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ORIGINAL ARTICLE

Corneal thickness and endothelial changes in long-term hydroxychloroquine use

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ABSTRACT

Objective: To determine possible associations between long-term HCQ use and corneal changes in patients who used HCQ for at least 3 years.

Materials and methods: The study included 62 healthy controls and 62 consecutive patients who used HCQ for the treatment of rheumatologic disease and were referred to the ophthalmology department between August 2018 and November 2018 for HCQ retinal toxicity screening. Central corneal thickness (CCT), corneal endothelial cell density (ECD), the coefficient of variation (CV) of cell size, and the percentage of hexagonal cells (HEX%) were measured to evaluate changes in the cornea.

Results: The mean age of the patient group and control group was 50.10 ± 10.91 and 50.53 ± 10.67 years, respectively. The mean ECD was 2742 ± 347 (cells/mm^2) in the patient group and 2875 ± 188 cells/mm^2 in the control group. There was a significant difference between groups ($p = 0.01$). The mean CCT was 567.05 ± 32.35 μm in the patient group and 540.15 ± 38.50 μm in the control group. CCT was significantly higher in the patient group compared with control group ($p < 0.001$). There was no significant difference between groups in terms of mean CV and HEX values ($p > 0.05$).

Conclusions: Patients using long-term HCQ demonstrated lower ECD and higher CCT than the control group. However, the CV of cell sizes and the HEX % values were not significantly different from the controls.

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Hydroxychloroquine; corneal thickness; endothelial cell density

Introduction

Hydroxychloroquine (HCQ) is a 4-aminoquinoline derivative that has been used to prevent malaria for years. It is a synthetic agent that is used widely in the treatment of diseases, such as rheumatoid arthritis (RA), Sjogren's syndrome (SS), dermatomyositis, systemic lupus erythematosus (SLE), and other rheumatologic and dermatologic diseases due to its anti-inflammatory and immunosuppressive properties[1,2].

Antimalarial agents are usually well tolerated, and the adverse systemic reactions that may cause treatment withdrawal are rarely encountered[3]. Its side effects, such as aquagenic pruritus, gastrointestinal intolerance, and other cutaneous manifestations, usually disappear when the dosage is reduced. These manifestations rarely require discontinuation. The other and rare but potentially severe side effects are retinal, neuromuscular, and cardiac impairments, which suggest toxic side effects[4].

There are several toxic ocular effects associated with the use of HCQ, including keratopathy, lens opacities, dysfunction of the ciliary body, and several types of retinopathy[5]. Toxic effects on the retina can lead to visual impairment, colour-vision abnormalities, and visual field defects[6–8].

According to our knowledge, the association of HCQ on corneal thickness and the endothelium have not been previously studied. In this study, we evaluated the changes in the cornea of HCQ users to determine possible association.

Material and methods

This study was conducted at the Ophthalmology Department of the Kırıkkale University, Medical Faculty. The study was planned according to the Declaration of Helsinki, and permission was received from the local ethics committee.

The study included 62 consecutive patients who used HCQ for at least 3 years for the treatment of rheumatologic diseases (RA, SLE, SS, and ankylosing spondylitis (AS)) and was referred to the ophthalmology department for HCQ retinal toxicity screening and 62 healthy controls. All patients used only HCQ. Exclusion criteria included history of contact lens use, history of previous laser therapy, past ocular surgery, use of antiglaucoma medications or history of glaucoma, history of uveitis, smoking, high refractive errors (spherical refractive error higher than +2 and −2 diopters and cylinder 1 diopters), previous corneal trauma or damage, any ocular or other systemic diseases, and use of the drug.

A complete ophthalmological examination was performed for all participants. Central corneal thickness (CCT) and corneal endothelial cell density (ECD) were measured to

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evaluate changes in the cornea. Also, all patients were evaluated with optical coherence tomography and visual field tests for possible HCQ toxicity. All the measurements were performed by the same observer (Akbulut Y).

A handheld pachymeter (İpac, Reichert, Inc. Depew, NY, USA) was used to measure CCT. A noncontact specular microscope (Noncon Robo SP8000 Konan Medical (No statistically significant differences in repeatability were observed[9]), Hyogo, Japan) was used to measure ECD. We used the centre method, which is a common technique in specular microscope. In this method, the computer mouse is used to place a dot at the centre of the captured specular microscope digital cell image. A cluster of adjacent cells grouped in a circle or rectangle is entered with dots[10]. The best technical quality image among three images was analysed. All corneal endothelial cells that were visible on the image were marked manually. At least 100 cells per measurement were included in each analysis. The percentage of hexagonal cells (HEX %) (Index of pleomorphism) and the coefficient of variation (CV) of the cell size were also included for analyses. Quantitative analysis of the corneal endothelial cells was performed using the variable frequency method of analysis. A single assistant performed all the corneal measurements between 13:30 and 16:00.

