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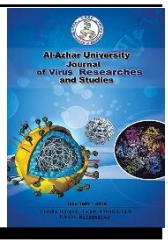

10-2 Visual Field for Detecting Early Hydroxychloroquine Retinopathy

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Abstract

Maculopathy is an irreversible adverse effect of Hydroxychloroquine (HCQ). The earlier the diagnosis and discontinuation of HCQ, the less severe maculopathy and the less likely of is to progress. The work aims to compare between 10-2 Visual field (VF) test as a subjective functional test and optical coherence tomography (OCT) as an objective structural imaging in diagnosing the HCQ retinopathy and to evaluate its severity. A prospective, case-control study, conducted at Al-Zahraa University Hospital (May 2021 - April 2022), included 30 patients (60 eyes) on HCQ for ≥ 5 years or on doses > 5mg/Kg (Group I) and 20 healthy subjects (40 eyes, Group II). All participants underwent a comprehensive ophthalmic examination, as well as 10-2 VF testing, and OCT. Mean patient age: 47.4 years, duration of HCQ treatment: 9.3 years. No statistically significant difference between both groups in macular thickness. PSD was significantly worse in group I (p = 0.045), while the difference in MD was not statistically significant (P = 0.066). In group I, there was a statistically significant decreased macular thickness (ETDRS 9 sectors) except the foveal area in eyes with outer nuclear layer thinning (10 eyes) when compared to eyes with normal OCT (50 eyes) and a statistically significant difference between eyes with VF changes (20 eyes) and eyes with normal VF (40 eyes) in MD, PSD (p = <0.001). The area under the curve (AUC) for OCT parameters ranged from 0.92 for the inner nasal area to 0.68 for the outer superior area, parafoveal thickness (except inferior) had the highest sensitivity at 90%. The AUC for VF parameters was 0.95 for PSD & 0.83 for MD with higher sensitivity for MD. The 10–2 VF is more sensitive than OCT in identifying retinal toxicity. Although we recommend the 10–2 VF test plus OCT for the initial screening of HCQ maculopathy.

Keywords: 10-2 Visual Field, Hydroxychloroquine Retinopathy, Spectral domain OCT.

1. Introduction

Hydroxychloroquine (HCQ) is widely prescribed by rheumatologists for the treatment of many autoimmune disorders [1]. Recently, it has been prescribed for treatment and prevention against severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2) [2]. Hydroxychloroquine is effective and has low systemic side effects, but retinopathy is the most feared adverse effect as it can cause loss of vision that may progress even after cessation of the drug [3]. According to UK-based audit, 6.3% of patients with long-term medication have retinopathy [4]. Previous studies have shown that a long duration of treatment (>5 years), a high dose (> 5.0 mg/kg), and

suboptimal renal function are the major risk factors for HCQ retinopathy [5]. The earlier disease is diagnosed, and HCQ discontinuation, the less severe retinopathy, and the less likely they are to progress [6].

In early retinopathy, patients may be asymptomatic, and the fundus may remain normal before the development of signs of maculopathy; so, screening for early detection is recommended [7].

Many examination techniques have been used to screen for HCQ retinopathy. Spectral-domain optical coherence tomography (SD-OCT), multifocal electroretinography (mf ERG), and fundus autofluorescence, along with 10–2 automated visual fields (VF) for early detection of toxicity [7].

Screening for HCQ retinopathy using many examination techniques as fundus autofluorescence, spectral-domain optical coherence tomography (SD-OCT), 10–2 automated visual fields (VF) and multifocal electroretinography (mf ERG), for early detection of toxicity [7]. The aim of this study to compare between 10-2 visual field test as a functional, subjective test and OCT as an objective structural imaging in diagnosing the HCQ retinopathy and to evaluate its severity.

2. Patients and Methods

The This prospective, case control study, conducted at Al-Zahraa University hospital (Cairo, Egypt), May 2021 - April 2022, included 30 patients (60 eyes) on HCQ treatment for more than 5 years or on doses of more than 5mg/Kg **(Group1)** and 20 healthy subjects (40 eyes) as a control group **(Group2)**, age ranged 30-65 years. The Ethics Broad of Al-Azhar University approved the study, in accordance with the Declaration of Helsinki Guidelines. A written informed consent taken from all participants after explanation of the nature and the aim of the study.

