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Possible Adverse Effects of Long-Term Use of Hydroxychloroquine on Corneal Endothelium

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Abstract

Background: Hydroxychloroquine (HCQ) is a less toxic metabolite of chloroquine which is used to treat rheumatic diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and Sjogren's syndrome. It can cause corneal deposits, ciliary body dysfunction, posterior subcapsular lens opacity, and most important, irregularity in the macular pigmentation in the early phase, a ring of macular pigment dropout in the advanced stage, and peripheral bone spicule formation, vascular attenuation, and optic disc pallor in the end stage. The American Academy of Ophthalmology recommendations for screening that were published in 2016 recommended the use of both automated visual field and SD-OCT for routine primary screening.

Aim of Study: Detection of possible adverse effects of long term hydroxychloroquine use on corneal endothelium in patients of rheumatological diseases who used the drug for at least three years.

Patients and Methods: This study included 30 eyes of 15 patients with rheumatological diseases who used hydroxychloroquine for at least 3 years. The control group included 30 eyes of 15 persons with normal healthy corneas. The participants were gathered from Rheumatology and Ophthalmology Outpatient Clinics of Ain-Shams University Hospital in the period from December 2019 till May 2020.

Results: The study assessed 60 eyes by specular microscopy, 30 eyes of patients of rheumatological diseases representing the study group and 30 eyes of normal healthy individuals representing the control group. The study revealed a highly significant change in coefficient of variation (CV) in patients who used HCQ for at least 3 years.

Conclusion: The present study revealed that there was a highly significant change in coefficient of variation (CV) in patients who used HCQ for at least 3 years. The study revealed a new ocular adverse effect of long term use of HCQ on corneal endothelium.

Key Words: *Hydroxychloroquine – Rheumatoid arthritis.*

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Introduction

THE cornea is a transparent avascular tissue that acts as a structural barrier and protects the eye against infections. Along with the tear film, it provides proper anterior refractive surface for the eye. The cornea contributes to two thirds of the refractive power of the eye **[1]**.

The cornea is formed of six layers which are epithelium, Bowman's Layer, stroma, Descemet's membrane, Dua's layer and endothelium. Dua's layer is a well defined, acellular and a strong layer in pre-Descemet's cornea which has gotten a great attention with the develop ment of lamellar keratoplasty surgeries. This layer has a range of thickness from 6.30 to 15.83 gm **[2]**.

The endothelium is a single layer, five gm thick structure. The cells are hexagonal and metabolically active. There is an endothelial pump which regulate water content of the cornea. The lateral membrane contains the highest density of Na+ K+ATPase pump sites. The two most important ion transport systems are the membrane bound Na+ K+ ATPase pump and the intracellular carbonic anhydrase pathway. Activity of both these systems produces the net flux of ions from stroma to aqueous leaving the stroma relatively dehydrated to keep its transparency. Endothelial cell density continues to change throughout life. Human central endothelial cell density decreases at an average of approximately of 0.6% per year in normal corneas throughout adult life. Endothelial cells compensate for this decline in cell number by polymegathism and pleomorphism as they lack the ability of regeneration **[3]**.

Hydroxychloroquine is an antimalarial drug commonly used in autoimmune rheumatological diseases such as systemic lupus erythematosus and

rheumatoid arthritis as immunomodulatory drug. Its action is mediated by several mechanisms. Despite the beneficial effect of hydroxychloroquine in preventing systemic lupus flares and reducing mortality, it has a toxic effect on retina and possibly on corneal endothelium. These effects may be related to the dose and the duration of drug therapy. There is no specific treatment for retinal toxicity other than cessation of treatment. Screening tests for retinal toxicity is important in early detection of toxicity and preventing irreversible vision loss [4].

Hydroxychloroquine may precipitate in corneal epithelium in a diffuse or whorl-like pattern causing vortex keratopathy or cornea verticillata. These precipitates are usually asymptomatic. This effect is much less with hydroxychloroquine than chloroquine [5].

Aim of the work:

Detection of possible association between long term hydroxychloroquine use on corneal endothelium in patients of rheumatological diseases who used the drug for at least three years.

Patients and Methods

Patients:

This study included 30 eyes of 15 patients with rheumatological diseases who used hydroxychloroquine for at least 3 years. The control group included 30 eyes of 15 persons with normal healthy corneas. The participants were gathered from Rheumatology and Ophthalmology Outpatient Clinics of Ain-Shams University Hospital in the period from December 2019 till May 2020.

The nature of the procedures was explained to the participants in details and a written informed consent was given by all participants. The study was consistent with the principles of Ain Shams University Ethical Commitee.

Inclusion criteria of the study group: Patients of rheumatological diseases who under hydroxychloroquine therapy for at least three years. Patients who can cooperate with ophthalmological examination.

