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Evaluation of Changes in the Ganglionic Cell inner Plexiform Layer and Macular Retinal Nerve Fiber Layer in Patients Receiving Hydroxychloroquine

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ABSTRACT

Backgrounds: To evaluate changes in the thickness of ganglion cell-inner plexiform layer and macular retinal nerve fiber layer using ocular coherence tomography in patients exposed to hydroxychloroquine .

Methods: This was a retrospective, cross-sectional study of patients on hydroxychloroquine therapy. Ocular coherence tomography images showing ganglion cell-inner plexiform cell layer and macular retinal nerve fiber layer thickness were obtained and compared to controls. The relationship between the thickness of ganglion cell-inner plexiform and macular retinal nerve fiber layer, duration and cumulative dose of hydroxychloroquine were evaluated.

Results: In all, 219 subjects were included. The Thickness of the ganglion cell-inner plexiform thickness was significantly less than controls (p = 0.006). The average macular RNFL thickness was less in the study compared to the control groups, but not statistically significant (p = 0.389). There was no significant correlation between ganglionic cell-inner plexiform and macular retinal nerve fiber layer with duration, daily dose, or cumulative dose of hydroxychloroquine.

Conclusion: Thinning of the ganglionic cell- inner plexiform layer could be an early indicator of retinal toxicity before the appearance of clinical retinopathy.

Keywords: Hydroxychloroquine, ganglion cell-inner plexiform layer, macular retinal nerve fiber layer, spectral-domain optical coherence tomography.

INTRODUCTION

Hydroxychloroquine (HCQ) is a well known treatment option for many rheumatological and autoimmune disorders like systemic lupus erythematosus and rheumatoid arthritis[1] and other diseases like malaria[2]. However, many side effects were reported. Deposits on the cornea, ciliary body, retina, and the choroid are the classical form of ocular side effects [3,4]. Early discontinuation of the medication may reverse most of the side effcts [1]. However, Bulls eye maculopathy is an irreversible form of retinal toxicity which affects the macula and leads to loss of central visual field, loss of visual acuity and color vision defects[1]. Animal studies confirmed that toxicity results in in damage to perifoveal retinal ganglion cell[5] . Early detection of toxicity before it is clinically visible on fundus examination is important, because immediate discontinuation of HCQ might reverse early retinal toxicity[3]. Many investigations are conducted to detect early changes such as visual field test, ocular coherence tomography, and electroretinogram (ERG)[3].

HCQ induced retinal toxicity was considered a rare condition; but higher incidence has been reported in a recent study than it was previously known and is dose dependent[5].

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The toxcity rate can reach up to 1% [2]. Furthermore, worsening of retinopathy may happen even after discontinuation of HCQ [1]. Toxicity can be detected by subjective tests like measurement of visual acuity , slit lamp examination, dilated fundus examination and automated central perimetry 10-2 test [5,6]. Useful objective tests are fundus autofluorescence photography, multifocal ERG, and spectral domain OCT (SD-OCT) macular measurements [7]. Screening recommendation by the Royal college of Ophthalmologist is to perform a colored fundus photograph along with a SD OCT, ideally within the first 6 months of treatment. If the patient has a normal examination with no additional risk factors screening tests should be performed after 5 years and theannuallyly. However, if the patient has at least one risk factor screening tests should be done after one year. Risk factors that are considered significant are: concamitant use of Tamoxefin , impaired renal function test, a daily dose of more than 5 mg/kg/day and chloroquine use[8]. In Jordan, these recommendations are adopted [8,9]. the Retinal toxicity should be demonstrated on two screening tests , being objective , before discontinuation of treatment in patients suspected to have HCQ-induced retinal toxicity[10,11].

The aim of this study was to evaluate the thickness of ganglion cell inner plexiform layer (GC-IPL) and that of the macular retinal nerve fiber layer (RNFL) in patients on HCQ therapy and to compare these values with those of age-matched controls. This might serve as a tool to detect early macular retinal changes before the changes are clinically visible.