Exclusion criteria:

- Age below 30 and above 65 years old,
- Eyes with significant media opacities, other macular pathology (diabetic maculopathy, dry macular degeneration, etc.) or high error of refraction (> ± 5 DS or ± 3 DC),
- VFs with poor reliability indices.

All patients underwent a comprehensive ophthalmic examination, History taking including demographic data of the patients (Name, age, sex), medical history (underlying disease and duration of medications and and its daily dose) and ocular history includes cataract, glaucoma, or medications. Ophthalmological examination includes: Best corrected visual acuity tested (BCVA), Pupil light reflex test, IOP measurement (Goldman applanation tonometer), Anterior segment examination (slit lamp), Fundus examination (slit lamp biomicroscope with + 90D lens and indirect ophthalmoscope), Color vision test (Ishihara test), Amsler grid testing, Visual Field Testing (Humphrey Field Analyser, Humphrey; Carl Zeiss Meditec Inc., Dublin, California, USA)., Macular scanning, SD-OCT (RTVue XR Avanti with AngioVue software (Optivue Inc, Freemont, USA)).

2.1 OCT Imaging and Analysis

Each participant underwent the RTVue-100 Fourier domain-OCT after pupillary dilatation. In high-quality images (signal strength ≥ 7), the macular thickness map was obtained for quantitative assessment of CMT, Perifoveal and parafoveal retinal thickness (in μm) in the four quadrants (superior, temporal, inferior and nasal). In color-coded macular thickness map, blue areas which represent <1% of the normative level is evidence of significant thinning. horizontal High Definition (HD) line scan centered on the fovea and radial scans used for photoreceptor inner

segment/outer segment junction (ellipsoid zone (EZ)) and outer nuclear layer (ONL)inspection.

2.2 Visual Field Testing and Analysis

Perimetric test using a standard 10-2 HVF Analyzer (Carl Zeiss Meditec, Inc, Dublin, CA), white test spot, was performed in a semi-dark room with best corrected near vison correction. The test was repeated whenever it was found non reliable to detect learning effect and maximize reliability indices. The mean deviation (MD) values, representing the overall mean departure of sensitivity at specific retinal points from the age-corrected normal values and the Pattern standard deviation (PSD), representing the focal loss or variability within the field, considering any generalized depression. The following findings were defined as abnormalities on the 10-2 VF: Reduction of the retinal points sensitivity, super nasal defects developed 2^{ry} to inferotemporal macular damage, Paracentral partial or complete ring scotoma.

2.3 Statistical Analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 24. Quantitative data were presented as mean ±SD. Qualitative data were presented as frequency and percentage. Independent-samples t-test used for normally distributed data to compare between two means. The Mann–Whitney U test used abnormal distributed data to compare between two means. Chi-square test used for comparing between non-parametric data. Pearson's correlation coefficient (r) test used for data correlation. P-value < 0.05 was considered significant. The cut-off points for each of the nine retinal sectors (for both OCT as well as the corresponding VF value) was determined, the following values were calculated automatically, sensitivity, specificity, Positive predictive value (PPV), Negative predictive value (NPV) and Area under curve (AUC).

3. Results

Sixty eyes of 30 patients, 86.7% female on HCQ treatment, mean age 47.4 years, and the mean duration of HCQ treatment was 9.3 years, the mean daily dose was 293.33mg (Table 1). When analyzing ETDRS charts for macular thickness of OCT, there were no statistically significant differences between the 2 groups in all parameters (ETDRS 9 sectors) (Table 2). When analyzing the VF, there was a statistically significant differences between the 2 groups in PSD values ($p = 0.045$). The MD value in groups 1 was higher than groups 2, but the difference was not significant ($P = 0.066$) (Table 3). The correlation analyses performed to assess the correlation between age, body weight, HCQ treatment duration, HCQ cumulative dose, BCVA, IOP, VF parameters, and OCT parameters measured. There was a statistically significant negative correlation between BCVA and OCT parameters (peri-foveal area except the temporal area and para-foveal area except the nasal area). There was a statistically significant positive correlation between VF MD & HCQ cumulative dose (Table 4). Our results showed that in group 1 there was 10 eyes had thinning of ONL and when comparing those eyes with others who had normal retinal layers configurations (50 eyes), we found a significant difference between them in the macular thickness values (in 8 quadrants according to ETDRS scoring) (Table 5). Regarding the VF, 20 eyes had VF affection in the form of paracentral scotomas, when comparing to other patients (40 eyes) who had normal VF, we found significant difference between them in both MD & PSD values ($p<0.001$), (Table 6).