The calculated power (1-beta) is 1 considering type 1 error (alfa) of 0.05, sample size of 62 in each group, effect size of 2.61 for ECC, and two-sided alternative hypothesis (H1). All statistical analyses were performed with SPSS (Statistical Package for the Social Sciences) version 18 (SPSS Inc., Chicago, IL). Right eye per subject was selected for the analyses. p Values less than 0.05 were considered significant. The Kolmogorov–Smirnov test was used to confirm data normality, and the independent t-test and Welch's t-test were used to compare variables between groups.

Results

Patients group included 6 (9.7%) males and 56 (90.3%) females, and control group included 5 (8.1%) males and 57 (91.9%) females. The mean ages of the study and control group were 50.10 ± 10.91 (28–69) years and 50.53 ± 10.67 (26–70) years, respectively. There were no statistically significant differences between the groups in terms of age ($p = 0.823$) and gender ($p = 0.752$). The mean duration of the HCQ treatment of patients was 5.97 ± 4.59 years. The distribution of diseases was as follows: 51 (82.3%) RA, 5 (8.1%) SLE, 4 (6.5%) SS, and 2 (3.2%) AS. Demographics and clinical characteristics of the groups are presented in Table 1.

The median daily dose of HCQ was 4.8 mg/kg and the median cumulative dose was 489 g.

The ECD, CV, HEX%, and CCT values for the two groups are shown in Table 2. The mean ECD was 2742 ± 347 (667–3165) (cells/mm^2) in the patient group and 2875 ± 188 (2451–3300) cells/mm^2 in the control group. There was a significant difference between groups ($p = 0.01$). The mean CV was 31.87 ± 8.27 (24–69) and 31.76 ± 4.26 (25–44) in the patient and control groups, respectively ($p > 0.05$). No significant difference was present between the patient and the control groups in terms of mean CV value. The mean HEX% values were 46.06 ± 7.12 (32–62) in the patient group and 45.37 ± 6.70 (28–58) in the control group. There was no significant difference between groups in terms of mean HEX value ($p = 0.578$). The mean CCT was 567.05 ± 32.35 (501–650) μm in the patient group and 540.15 ± 38.50 (460–606) μm in the control group. CCT was significantly higher in the patient group compared with the control group ($p < 0.001$).

There was no correlation between the duration of HCQ use and increased CCT and decreased ECD ($p = 0.310$). The mean ECD, CCT, CV, and HEX% values in patients with RA were 2722 ± 373 (667–3165), 562.55 ± 31.34 (501–647), 32.22 ± 8.98 (24–69), and 45.76 ± 7.47 (32–62), respectively. The statistical difference was similar with all patients enrolled in the evaluation.

Mean foveal thickness (FT) was 233.40 ± 14.8 (205–261) and 235.65 ± 13.5 (215–258) and mean retinal nerve fiber layer (RNFL) was 104.7 ± 12.1 (83–132) and 107.3 ± 13.7 (81–143) in patients and control group, respectively. There was not a significant difference between groups in terms of mean FT and RNFL values ($p > 0.05$). None of the patients had retinal toxicity.

Table 1. Demographic and clinical characteristics of groups.

	HCQ	Control	p Value
Age mean ± SD	50.10 ± 10.91	50.53 ± 10.67	0.823
Gender n (%)			0.752
Male	6 (9.7)	5 (8.1)	–
Female	56 (90.3)	57 (91.9)	–
Duration of HCQ treatment mean ± SD	5.97 ± 4.59	–	–

No: number; SD: standard deviation; HCQ: Hydroxychloroquine.

Table 2. Changes of corneal endothelial cell parameters in patients group and controls.

	HCQ	Control	p Value
ECC cell/mm^2 mean ± SD	2742 ± 347	2875 ± 188	0.01
CV% mean ± SD	31.87 ± 8.27	31.76 ± 4.26	0.924
HEX% mean ± SD	46.06 ± 7.12	45.37 ± 6.70	0.578
CCT μm mean ± SD	567.05 ± 32.35	540.15 ± 38.50	<0.001

ECC: endothelial cell count; CV: coefficient of variation; HEX: % of hexagonal cells; CCT: central corneal thickness; SD: standard deviation; HCQ: hydroxychloroquine.

Discussion

This study showed that long-term HCQ use is associated with a substantial change in corneal ECD values compared with the healthy controls. In particular, it is associated with elevated corneal thickness. No significant differences were found between CV and HEX%.

Chronic diseases require regular and longitudinal care and long-term medication[11]. Usually, the agents used in the treatment of many chronic diseases are proven and essential for effective treatment. These agents may have systemic or local side effects as well as their benefits. Some of these may be either dose-dependent and reversible or independent and irreversible. They remain popular in the treatment of chronic diseases because of the lack of alternative options and their proven efficacy despite the side effects.

Rheumatologic diseases are some of the most important diseases among chronic and progressive systemic disorders. Their treatment is usually long-term or lifelong. The most widely used, effective, and popular treatment for autoimmune and rheumatic diseases is HCQ[12].