METHODS:

The study was approved by the Institutional Review Board of the University of Jordan number 19/20/279 and written informed consent was obtained from every participant in the study. It was performed in accordance with the Helsinki Declaration of 1964, and its later amendment.

This was a retrospective cross-sectional study. Patients on HCQ therapy who visited Jordan University Hospital between September 2018 and September 2019 and who were taking the medication for systemic lupus erythrematousus were included. All participants data who underwent a standard ophthalmic examination including measurement of GL-IPL and macular RNFL by OCT extracted. Thickness of GI-IPL and macular RNFL of age-matched healthy subjects were measured and compared. Patients on HCQ therapy and those in the control group underwent a complete ophthalmic examination including best corrected visual acuity, intraocular pressure measurement, dilated fundus exam, color examination using Ishihara pseudoisochromatic plates (Kanehara Shuppan Co. Ltd., Tokyo Japan) and OCT.

The inclusion criteria were: best corrected visual acuity$\geq$ 0.8, normal ophthalmic examination, intraocular pressure at baseline and at any ophthalmic visit of < 21 mmHg,normal appearance of the optic disk and the retina.

Exclusion criteria were as follows: any ocular or systemic disease that may affect the retina or the optic nerve excluding systemic lupus erythematosus for which participants were receiving the drug, history of ocular surgery, history of eye trauma, ocular inflammation, spherical equivalent more than 6 diopters, optic disc or retinal disease, or optic disc anomaly or glaucoma. Any patient with media opacity that interfered with the quality of the OCT was also excluded.

To measure the macular thickness, an 8x8 mm macular area centered around the foveal thickness was recorded using the OPTOPOL SD OCT machine (SD OCT version 7.2.0, OPTOPOL Technology Sp. z.o.o., Poland). The central foveal and average macular thickness were recorded. The OCT machine differentiated between the retinal tissue interfaces and detected the thickness of GC-IPL and RNFL. RNFL thickness was measured from the inner margin of the internal limiting membrane to the outer margin of the RNFL layer after being automatically segmented using OCT. all the images were revised and manual resetting was carried for any artifact. A machine

tracking system was used to compensate for any eye movement.

Statistical analysis:

We used SPSS version 21.0 (Chicago, USA) for analysis. Continuous variables like age were described as mean (± standard deviation). Other nominal variables (e.g., gender) were described as count (frequency). We performed an independent sample t-test to analyze the difference in the mean values between cases and controls and between mean difference in age between the groups. Paired-sample t-tests were used to analyze the mean differences in OCT measurements at baseline and at follow-up in both groups, using the filter function to isolate the study subjects and controls for the test. Data is presented as means (95% confidence interval [CI]). The chi-square test was used to compare the frequency of gender and other risk factors between the groups. Pearson correlation coefficient was used to analyze the correlation between the OCT findings, duration of treatment, and cumulative dose of HCQ. The correlation between the thickness of GL-IPL and macular RNFL, and daily and cumulative HCQ doses were analyzed. All underlying assumptions were met unless otherwise indicated. Ap value of less than 0.05 was considered as statistically significant.

RESULTS

In all, 219 participants were included in this study with a mean age of 43.38. ±17.39. years. The study group comprised100 (20 male and 80 female) patients with a mean age of 45.28 (± 12.24) years, and the control group comprised119 patients (44 males and 75 females), with a mean age of 41.79 (± 20.67) years. There was no significant difference in age, gender or spherical equivalent between the groups (p= 0.123). The mean cumulative dose of HCQ was 5666.4± 4329.0 g, and the mean duration of HCQ therapy was 56.5 ± 36.3 months. The mean daily dose was 313.9 ± 96.9 mg. The cumulative dose was measured by multiplying the daily dose by the number of days in which the participant used the drug. The participants' demographic data are presented in table 1 and HCQ treatment data in table 2.