Table (1): Demographic and clinical data of the study groups.

	Group 1 (N = 60 eye)	Group 2 (N = 40 eye)	*P*- value
Age (year)	47.4 ± 9.6	44.5 ± 9.6	0.346 (2)
Gender (female)	26 (86.7%)	17 (85%)	0.868 (3)
BCVA (Log MAR)	0.2 ± 0.1	0.07 ± 0.1	0.001 (2)
IOP (mmHg)	13.4 ± 2.3	12.5 ± 1.7	0.015 (2)
Color Vision (Intact)	60 (100%)	40 (100%)	
Amsler testing (Normal)	58 (96.7%)	40 (100%)	0.409 (3)
Body Weight (BW) (kg)	83.5 ± 9.2	81.7 ± 9.6	0.504 (1)
HCQ Duration (years)	9.3 ± 6.3	-	
HCQ Daily Dosage (mg)	293.33± 101.48	-	
Total HCQ dose (g)	927.1 ± 639.9	-	

(1): Independent sample t test; (2): Mann Whitney U test; (3): Chi-square test, Data are expressed as mean ± standard deviation. Abbreviations: BCVA: best corrected visual acuity, IOP: intraocular pressure, BW: Body Weight, HCQ: Hydroxychloroquine, SE: spherical equivalent.

Table (2): OCT Macular thickness values measured in 9 quadrants according to ETDRS scoring; Comparisons between studied groups.

OCT ETDRS	Group 1	Group 2	*P* value (Independent sample t-test)
Fovea	244.7 ± 23.9	247.4 ± 20.3	0.570
Outer Inferior	271.8 ± 16.5	266.8 ± 24.0	0.226
Outer Superior	280.3 ± 19.5	279.1 ± 20.7	0.779
Outer Nasal	293.0 ± 18.0	291.8 ± 21.6	0.754
Outer Temporal	268.1± 20.8	267.1± 21.7	0.822
Inner Inferior	306.8 ± 15.6	306.0 ± 23.8	0.823
Inner Superior	309.8 ± 16.7	309.6 ± 20.7	0.9.66
Inner nasal	307.2 ± 15.9	309.2 ± 21.5	0.595
Inner Temporal	292.4 ± 17.9	293.5 ± 28.2	0.822

Table (3): Comparison between studied groups as regard VF indices (MD & PSD).

	Group 1	Group 2	*P* value (Mann Whitney U test)
MD	-2.4 ± 3.1	-1.18 ± 1.3	0.066
PSD	1.5 ± 0.85	1.16 ± 0.26	0.045

MD: mean deviation; PSD: Pattern standard deviation

Table (4): Correlation study between OCT and VF parameters vs age, HQ duration, BW, Cumulative dose, BCVA, IOP in group 1.

Variables	Age		HQ duration		BW		Cumulative dose		BCVA		IOP	
	r	*P* value	r	*P* value	r	*P* value	R	*P* value	r	*P* value	r	*P* value
Fovea	-0.16	0.22	0.03	0.80	0.10	0.46	0.06	0.676	-0.10	0.464	0.15	0.246
Outer Inferior	-0.02	0.89	-0.14	0.30	0.16	0.23	0.02	0.868	-0.37	0.004	0.02	0.89
Outer Superior	0.07	0.58	-0.05	0.69	-0.02	0.86	0.10	0.433	-0.30	0.019	-0.04	0.737
Outer Nasal	0.04	0.79	-0.08	0.54	-0.13	0.31	0.01	0.954	-0.29	0.024	-0.05	0.706
Outer Temporal	0.03	0.84	-0.08	0.54	0.14	0.28	0.06	0.63	-0.20	0.126	-0.03	0.834
Inner Inferior	-0.11	0.39	-0.12	0.36	-0.04	0.76	-0.02	0.886	-0.31	0.017	0.04	0.747
Inner Superior	-0.09	0.51	-0.05	0.71	-0.04	0.77	0.02	0.879	-0.33	0.011	-0.03	0.847
Inner Nasal	-0.21	0.10	-0.02	0.90	-0.15	0.25	-0.01	0.922	-0.25	0.052	0.01	0.97
Inner Temporal	-0.15	0.25	-0.22	0.09	-0.25	0.06	-0.14	0.305	-0.26	0.042	0.01	0.971
VF MD	0.09	0.52	0.19	0.16	0.24	0.07	0.27	0.04	-0.13	0.342	0.21	0.105
VF PSD	-0.10	0.44	-0.24	0.06	-0.20	0.14	-0.26	0.051	0.02	0.861	-0.20	0.138

(r): Pearson correlation coefficient.

