)].

Previous studies on symptomatic patients receiving hydroxychloroquine therapy reported retinal thinning and loss of outer retinal layers with early retinal toxicity

[8][9]. The loss in full retinal thickness has been found to precede the changes in individual layers of the retina, such as the photoreceptor IS/OS junction loss [9]. Many studies reported the retinal thinning affecting mainly the parafoveal regions on SD-OCT [9][10][11]. This finding is thought to be due to loss in pericentral outer nuclear layer, photoreceptors layer, and retinal pigment epithelium (RPE) abnormalities [12]. However, these studies were done on clinically symptomatic patients. In this study we confirm that these findings could also be detected in asymptomatic patients with normal ophthalmic examination, visual field and FAF.

The central foveal thickness (CFT) was found to differ significantly between the patients and the control groups in this study. To the best of our knowledge, this finding was only reported by ***Allam et al. (2015)*** [13]. Parafoveal thickness in the patient group showed statistically significant thinning as compared to the control group in all quadrants. Perifoveal thickness in the patient group showed statistically significant thinning in all quadrants except the nasal quadrant which was not statistically significant when compared to the control group. Significant loss of parafoveal and perifoveal retinal thickness have been reported in preclinical hydroxychloroquine maculopathy in some studies [13] [14]. The extent of damage in the macular area is thought to be related to ganglion cell distribution, as suggested by primate studies [3]. Furthermore, the binding of HCQ to melanin pigment in the RPE and presence of an avascular zone at the center of the fovea has been suggested as a possible explanation for the distribution of damage [14].

By further analysis, thinning in the foveal, parafoveal and perifoveal regions was not found to be correlating with the duration of treatment nor the cumulative dose. This came in agreement with the study by ***Allam et al. (2015)***[13].

In this study, no significant difference was found between the control and patient groups regarding the average ganglion cell complex (GCC) thickness. This came in agreement with recent studies by ***Allam et al. (2015)*** [13], ***De Sisternes et al. (2016)*** [15] ***and Amin et al. (2020)*** [16]**.** On the contrary**,** previous studies have reported localized thinning of the parafoveal inner retina on SD-OCT in patients with chronic exposure to HCQ. ***Pasadhika and Fishman (2010)*** [17] found that patients with abnormal fundus showed thinning of the inner, outer, and full-thickness retina, and patients with chronic exposure to HCQ without fundus changes showed significant thinning of the inner retina only. Another study by ***Pasadhika et al. (2010)*** [11]on patients who were visually normal and without fundus abnormality or any defect on Humphrey 10-2 visual field testing reported that selective thinning of the GCC was observed only in the parafoveal area. However, this study enrolled only eight patients and eight controls. On the contrary, the current study and other recent studies included a larger number of asymptomatic patients with normal fundus and varying duration of exposure to HCQ.

Conclusion & Recommendations:

By analysis of OCT macular thickness values, statistically significant thinning was found in the foveal, parafoveal and perifoveal regions in the patient group when compared to the control group. No correlation was found with the duration of treatment.

Limitations of this study included relatively small sample size, absence of a baseline OCT and functional correlation with visual field or multifocal ERG.

Future studies are recommended with a larger sample size and long follow up periods. SD-OCT is recommended as a first line in screening to be combined with visual field.

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التصوير المقطعي للشبكية في المرضى الذين يخضعون للعلاج بالهيدروكسيكلوروكوين

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المقدمة: إن اعتلال الشبكية المبكر في المرضى الذين يخضعون للعلاج بالهيدروكسيكلوروكوين قد يظهر بدون أعراض، وقد يظل قاع العين طبيعيًا لفترة من الوقت قبل ظهور أي علامات على اعتلال الشبكية. ومن ثم، يوصى بإجراء فحص للكشف المبكر عن اعتلال الشبكية. التصوير المقطعي للشبكية له دور في الكشف المبكر عن التغييرات الهيكلية التي قد تحدث في مقولة الإبصار في هؤلاء المرضى.

هدف الدراسة: تقييم دور التصوير المقطعي للشبكية في التشخيص المبكر لاعتلال الشبكية في المرضى الذين يخضعون للعلاج بالهيدروكسيكلوروكوين.

المرضى وطرق البحث:

المرضى: ضمت هذه الدراسة ١٠٠ مريضة بالغة تتناول هيدروكسيكلوروكوين ومحولات من عيادات طب العيون وأمراض الروماتيزم بمستشفى جامعة عين شمس. تراوحت أعمار المشاركات بين ٢٥ و٦٠ سنة. تم تقييم ٥٠ من الصحيحات المتطابقات في العمر والجنس كمجموعة مقارنة.

معايير الاشتمال هي: اشتملت الدراسة على مرضى تم علاجهم بالهيدروكسيكلوروكوين لأكثر من عام.

معايير الاستبعاد هي: أمراض شبكية الموجودة مسبقًا سواء كانت خلقية أو مكتسبة، عتامة تعوق فحص قاع العين، ارتفاع ضغط العين (الجلوكوما)، التاريخ السابق لالتهاب القزحية ، إصابة العين السابقة، جراحة الشبكية السابقة، أمراض العصب البصري مثل التهاب العصب البصري، أو قصر النظر الشديد.

خضعت جميع المريضات إلى ما يلي: أخذ التاريخ المرضي والفحص السريري الشامل بما في ذلك فحص المصباح الشقي، وقياس ضغط العين، وأفضل دقة بصرية مصححة، وفحص قاع العين، وشبكة أمسلير، واختبار رؤية الألوان باستخدام لوحات إيشيهارا، والتصوير المقطعي للشبكية.

النتائج: من خلال التحليل لقيم سمك طبقات الشبكية بالتصوير المقطعي، تم العثور على ترقق معتد به إحصائيًا في المناطق المركزية بمقولة الإبصار في مجموعة المرضى عند مقارنتها بمجموعة المقارنة. لم يتم العثور على ارتباط مع مدة العلاج ولا الجرعة التراكمية.

الخلاصة: في هذه الدراسة، وجدنا أن التصوير المقطعي للشبكية كان موثوقًا وحساسًا وسهل الأداء وأن استخدامه كخط أول في الفحص يوفر الوقت والتكلفة والجهد.