Table 1. Description of the - overall demographic characteristics of the study population

	N	Minimum	Maximum	Mean	Std. Deviation
Age	219	9.0	91.0	43.384	17.3852
RNFL thickness(um)	219	22.0	38.0	28.9	2.6
GCL+IPL thickness(um)	219	50.0	110.0	87.37	7.2

Table 2. Shows HCQ treatment data

	N	Minimum	Maximum	Mean	Std. Deviation
Duration of HCQ therapy (months)	100	6.0	168.0	56.5	36.3
Accumulative dose in grams	100	36000.0	2016000.0	566640.0	432896.6
Average daily dose in grams	100	100.0	400.0	314.0	96.9

The average GCL-IPL thickness was 85.9 ± 8 μm (Range: 50 - 98) in patients on HCQ therapy compared to 88.6 ± 6.2 μm (Range: 75 - 110) in the control group (p=0.006) The average RNFL thickness was 28.2 ± 2.8 μm (range: 22 - 35) in patients on HCQ therapy and 29.2±2.5 μm (range: 23 - 38) in) in the control group (P>0.05).

There was a significant difference in the mean GCL-IPL thickness between the groups (p = 0.006), with a mean

difference of 0.31 μm (95% confidence interval ranging from 0.79 to 4.56); the mean thickness was higher in the control group. However, the average macular RNFL thickness was statistically similar in both groups (p = 0.389).Table 3 shows details of the differences between the groups.

Table 3. Shows details of the differences between the groups.

	Group	Mean thickness (µm)	Std. Deviation	p value
RNFL thickness	HQC group	28.160	2.8203	0.389
	Control group	29.180	2.5165	
GCL+IPL thickness	HCQ group	85.910	7.9647	0.006
	Control group	88.588	6.1869	

There was no significant correlation between GCL+IPL and macular RNF thickness with either daily dose (p = 0.229) or the cumulative dose (p = 0.678), as demonstrated in Table 4.

Table 5 shows the correlations between SD-OCT measurements (average RGC-IPL and RNFL thickness) and mean age of patients in both groups. There was a statistically significant negative relationship between age and average GC-IPL thickness in controls ($p < 0.05$) but not in patients on HCQ therapy . There was no statistically significant correlation between the age of patients and average macular RNFL thickness in control group ($p > 0.05$). However, a significant positive correlation in RNFL was found in patients receiving HCQ (P=0.013)

Table 4. Correlations between measured thicknesses and cumulative and daily HCQ dose, and duration of HCQ therapy

	Cumulative dose		Daily dose		Duration of therapy	
	R	p*	R	p*	R	p*
Avarage RGC-IPL th	-0.042	0.678	-0.121	0.229	-0.046	0.649
Avarage RNFL	-0.139	0.168	-0.087	0.389	-0.175	0.081

* Pearson's correlation test; RGC-IPL: Retinal ganglion cell-inner plexiform layer; RNFL: Retinal nerve fiber layer

Table 5. Correlations between Age of both groups and Retinal ganglion cell-inner plexiform layer thickness and Retinal nerve fiber layer thickness

	Group 1 patients on HCQs		Group 2 Controls	
	R	p*	R	p*
Average GCL-IPL	0.000	0.678	-0.241	0.008
Avarage RNFL	0.248	0.013	0.069	0.453

* Pearson's correlation test; GCL-IPL: Retinal ganglion cell-inner plexiform layer; RNFL: Retinal nerve fiber layer

DISCUSSION

Our study shows that the GC-IPL layer was significantly thinner in patients receiving HCQ compared to controls ,thinning of the macular RNF was also detected in patients receiving hydroxychloroquiene but was not statistically significant . However, the thickness of the GC-IPL and macular RNFL were not negatively related to the duration and cumulative dose of HCQ. Our study is the

first study to be carried on a Middle Eastern population with large sample size and longer duration.

