ORIGINAL ARTICLE

Use of microperimetry to evaluate hydroxychloroquine and chloroquine retinal toxicity

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ABSTRACT • RÉSUMÉ

Objective: To check the ability of microperimetry to detect early retinal damage in patients with rheumatism taking hydroxychloroquine (HCQ), chloroquine (CQ), or both, and to describe the microperimetric alterations attributable to these drugs and their correlation with some clinical variables.

Design: Controlled cross-sectional study.

Participants: Patient group was 209 patients taking HCQ or CQ. Control group was 204 individuals not taking antimalarials. Exclusion criterion was other diseases that could alter microperimetry.

Methods: An ophthalmic examination and a microperimetry were performed on all individuals. Outcomes measured were average threshold, fixation stability, and macular integrity. Information about patient weight, height, main diagnosis, daily and cumulative dose, and creatinine, bilirubin, and transaminases levels were collected. Analysis of variance, *t* tests, and a regression analysis were carried out to detect differences between groups.

Results: Significant differences in microperimetry indexes were detected between cases and control subjects, between patients of different age groups, and between patients taking CQ and HCQ. Significant differences were also detected in retinal sensitivity between patients overdosed for CQ, but not for those overdosed for HCQ. Daily overdosing per ideal weight alone cannot explain retinal toxicity, although the effect of cumulative dose in macular sensibility is significant to explain both average threshold and macular integrity.

Conclusions: Microperimetry is an accurate tool for detecting early macular hyposensibility caused by CQ and HCQ. Microperimetry indexes of retinal sensibility are worse in elderly patients taking these drugs and in short-stature patients taking CQ. A high cumulative dose is an important factor in explaining retinal hyposensibility on microperimetry.

Objet : Vérification de la capacité de la micropérimétrie de détecter les dommages précoces de la rétine chez les patients qui, atteints de rhumatisme, prennent de l'hydroxychloroquine (HCQ) et/ou de la chloroquine (CQ). Description des modifications micropérimétriques attribuables à ces médicaments et de leur corrélation avec certaines variables cliniques.

Nature : Étude transversale contrôlée.

Participants : Groupe de patients : 209 patients prenant de la HCQ ou de la CQ. Groupe témoin : 204 personnes qui ne sont pas sous antipaludiques. Critères d'exclusion : autres maladies qui pourraient affecter la micropérimétrie.

Méthodes : Toutes les personnes ont été soumises à un examen oculaire et à une micropérimétrie. Données : Le seuil moyen (SM), la stabilité de la fixation (SF) et l'intégrité maculaire (IM). Pour les patients, les informations concernant leur poids, leur grandeur, leur diagnostic principal, leurs doses quotidiennes et cumulatives, leurs taux de créatinine, bilirubine et transaminase ont été recueillies. L'ANOVA, des tests T et une analyse de régression ont été appliqués pour détecter les différences entre les groupes.

Résultats : D'importantes différences ont été détectées à partir des indices micropérimétriques entre les cas et les contrôles, entre les patients des divers groupes d'âge et entre les patients qui prennent de la CQ ou de la HCQ. D'importantes différences ont aussi été détectées concernant la sensitivité rétinienne chez les patients ayant une surdose de CQ mais non pas ceux en surdose de HCQ. La surdose quotidienne par poids idéal seulement n'a pas pu expliquer la toxicité rétinienne, bien que l'effet de la dose cumulative sur la sensibilité maculaire explique significativement le SM et l'IM.

Conclusions : La micropérimétrie est un outil précis de détection précoce de l'hyposensibilité maculaire causée par la CD et la HCQ. Les indices micropérimétriques de la sensibilité rétinienne sont pires chez les patients plus âgés qui prennent ces médicaments, et chez les patients de petite taille qui prennent de la CQ. Une dose cumulative élevée est un facteur important dans l'explication de l'hyposensibilité rétinienne par micropérimétrie.