In the early 1950s, acceptance of HCQ, as well as chloroquine (CQ), increased for the treatment of both dermatologic and rheumatologic diseases[13]. Headache, skin rash, and gastrointestinal upset are the common side effects of HCQ, but the major concern is ocular side effects[13,14]. Ocular side effects of HCQ include lens opacities, ciliary body involvement, retinopathy, and consequent permanent visual loss[15]. It has also been associated with keratopathy[15].

Corneal deposits are one of the first signs of HCQ toxicity. These deposits are composed of antimalarial salts limited to the corneal epithelium[16,17]. Their presence is associated with high doses of HCQ and may appear as early as 2–3 weeks from initiation of the treatment and is completely reversible upon discontinuation of the offending HCQ[18,19]. Corneal deposits have decreased due to lower doses of HCQ and use of HCQ instead of CQ.

Keratopathy seems to be much less frequent with HCQ than with CQ[16]. In a large series study, corneal changes were observed in only 6 subjects among 758 patients on HCQ[20]. In another study, it was suggested that HCQ induced corneal inclusion bodies, which were visualized by *in vivo* confocal miscroscopy[21].

Endothelial cell analysis is important to evaluate corneal function and viability. Endothelial cell layers can be affected by several factors, including corneal degeneration, dystrophy trauma, infection, cataract surgery, or drug toxicity, which may lead to loss of corneal transparency[22]. Endothelial cells have no mitotic activity. Therefore, the effects on the corneal endothelial cells can be irreversible even if patients stop using drug.

In our study, we evaluated the CCT and ECD of the cornea with noncontact specular microscopy, which is a noninvasive method for evaluating healthy endothelial cells. A significant decrease in ECD was found in patients who used HCQ, compared with healthy subjects. The reduction of ECD in HCQ users may occur due to endothelial cell death. For that reason, we think that the loss of endothelial cells may be associated with the long term HCQ use. This study advises that sustained use of HCQ may cause corneal changes.

The exact mechanism of the ocular effects of HCQ is indefinite. The direct pharmacological effect of the drug may play a role in these effects[16]. The main theories about the effects on the retina include disturbing the metabolism of the retinal pigment epithelium and binding to melanin in the retinal pigment epithelium[16,23]. A recent study evaluated subclinical aqueous humour flare and cellularity with laser flare-cell photometry in patients using HCQ for rheumatoid arthritis and found that higher laser flare-cell photometry values correlated with higher cumulative doses of HCQ[14]. They hypothesized that HCQ, binding to melanin in iris pigment epithelial cells and breakdown of the blood-retinal barrier can lead to a flare. In addition, we think that HCQ may penetrate into the anterior chamber of the eye after systemic administration, which can lead to corneal changes. Also, a chronic flare reaction within the anterior chamber might act on the corneal endothelium directly.

We found no significant change in HEX% and CV, though there was a significant reduction in ECD in patients using HCQ. Even though ECD was found to be decreased in the HCQ group, it is still in the normal ranges of the age group. Even the difference in ECD counts was very small and of unclear clinical importance.

Similiar values of HEX% and CV in both groups may be due to the preservation of cellular migration and enlargement in the patients taking HCQ. In the patient's group, CCT was significantly increased. A question might come to mind that what is the mechanism of increased CCT even so there was no difference HEX% and CV between the groups. We think it related with the other corneal layer which *in vivo* confocal microscopy showed the presence of CQ deposits in epithelium and anterior stroma[21]. Also, it is possibly because of inhibition of leukocyte replication and release of inflammatory mediators on the ocular surface protecting against collagenolysis[24].

One limitation of the study is that we excluded only high refractive errors, but even small amounts of myopia can lead to changes in CCT[25]. However, most of the patients in our study group had emmetropic eyes. The other limitation of the study is the selection of a heterogeneous group of rheumatological diseases and the absence of a control group with a diagnosis of rheumatological disease but without the use of HCQ. The differences in ECD and CCT might be related to the use of HCQ or the disease process alone. Since HCQ is part of the initial treatment protocols for many rheumatic diseases. Nowadays, it is not possible to create a group of RA, SLE, Sjogren's, or AS patients who do not use any HCQ. However, Villani et al. showed decreased CCT in patients with RA and Heinke et al. reported no change in the ECD of patients with RA, which supports our findings[26,27].

As far as we know, this is the first report showing the association of HCQ on corneal thickness and corneal endothelial layers. No effect was demonstrated but only an association between HCQ and decreased ECD. Also, we found that the CCT increased, but cell morphology did not change in patients using long-term HCQ. This study also revealed that corneal examinations including noncontact specular microscopy and pachymetry may be considered in patients using long-term HCQ. Further studies are required for the possible association of HCQ on the cornea.

Disclosure statement

The authors report no declarations of interest. The authors alone are responsible for the content and writing of this article.

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