Retinopathy secondary to HCQs is associated with macular retinal pigmentary changes[6]. It was proposed that HCQ toxicity early alters the ganglionic cells with possible secondary macular RNFL thinning and damage[2,3]. The exact way of HCQ toxicity is not fully understood. At the first stages , the drug accumulates in the cytoplasm of retinal ganglion cells which leads to degeneration of the ganglion cells. Later on, degeneration of the photoreceptors and retinal pigment epithelium result from binding to melanin[12,13] with resultant visual field loss, decreased visual acuity and impaired color vision[5,7] Animal studies showed that accumulation of HCQ in the retinal ganglionic cells may affect the photoreceptors long before the RPE shows signs of toxicity [14]. SD- OCT imaging showed loss of the parafoveal photoreceptor inner segment – outer segment junction and thinning of the outer nuclear layer in patients receiving HCQ, as a result retinal thinning may be an early indicator of retinal toxicity.[15,16,17] . It was demonstrated that SD-OCT images might indicate retinal toxicity long before occurrence of visual field loss [11,12].

Until recently, there are few studies with limited sample sizes, using variable imaging techniques, different treatment regimens and short duration of follow up , moreover, the results are variable and conflicting [11]. Most previous studies investigated pathologies associated with the outer retinal segment, involving the retinal pigment epithelium and photoreceptors[9],other studies have demonstrated HCQ-associated damage in the inner retinal segment only in normal-looking retinae [11]; however,damage was also observed in the inner and outer retina when abnormal fundus was clinically evident [14]. Few studies have evaluated the thickness of the GP-IPL layer, which is part of the inner retina; unfortunately, the number of subjects enrolled was small and the duration of HCQ therapy was short [15,16,18]. In the study conducted by Bulut et al demonstrated that retinal ganglion cell-inner plexiform layer of patients receiving hydroxychloroquine was statistically thinner than controls, which is consistent with our results, however, their totat number was small , the follow up duration was shorter and the sample was composed of females only [15].

Pasadhika S et al in their work demonstrated selective thinning of the macular inner retinae in the absence of clinically apparent fundus changes,[15] which is consistent with our finding as macular RNF and GC-IPL are parts of the inner layer. In our work the inner retina was further segmented into macualr RNFL and GC-IPL and we concluded that significant thinning was evident in the GC-IPL rather than in the macular RNFL.

Moreover, inconsistent results were found regarding the relationship between GC-IPL thickness, and cumulative dose and duration of HCQ therapy. While a group of investigators demonstrated that dose and duration of HCQ correlate negatively with average GC-IPL thickness [1], another study demonstrated no significant association [7], which is consistent with our results. It was postulated that retinal ganglionic cells show changes as early as first week after starting treatment with HCQ therapy and in photoreceptors soon afterward [8]. This might explain our findings that changes in the GC-IPL were not correlated with the duration of treatment or cumulative dose of HCQ.

The findings of this study are consistent with those reported in similar study recently conducted by Lee et al. [7]. It was observed that macualr RNFL thinning develop after clinically visible HCQ retinopathy [13,14]. In our cohort , all had normal looking retinae which may explain why patients on HCQ didn't have significantly thinner macular RNFL compared to controls.

However, paradoxical thickening of the macular RNFL was observed, compared to controls. Thickening of the RNFL was observed in many ocular pathologies such as retinitis pigmentosa and drug-related changes. It was explained that it is a chronic reactive change, secondary to retinal ganglionic cell stroma and axonal degeneration [16,17]

The sample size in our study is larger than that in previous works, and the control group had no previous ocular factors that might affect the quality of the OCT scan

and all the study population had the same indication for HCQ treatmemt and was composed of males and females.