Chloroquine (CQ) and its analog, hydroxychloroquine (HCQ), are antimalarial drugs that have been used as treatment of various rheumatologic and dermatologic diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and chronic discoid lupus.[1] However, retinal toxicity has been described. Although the risk for toxicity from CQ and HCQ is low, many thousands of individuals are taking these drugs. After 5 to 7 years of use, the prevalence rate of retinal toxicity increases to 1%.[2] The risk for toxicity depends on cumulative exposure (a cumulative dose of 1000 g HCQ, which is reached in 7 years with a typical daily

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dose of 400 mg, and a cumulative dose of 460 g CQ, which is reached in 5 years with a typical daily dose of 250 mg). Other risk factors are renal or liver diseases, underlying retinal disease, and age. The clinical sign of CQ and HCQ toxicity is characterized by a ring of retinal pigment epithelium depigmentation, often sparing the foveal centre, known as a bull's-eye maculopathy. Paracentral scotomas appear before changes are seen on a fundus examination. Drug use cessation at this stage of early functional loss might prevent future visual loss, but after maculopathy develops, cessation of the drug does not show clinical recovery.[3] Recommendations on screening for CQ and HCQ retinopathy are automated visual field and, where available, testing with ≥1 of the recommended objective tests: spectral-domain optical coherence tomography (SD-OCT), multifocal electroretinogram (mfERG), or fundus autofluorescence (FAF).[4,5] However, visual field accuracy relies on patient's cooperation, and the objective procedures are not readily available in many offices. The goal of screening is to recognize toxicity before a severe degree of visual field loss occurs. Currently, there is no established gold standard test for screening.

Microperimetry consists in testing perimetry under simultaneous visualization of the fundus. Exact correlation between retinal pathology and functional alteration is obtained. It allows a precise evaluation of macular sensitivity, providing an accurate detection of small scotomic areas in terms of their position, extension, and severity in the macular area with a real-time correction of eye movements.[6] Its uses are both clinical and for research.[7–11] In this study, we assess CQ and HCQ toxicity using microperimetry. Our purpose is to describe the value of microperimetry as a high-sensitivity test for the screening of CQ and HCQ retinopathy. We study whether macular sensibility indexes provided by microperimeter are decreased in our patients with respect to persons not taking antimalarials. Moreover, we look for the correlation between microperimetry abnormalities and the main clinical variables influencing retinal damage.

Table 1—Description of the database

	Control subjects	Cases	*p*
Female sex	84.00%	80.42%	0.42
Age, mean ± SD (y)	53.74 ± 13.37	51.24 ± 15.13	0.08
Weight, mean ± SD (kg)	—	70.15 ± 15.35	—
Height, mean ± SD (cm)	—	159.71 ± 12.98	

Methods

All patients and controls gave written informed consent to participating in the study, which was approved by the ethical committee of our hospital (code 09/046). Moreover, the procedures complied with the tenets of the Declaration of Helsinki.

A total of 413 individuals were included in this cross-sectional case—control study. We studied 209 patients taking CQ and HCQ. In addition, 204 individuals not being treated with antimalarials were included as control subjects. Control subjects were chosen from healthy volunteers (57%) and from patients affected by rheumatic diseases that have never been managed with antimalarials (43%). In the patient group, we obtained data about weight, height, diagnosis, daily doses, months under treatment, and cumulative dose. A complete ophthalmologic examination was performed in patients and control subjects that included visual acuity, biomicroscopy, intraocular pressure, and funduscopy. The presence of corneal drug deposits attributable to CQ and HCQ was recorded. Data from 3 consecutive blood analyses (creatinine, bilirubin, and transaminases aspartate transaminase/alanine transaminase) were also obtained to identify renal or liver disfunction that could increase CQ and HCQ retinal toxicity. Patients suffering from other diseases that could alter the fundus perimetry such as glaucoma, gross ametropia, macular drusen, other maculopathies, among others, were excluded. Finally, a microperimetry was done using the expert examination strategy of Macular Integrity Assessment microperimeter (CenterVue SpA, Padova, Italy). Then we recorded 3 indexes

Table 2—Description of patient group

	HCQ	CQ	CQ → HCQ	*p*
n (%)	130 (67.01)	30 (15.46)	34 (17.52)	
Mean BCVA (logMAR)	0.06 ± 0.09	0.10 ± 0.13	0.12 ± 0.21	0.03
Diagnosis, n (%)				
SLE	64 (68.81)	10 (10.75)	19 (20.43)	
RA	33 (55.00)	15 (25.00)	12 (20.00)	
Other	32 (84.21)	4 (10.53)	2 (5.26)	
Duration of therapy, mo	38.29 ± 38.88	103.66 ± 63.88	121.55 ± 59.31	< 0.001
Cumulative HCQ dose (g)	357.61± 381.04	0	503.23 ± 445.46	0.09
Cumulative CQ dose (g)	0	733.53 ± 432.96	475.76± 411.97	0.02
Overdosed, n (%)*	22 (16.92)	25 (83.33)	7 (20.58)	< 0.001
Aspartate transaminase (UI/L)	21.72 ± 8.26	22.24 ± 7.67	22.94 ± 8.73	0.73
Alanine transaminase (UI/L)	21.37 ± 14.58	20.41 ± 7.19	22.68 ± 17.08	0.81
Bilirubin (mg/dL)	0.49 ± 0.34	0.56 ± 0.32	0.43 ± 0.19	0.31
Creatinine (mg/dL)	0.79 ± 0.23	0.81 ± 0.16	0.89 ± 0.46	0.17
Corneal drug deposits, n	0	3	0	