Table (5): OCT parameters in group 1; comparison between eyes with normal macular scanning and eyes with thinning of the ONL thickness.

OCT ETDRS	Normal macular scanning (N = 50 eye)	Thinning of the ONL (N = 10 eye)	*P*-value (Independent sample t-test)
Fovea	264.5 ± 20.9	236.0 ± 35.2	0.208
Outer Inferior	274.9± 13.6	256.2± 21.4	0.001
Outer Superior	282.6± 18.5	268.7± 21.1	0.039
Outer Nasal	295.4± 16.7	281.2± 20.8	0.022
Outer Temporal	270.5± 20.9	256.2± 17.0	0.047
Inner Inferior	310.7 ± 12.2	287.6± 17.4	<0.001
Inner Superior	313.6 ± 14.0	290.5 ± 16.1	<0.001
Inner nasal	311.3 ± 12.9	286.5 ± 13.2	<0.001
Inner Temporal	295.5 ± 17.3	277.0 ± 12.5	0.002

Table (6): Visual field parameters in group 1; comparison between eyes with normal visual field & eyes with visual field abnormalities.

VF	Normal VF (N = 40 eye)	VF abnormalities (N = 20 eye)	*P* value (Independent sample t-test)
VF; MD	-1.3 ± 1.8	-4.5 ± 3.9	<0.001
VF; PSD	1.14 ± 0.2	2.2 ± 1.2	<0.001

Table (7): Diagnostic performance of OCT macular thickness values measured in 8 quadrants according to ETDRS scoring, VF values (MD & PSD) in discrimination of affected cases.

OCT ETDRS	Cut off	AUC	Sensitivity	Specificity	PPV	NPV	p-value
Outer Inferior	< 268.5	0.77	70%	68%	68.6%	69.4%	0.007
Outer Superior	< 280.5	0.68	60%	58%	58.8%	59.2%	0.069
Outer Nasal	< 292.5	0.69	70%	62%	64.8%	67.4%	0.048
Outer Temporal	< 258.5	0.75	70%	84%	81.4%	73.7%	0.012
Inner Inferior	< 302.5	0.88	80%	84%	83.3%	80.8%	0.0001
Inner Superior	< 307.5	0.88	90%	76%	78.9%	88.4%	0.0001
Inner nasal	< 302	0.92	90%	76%	78.9%	88.4%	< 0.001
Inner Temporal	< 292.5	0.81	90%	64%	71.4%	86.5%	0.002
VF MD	< -2.2	0.83	85%	70%	73.9%	82.4%	< 0.001
VF PSD	> 1.4	0.95	84.2%	87.5%	87.1%	84.7%	< 0.001

PPV: positive predictive value; NPV: negative predictive value; AUC: Area under curve.

Diagnostic performance of OCT and VF parameters in discrimination of affected cases: Our results showed that PSD had the largest area under curve (AUC =0.95) then inner nasal subfield of the retina (AUC=0.92), then the inner superior and inner inferior subfields (AUC=0.88), then VF MD (AUC=0.83) then the inner temporal subfield (AUC=0.81). Also, our results found that PSD has 84.5 % sensitivity, 87.5% specificity at a cut-off level >1.4. which exceeds those of the OCT (Table7).