Our study has several limitations. First, is the retrospective nature and the small sample size, which was due to the low incidence of patients receiving HCQ therapy. Second, the control group consisted of healthy subjects. The ideal group would be an age-matched group with the same rheumatological disorders but not receiving HCQ therapy. This is difficult as it is not always possible to perform ocular examinations in patients with rheumatological disorders without any concerned reasons. Third, the cross-sectional nature of the study made it difficult to evaluate the longitudinal effect of the medication. Further prospective studies with long-term changes are required to confirm our findings and to investigate if thinning of the GC-IPL precedes retinopathy.

In conclusion, macular GC-IPL showed significant thinning in patients on HCQ therapy but did not correlate with the duration and cumulative dose. Therefore, GC-IPL might serve as early biomarkers for HCQ toxicity. We suggest measuring GC-IPL thickness as an objective tool for early detection of HCQ induced toxicity using SD-OCT before it appeared clinically.

List of Abreviatoinns :

OCT: ocular coherence tomography

GC-IPL : ganglionic cell- inner plexiform cell layer

RNFL: retinal nerve fiber layer

ERG: and electroretinogram

SD-OCT: spectral domain ocular coherence tomography.

Declarations :

Ethics approval and consent to participate: The study was approved by the Institutional Review Board of the University of Jordan number 19/20/279 and written informed consent was obtained from every participant in the study. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendment

Consent to publish: all authors: all participants give their consent to publish the manuscript

Availability of Data and materials: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request

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تقييم سماكة االطبقة العنقودية والطبقة الداخلية الضفيرة وطبقة الالياف الشبكية عند الذين يتناولون عقار الهيدروكسي كلوروكوين

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ملخص

الخلفية: لمعرفة التغيرات التي تحدث باستخدام جهاز التصوير الطبقي للشبكية عند المرضى الذين يستخدمون عقار الهيدروكسي كلوروكوين.

الطريقة: دراسة رجعية مقطعية للمرضى اذين يستخدمون عقار الهيدروكسي كلوروكوين. من خلال جهاز التصوير الطبقي للشبكية، تم الحصول وتحليل صور للطبقة العنقودية والطبقة الداخلية الضفيرة وطبقو الالياف الشيكية ومقارنتها مع الناس الاصحاء. تم دراسة العلاقة بين سماكة هذه الطبقات والمدة الزمنية للعلاج والجرعة الكلية.

النتائج : كان هناك 219 مشارك، كان معدل أعمارهم سنة 43.38 (±17.39). كان هناك 100 شخص من الذين يناولون العقار وكان معدت اعمارهم 45.28 +−(± 12.24) سنة وكان هناك 119 مشارك من مجموعة التحكم معدل اعمارهم 41.79(± 20.67) بدون وجود فارق عمري بينهم . كان هناك فرق بين سماكة الطبقة العنقودية والضفيرة الداخلية بين المجموعنين . ,(p = 0.006) (88.6+/-6 µm) vs. (85.6+/- 8 µm) معدل سماكة الخلايا الشبكية كانت أقل عند الذين يأخذون العقار بالمقارنة مع الأصحاء، 28.2±2.5 µm (range: 23 – 38) and 29.2±2.8 µm (range: 22 – 35) بالترتيب، لكن الفرق لم يكن ذو اهمية احصائية. لم يكن هناك علاقة بين سماكة الخلايا العنقودية والضفيرة الداخلية والالياف الشبكية المركزية مع مدة العلاج، الجرعة اليومية والرعة الكلية

الاستنتاج: سماكة الخلايا العنقودية والضفيرة الداخلية أقل عند الذين يأخذون عقار الهيدروكسي كلوركوين مقارنة مع الاصحاء. سماكة هذه الطبقة ممكن ان تستخدم كدليل مبكر لوجود سمية من هذا العقار قيل ان تظهر علامات سريرية.

الكلمات الدالة: هيدروكسي كلوركوين، الطبقة العنقودية والضفيرية الداخلية، الالياف الشبكية المركزية، التصوير الطبقي للشبكية.

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