HCQ, hydroxychloroquine; CQ, chloroquine; BCVA, best corrected visual acuity; logMAR, logarithm of the minimum angle of resolution scale; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; other, undifferentiated arthritis, cutaneous diseases.

*Overdosed: HCQ, patients receiving more than 6.5 mg/kg ideal weight/d; CQ, patients receiving more than 3 mg/kg ideal weight/d; CQ → HCQ, patients first on CQ and switched to HCQ over the evolution of the disease.

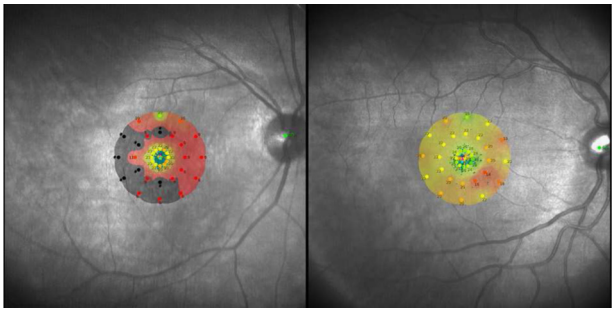

Fig. 1—Interpolation maps of microperimetries corresponding to (left) a patient diagnosed as definite maculopathy with stable fixation and good central responses but severe pericentral hyposensitivity with an absolute scotoma and (right) a patient diagnosed with probable maculopathy with stable fixation and good central sensitivity but nasal pericentral scotoma. (Colour version of figure is available online.)

provided by the microperimeter: average threshold (AT), fixation stability (FS), and macular integrity (MI). A stimulus intensity ranged from 0 to 36 dB. A predefined grid of 37 points and 10º macular coverage was used. Threshold sensitivities at each predefined point were calculated using a staircase 4-2 strategy. A patient's AT results were compared with age-adjusted normative data. Two variables in the data set measured patients' fixation stability: FSp1 and FSp2. Both variables measure the percentage of fixation points located within a circle centred on the gravitational centre of all fixation points. The difference between them arises on the diameter of their respective circles, the diameter for FSp2 being greater than for FSp1. MI is an index of macular health that is calculated using a neural network multivariate model (see Discussion section for a detailed explanation). Best corrected visual acuity (BCVA) was measured in decimal units on a decimal chart. The results were then converted to the logarithm of the minimum angle of resolution scale (logMAR).

Results

All the examinations with less than 75% reliability were excluded, finally resulting in 200 control subjects and 194 patients. Table 1 shows the demographics of our sample. Regarding the patient group, Table 2 shows the main variables collected in a more detailed way. A total of 17 (8.76%) cases were diagnosed as having a toxic maculopathy (see Table 3) considering clinical and microperimetric findings: 7 of them were considered as probable maculopathy and 10 (5.15%) as definite toxic maculopathy (see Fig. 1). Probable maculopathy was diagnosed if the patient had a pericentral scotoma with ≥3 adjacent points between 2 and 3 SDs from the normal average (in yellow in Fig. 1) and/or ≥2 adjacent points with a sensitivity beyond 3 SDs from the normal average (in orange, red, and black in Fig. 1). Definite maculopathy was diagnosed if the patient also had characteristic pigmentary changes of antimalarial toxicity. Among these 10 patients, 4 had complete bull's-eye maculopathy and 6 had only subtle sectorial depigmentation of the macular area. FS and BCVA were good (less than logMAR 0.2) in 9 patients with definite maculopathy. The remaining patient had an advanced bull's-eye maculopathy with foveal involvement: unstable fixation and BCVA 0.5 logMAR. All 10 patients diagnosed as having definite maculopathy were women, and all were less than 163 cm in height. In addition, 3 patients presented with corneal drug deposits. All 3 were receiving CQ therapy: 1 had no signs of macular toxicity and continued under CQ treatment, 1 was diagnosed with definite CQ maculopathy (cumulative dose, 548 g) and the other was diagnosed as probable CQ maculopathy (cumulative dose, 274 g). In these 2 patients, corneal deposits disappeared a few weeks after stopping antimalarial therapy.