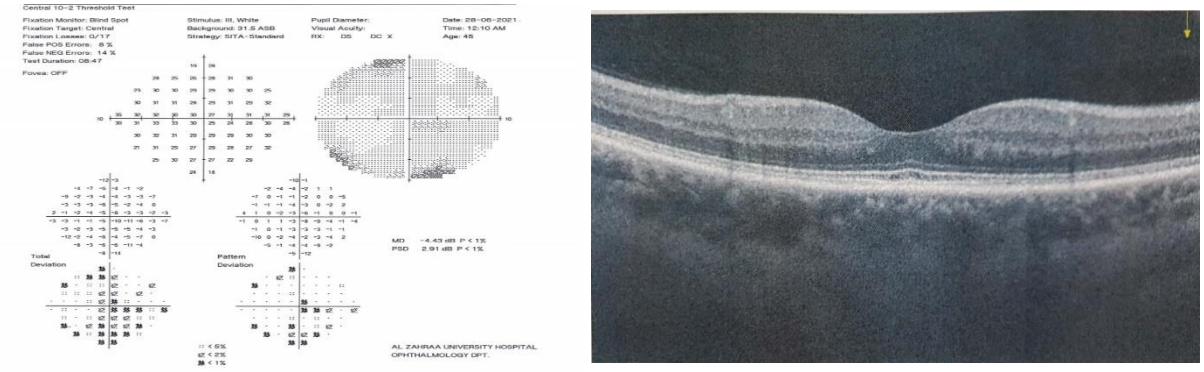

Figure 1: visual field and OCT finding in female patient 54 years old on HCQ 200 mg/day for 7 years, shows paracentral scotoma (right) and thinning in the outer nuclear layer (left)

4. Discussion

Our study included 30 patients (60 eyes) on HCQ treatment for more than 5 years or on doses of more than 5mg/Kg (Group1) & 20 healthy subjects (40 eyes) as a control group (Group2), age ranged 30-65 years. All patients in group 1 have normal fundus, color vision is normal, also Amsler testing. We found a statistically significant difference between the 2 groups regarding BCVA (p = 0.001) and IOP (p = 0.015); The in IOP in patients who used HCQ compared to healthy subjects can be explained that 17 (56.6%) of the cases were on previous history of steroids in their protocol of treatment. Similarly, Mohamed et al. [8] found a statistically significant difference in IOP between case group (15 patients with rheumatological diseases on HCQ > 3 years) & control group (15 persons), P=0.038. Also, they found a statistically significant difference between the 2 groups regarding the BCVA, P=0.006. Our study showed no statistically significant difference between studied groups in OCT macular thickness values measured in 9 quadrants according to ETDRS scoring. El Habbak et al. [9] in their study also found no statistically significant difference between cases on HCQ > 2 years and control group (20 eyes in each group) in OCT parameters (perifoveal region thickness), but they found a statistically significant decrease central foveal thickness (CFT) in HCQ group. In contrary to our results Osman et al. [10] in their study that included 100 females on HCQ and 50 age matched healthy subjects, found a statistically significant difference between the 2 groups in central foveal thickness (p = 0.042), the parafoveal thickness (upper, lower, nasal and temporal) (p = 0.001, 0.020, 0.001 & 0.001 respectively), The perifoveal thickness (upper, temporal and lower)(p value = 0.002, < 0.001 & 0.041 respectively). El-Sayed et al. [11] reported a significant reduction in the peri-foveal macular thickness (superior, inferior & nasal) in comparison to control group, but the foveal and parafoveal thickness showed no significant difference between both groups. Our study showed that there was thinning in the ONL in 10 patients in group 1 with no disruption of ellipsoid zone (EZ). We found a significant difference in OCT macular thickness values measured in all quadrants (according to ETDRS) except the foveal area when comparing those affected (10 eyes) and eyes with normal retinal layers configurations (50 eyes). Cukras et al. [12] in their study that included 57 patients on HCQ treatment > 5 years' duration, divided into 2 groups based on mf ERG criteria: those unaffected (n=38) and those affected (n=19), they found a significantly lower retinal thickness measurements in each of the 9 macular subfields in the affected group (P < 0.01 for all comparisons) compared with those in the unaffected group. In the affected group, 84.2% had clinical features of retinal toxicity and perifoveal loss of the EZ. Aydın Kurna et al. [13] in their study that included 145 patients divided into 3 groups, 81 on HCQ for ≥ 6 months (group 1), 34 patients with rheumatological diseases and with no HCQ therapy (group 2), and 30 healthy subjects (group 3). The macular thickness was thinner in the outer and inner nasal quadrants subfields in group 1. Our results showed no statistically significant difference between studied groups as regard MD (P = 0.066), but there was statistically significant difference as regard PSD (p = 0.045). Twenty eyes had VF changes in the form of paracentral scotoma (18 eyes), upper half scotoma sparing paracentral nasal (1 eye), lower half scotoma except lower nasal island (1 eye), 1 eye had early changes decrease in retinal sensitivity & 7 eyes had nonspecific changes. We found a significant difference between those 10 eyes and others (40 eyes) who had normal VF parameters in both MD and PSD values. Aydın Kurna et al. [13] found a significantly worse VF scores in

patients with rheumatologic diseases, on HCQ (group 1) than patients with rheumatologic diseases, did not receive HCQ therapy (group 2) and healthy subjects (group 3) in MD (P = 0.000) and PSD between group 1 and group 3 (P= 0.001). In contrary to our results, Allahdina et al. [14] reported a significant difference in the MD between the affected group (n=19) and the unaffected group (n=38) (based on mf ERG) criteria) (P < 0.0001).