Because there were no significant differences between AT and MI indexes corresponding to the right and left eye of each patient, from now on, when talking about AT and MI values, we will refer to the mean value between both eyes for each patient.

Significant differences in AT between cases and control subjects were detected (see Table 4). However, MI was higher in control subjects. This result seemed paradoxical, because higher MI suggests a greater likelihood of abnormal findings. In trying to investigate whether a higher MI value in control subjects could correspond to a lower fixation stability, this variable was also analyzed (Table 4). Nevertheless, no significant differences were detected between the mean fixation stability (FSp1 and FSp2) of control subjects and patients. If age stratification was done, we could see that MI was significantly higher in individuals aged 60 years or less than in patients, but patients older than 61 years who were taking antimalarials had higher MI than healthy control subjects (Table 5).

Table 3—Characteristics of patients with toxic maculopathy

	HCQ	CQ	CQ → HCQ	Global
n	2	10	5	17
Probable maculopathy	1	4	2	7
Definite maculopathy	1	6	3	10
Age, mean ± SD (y)	41.00 ± 9.89	57.00 ± 11.56	60.60 ± 20.21	56.17 ± 14.78
Cumulative HCQ dose (g), mean ± SD	200.5 ± 180.31	0	251.8 ± 308.24	207.50 ± 257.88
Cumulative CQ dose (g), mean ± SD	0	648.10 ± 252.13	689.40 ± 763.23	661.87 ± 455.75
Overdosed, n (%)	1 (50.00)	8 (80.00)	2 (40.00)	11 (64.70)
Deposits, n (%)	0	2 (20)	0	2 (11.76)

HCQ, hydroxychloroquine; CQ, chloroquine.

Table 4—Differences between control subjects and cases in fixation stability, average threshold, and macular integrity

	Global	Cases	Control subjects	Cases vs control subjects, *p*
Mean AT ± SD	26.83 ± 2.27	26.52 ± 2.64	27.12 ± 1.81	0.0092
Mean MI ± SD	43.56 ± 34.02	32.72 ± 34.33	54.07 ± 30.29	0
Mean FS p1 ± SD	90.83 ± 11.57	89.9 ± 12.58	91.83 ± 10.42	0.0827
Mean FS p2 ± SD	97.18 ± 5.82	96.93 ± 5.98	97.42 ± 5.67	0.4062

AT, average threshold; MI, macular integrity; FS, fixation stability.

We did not find significant differences in AT or in MI with respect to liver and renal functional blood analysis. The creatinine, transaminases, and bilirubin levels of our patients did not show any correlation with macular hyposensibility on microperimetry.

An analysis of variance and a Tukey test were done to establish whether there were significant differences in microperimetry indexes between patients taking CQ, HCQ, or both drugs. As shown in Table 6, significant differences in retinal sensitivity (AT and MI) were detected between patients taking CQ and HCQ, but there were no differences in the patients who had been managed successively with both drugs with respect to those managed just with 1 drug.

Because CQ and HCQ are not retained in fatty tissues, we calculated the daily dose per kilogram of ideal weight and looked for its relation with macular sensibility indexes. Our conclusion was that a daily overdose per ideal weight alone cannot explain retinal toxicity (Fig. 2). However, using the cutoff value of toxic doses traditionally considered in medical literature, that is, more than 3 mg/kg/d for CQ and more than 6.5 mg/kg/d for HCQ, we found significant differences in retinal sensitivity between patients overdosed for CQ, but not for those overdosed for HCQ. We also checked whether macular toxicity was influenced by our patients' ages. Three age groups were considered: younger than 40 years, between 41 and 60 years old, and older than 60 years. In our sample, patients older than 60 years receiving treatment with CQ and HCQ presented worse sensitivities in microperimetry indexes. In fact, when the effect of daily dose per ideal weight, months under treatment, and age were considered together, the most important variable that influences macular damage was the patient's age (adjusted R^2 linear regression = 0.6628). Finally, we looked for the effect of the cumulative dose of antimalarials on macular sensibility. Again, we found that patients' indexes AT and MI were worse for higher values of cumulative dose, and that this effect was greater for CQ than for HCQ. When considering a model including cumulative doses, age, and height as explicative covariates, we found that age, height, and cumulative dose of CQ affected AT independently (adjusted R^2 linear regression = 0.3187). Age and cumulative dose of CQ were also related to MI (adjusted R^2 linear regression = 0.6353).

Discussion

The incidence of toxic maculopathy caused by CQ and HCQ varies greatly. More accurate diagnostic methods, or the combination of objective and subjective tests, will allow an earlier diagnosis and probably an increase in the incidence ratios. It must be taken into account that bull's-eye maculopathy is an advanced sign, and that incidence ratios should also include early cases of retinal toxicity. These cases are sometimes difficult to diagnose because pericentral scotomata can be produced by a lot of clinical entities that can damage the macula in addition to or instead of antimalarials. Because retinal damage will not reverse after stopping the drug, the clinician cannot always be sure whether that was the cause of maculopathy.

The appearance of corneal drug deposits in patients taking CQ and HCQ is well known.[1] Confocal microscopy has recently been used to detect these deposits that correlate with high cumulative doses.[12] In this study, we found slit-lamp visible deposits in 3 patients, all 3 taking CQ. Two of them also presented CQ maculopathy.

Table 5—Comparison of macular integrity and fixation stability p1 mean values between cases and control subjects for different ages

	Age, y			
	≤40	40–60	>60	*p*
MI, ± sd				
Cases	5.45 ± 9.57	21.75 ± 23.26	73.61 ± 23.61	< 0.0001
Control subjects	26.38 ± 26.31	50.8 ± 26.12	74.77 ± 23.11	< 0.0001
p	< 0.0001	< 0.0001	0.7842	
FS p1,% ± sd				
Cases	93.68 ± 6.74	90.87 ± 9.68	84.66 ± 17.83	0.0003
Control subjects	92.66 ± 12.01	92.45 ± 8.53	90.42 ± 11.92	0.4148
p	0.6406	0.2521	0.0402	

MI, macular integrity; FS, fixation stability.

Table 6—Differences between average threshold and macular integrity mean values depending on the drug

	HCQ	CQ	CQ → HCQ	*p*
Mean AT ± SD	26.90 ± 2.08	24.96 ± 3.61	26.44 ± 3.06	0.0011
Mean MI ± SD	27.78 ± 31.26	49.97 ± 38.18	36.36 ± 37.56	0.0042

HCQ, hydroxychloroquine; CQ, chloroquine; AT, average threshold; MI, macular integrity.

In this article, we look for differences in global indexes provided by microperimetry between a group of patients taking CQ, HCQ, or both, and a group of untreated persons. We found that the AT of retinal sensitivities at the predetermined points near the foveal centre was significantly lower in cases than in control subjects. This would indicate that antimalarials induce a global hyposensibility at the macula that does not appear in a similar group who never took those tablets. All except 1 of our patients had good BCVA and stable fixation on microperimetry, and the vast majority had no pigmentary changes. This corroborates the fact that a loss of central vision and anatomical changes are advanced signs that should not be used for screening purposes.[4] The other index studied (MI) shows a paradoxical finding, because for individuals younger than 60 years it is significantly higher, that is, more impaired, in control subjects than in patients. To look for some explanation of this result, let us analyze the composition of these 2 groups. In all patients, ≥1 conventional macular perimetry were performed previously because they were included in our clinic's screening program of antimalarial toxicity. The control group included people without any eye disease, so they never underwent visual field testing. It is possible that the learning effect explains, in part, why control subjects have worse MI than patients. Test—retest reliability of macular fundus perimetry was checked by Chen et al.[13] MI uses a neural network multivariate model that includes age, AT value, a measure of points with threshold below 25 dB, and all measured threshold values. MI is a numerical value that describes the likelihood that a patient's responses are normal when compared with age-adjusted normative data. The neural network has been trained on normal and pathologic examinations (age-related macular degeneration). With respect to normative data used in the elaboration of the Macular Integrity Assessment neural network,[14] our patients and control subjects had lower AT. A neural network is a classifier where the aforementioned inputs are used to obtain that likelihood. Unlike other classifiers such as the classical linear discriminant, neural networks are black boxes, and you cannot know which variables are the most discriminative. Furthermore, care should be taken with the training to avoid overlearning, that is, a good performance with the training sample but with a poor generalization with unseen samples. The images of our young control subjects with high MI were revised, and we found that they had a threshold below 25dB in a few points, which probably produced those high MI despite having good AT. Furthermore, in those cases, the MI difference between both eyes was high, which was not so frequent among the patients. Larger prospective studies must be done to validate MI as a good index for evaluating other diseases distinct from age-related maculopathy.