In our results, all patients had normal fundus examination, no change in the EZ or external limiting membrane (ELM). Ten eyes in group 1 had thinning in ONL, 20 eyes had VF changes, so visual field changes developed before OCT changes. Our findings are in agree with Pandey et al. [15], their study included 167 patients receiving systemic HCQ, 4.8% had VF findings consistent with HCQ retinopathy and 2.4% had OCT changes (ELM loss or EZ disruption). Also, Marmor and Melles [6] in their review of charts and clinical data of patients with HCQ retinopathy at the Byers Eye Institute (at Stanford and the Kaiser Permanente health system in California), found that among 150 patients with HCQ toxicity, 11 had normal OCT scanning but had parafoveal ring scotomas, and all cases with evidence of parafoveal damage showed at least some focal spots of parafoveal VF loss. On the other hand, Garrity et al. [16] in their multicenter, retrospective study reported that eyes with early HCQ retinopathy with subtle OCT abnormalities and normal VF testing, by time progressed to advanced ONL disruption and/or paracentral VF defects, so the structural changes may occur before functional impairment in some cases of early HCQ toxicity. Our results showed a statistically significant negative correlation between BCVA and OCT parameters (peri-foveal thickness except the temporal area and para-foveal thickness except the nasal area). No significant correlation between the duration of treatment or the cumulative dose and any of the OCT parameters measured. This agreed with Osman et al. [10] who showed no statistically significant correlation between the duration of the treatment or the cumulative dose of HCQ with any of the OCT parameters measured in the patients' group. Also, Allam et al. [7] showed no statistically significant correlation between the duration of treatment or the cumulative dose of Chloroquine with any of the OCT parameters measured in the patients' group. In contrary to our results, Bertoli et al. [17] found a statistically significant correlation between the duration of treatment and the cumulative dose of Chloroquine with the paracentral and pericentral thickness measurements in ETDRS circles. Bulut et al. [18] found a statistically significant negative correlation between the cumulative dose of HCQ and its duration with the average macular retinal ganglion cell inner plexiform layer thickness. Casado et al. [19] found that the duration of HCQ treatment was significantly correlated with ONL in seven sectors out of central 16 sectors of the posterior pole analysis (P < 0.047).

Our results showed a statistically significant positive correlation between MD & the cumulative dose of HCQ (p=0.04). Uğurlu et al. [20] found that the VF changes were not associated with duration of HCQ use (p=0.124) or the cumulative dose (p=0.234). Al Adel et al. [21] reported that the daily dose per weight was most significant risk factor for toxicity and that the risk much increased when the daily dose was >5mg/kg. Adhering to doses of<5mg/kg was associated with a relatively lesser risk of toxicity in who underwent annual screening.

Our results showed that PSD had the largest area under curve (AUC =0.95) then inner nasal subfield of the retina (AUC=0.92), then the inner superior and inner inferior subfields (AUC=0.88), then VF MD (AUC=0.83) then the inner temporal subfield (AUC=0.81). Also, our results found that PSD has 84.5 % sensitivity, 87.5% specificity at a cut-off level >1.4 which exceeds those of the OCT subfields.

In agreement to Hasan et al [22] in their retrospective study that included 100 patients on HCQ for ≥ 5 years and 70 age matched controls, they reported that areas of retinal damage indicative of toxicity are the parafoveal area (superior, inferior, and nasal) and the superior perifoveal area. Also, Browning & Lee [23] found that the sensitivity was 85.7 and 78.6% for 10–2 VF, and OCT and the specificity was 92.5, and 98.1% in detecting HCQ retinopathy, respectively.

5. Conclusion

Based on our study the 10–2 VF is more sensitive than OCT in identifying retinal toxicity. Although we recommend the 10–2 VF test plus OCT for the initial screening of HCQ maculopathy.

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