In our sample, mean age and cumulative dose are significantly higher for patients taking CQ and both drugs than in patients who are treated with HCQ only. In Spain, HQC was not available until 2002. Moreover, the first commercially available presentation of HCQ presented some problems of tolerance,[15] and some patients were either switched back to CQ or their physicians postponed the use of HCQ until this problem was solved some years later. This is why in our sample, patients taking HCQ are younger and their cumulative doses are smaller than those treated with CQ. This bias can explain why we found a low incidence of maculopathy in patients taking just HCQ, even though a greater retinal toxicity for CQ has largely been evidenced.[16] However, it has been considered that the increased toxicity rates of CQ could be because of pill size for CQ (250 mg), which makes overdosing much easier than with HCQ.[17] In

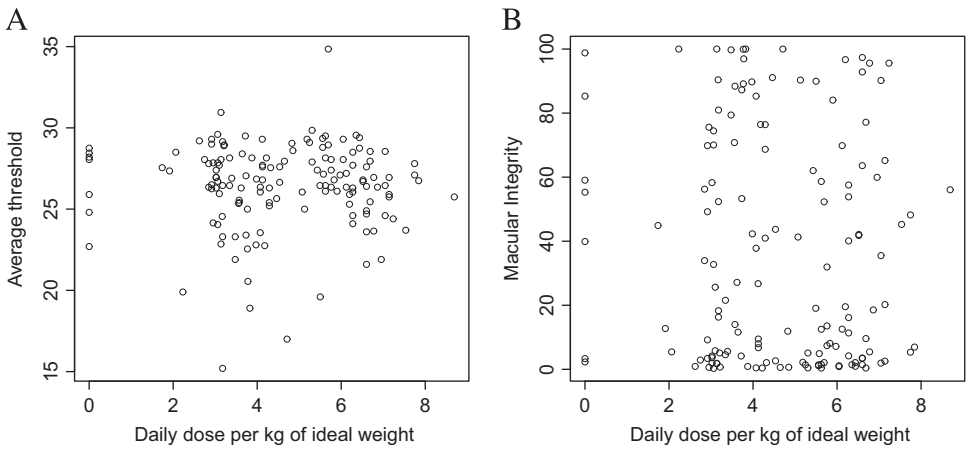

Fig. 2—Daily dose per kilogram of ideal weight versus (A) average threshold and (B) macular integrity.

fact, all patients measuring shorter than 160 cm would be at risk for CQ toxicity because of overdosing.[2] In our study, 80% of patients diagnosed as having toxic maculopathy were overdosed for CQ, and all of them were of short stature.

Because anatomical changes seen on funduscopy appear late, new imaging techniques have been used to improve early diagnosis, such as FAF and SD-OCT. Electrophysiologic tests of retinal function, mainly mfERG, are also considered in early diagnosis or as an additional tool to confirm doubtful cases.[18] However, in a recent article,[19] mfERG failed to detect as much as approximately 28% of individuals with HCQ retinal toxicity. False negatives appear to be even higher for SD-OCT than for mfERG testing. Evidence about the usefulness of FAF in early diagnosis is lacking.[19,20] Macular perimetry, funduscopic examination, and photography continue to provide the highest yields of early cases.[18] It has been recently considered that revised guidelines,[4] emphasizing mfERG, SD-OCT, or FAF, raised screening cost without improving case detection.[17] We believe that fundus microperimetry provides more detailed information about retinal sensibility at the macular area and gives the clinician a precise correlation with anatomical changes. Our results indicate that microperimetry is a very good test to detect early and subtle functional impairment caused by CQ and HCQ.

CQ and HCQ are effective drugs in the management of severe rheumatic disease, but to avoid retinal damage, dosage must be careful, particularly in short patients who are expected to be treated for many years. Advanced age is an important risk factor for toxicity.[18] To the best of our knowledge, this is the first study that uses microperimetry as a screening test for retinal toxicity caused by antimalarials. In fact, this is the first work that uses microperimetry in a sample of more than 200 individuals.

Conclusions

Microperimetry is an accurate tool for detecting early macular damage associated with CQ and HCQ therapy. Patients taking CQ, HCQ, or both show reduced threshold retinal sensibility in the macular area. High HCQ and/or CQ cumulative doses, advanced age, daily CQ overdosing per ideal weight, and short stature are independently associated with worse macular indexes on microperimetry. There are several limitations to this study. Larger prospective studies must be carried out to confirm the presence of macular hyposensibility over time. Future directions will be the description of spatial localization and characterization of early central scotomas induced by CQ and HCQ.

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