Exclusion criteria of all participants: Any previous ocular trauma or surgery. Corneal lesions like scars, degenerations or dystrophies, glaucoma or cataract.

Methods:

All participants were subjected to history taking including the general, medical and the ocular morbidity. Complete ophthalmological examination was carried out including uncorrected and best corrected visual acuities, slit lamp biomicroscopy, IOP measurement and fundus examination.

All participants underwent specular microscopy for central corneal endothelium.

Specular microscopy procedure: Each participant was comfortably seated and positioned with her chin resting on the chin rest and her forehead supported against the forehead rest. The chin rest was adjusted, so that the participant's lateral canthus align with the black mark on the forehead rest shaft. The participant's eye was observed and brought into focus using joystick of the specular microscope. A perfectly focused image of corneal endothelium was taken and printed out for documentation and further analysis.

Statistical analysis of the collected data:

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done: Paired sample *t*-test of significance was used when comparing between related samples.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *p*-value was considered significant when:

- *p*-value <0.05 was considered significant.
- *p*-value <0.01 was considered as highly significant.
- *p*-value >0.05 was considered insignificant.

Results

The mean age of participants was 31.53 SD ± 6.32 years. All participants were females (Table 1).

Table (1): Demographic data of the studied cases.

	Total No.=30
Age:	
Mean ± SD	31.53±6.32
Range	22-43
Sex:	
Females	30 (100.0%)

SD: Standard deviation. No: Number.

There was no statistically significant difference between the study and the control groups regarding mean age with *p*-value=0.094 (Table 2).

Table (2): Comparison between the study and the control groups regarding demographic data.

	Study group No.=15	Control group No.=15	Test value	*p*-value	Sig.
Age:					
Mean ± SD	33.47±7.16	29.60±4.84	–1.733•	0.094	NS
Range	22-43	23-39			
Sex:					
Females	15 (100.0%)	15 (100.0%)	–	–	–
Dose of HCQ (mg/day):					
Mean ± SD	400.00±0.00	–	–	–	–
Range	400-400	–			
Duration of HCQ intake (years):					
Mean ± SD	7.33±4.47	–	–	–	–
Range	3-18	–			

p-value >0.05: Non significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
•: Independent *t*-test.
SD : Standard deviation.
HCQ: Hydroxychloroquine.
No: Number.
Sig: Significance.
NS: Not significant.

There was a highly statistically significant difference between the study and the control groups regarding mean BCVA with *p*-value=0.006 (Table 3).

Table (3): Comparison between the study and the control group regarding BCVA.

BCVA	Study group No. = 30	Control group No. = 30	Test value	*p*-value	Sig.
Mean ± SD	0.86±0.27	1.00±0.00	2.864•	0.006	HS
Range	0.25-1	1-1			

p-value >0.05: Not significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
•: Independent *t*-test.
BCVA: Best corrected visual acuity.
SD: Standard deviation.
No: Number.
Sig: Significance,
HS: Highly significant.

There was a highly statistically significant difference between the study and the control groups regarding CV. There was no statistically significant difference between the two groups regarding the other parameters (Table 4).

There was a statistically significant difference in IOP between the study and the control groups (Table 5).

There was no statistically significant difference between the study and the control groups regarding posterior segment examination (Table 6).

There was no statistically significant difference in errors of refraction between the study and the control groups (Table 7).

Table (4): Comparison between the study and the control group regarding results of specular microscopy.

Results of specular microscopy	Study group No. = 30	Control group No. = 30	Test value	*p*-value	Sig.
CCT:					
- Mean ± SD	534.80±38.14	545.60±36.76	1.117•	0.269	NS
- Range	478-608	483-676			
CD:					
- Mean ± SD	2850.87±298.35	2961.67±303.66	1.426•	0.159	NS
- Range	2214-3407	2468-3584			
CV:					
- Mean ± SD	30.73±5.48	26.90±3.72	–3.172•	0.002	HS
- Range	19-42	20-34			
HEX %:					
- Mean ± SD	65.57±5.53	66.77±4.42	0.929•	0.357	NS
- Range	55-76	59-78			

p-value >0.05: Not significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
•: Independent *t*-test.
CCT: Central corneal thickness.
CD: Cell density.
CV: Coefficient of variation,
HEX%: Percentage of hexagonal cells.
SD: Standard deviation.
No: Number.
HS: Highly significant.
NS: not significant.

Table (5): Comparison between the study and the control group regarding IOP.

IOP measured by GAT. (mmHg)	Study group No.=30	Control group No.=30	Test value	*p*-value	Sig.
Mean ± SD	15.47±2.10	14.40±1.77	–2.128•	0.038	S
Range	12-18	12-18			

p-value >0.05: Not significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
• : Independent *t*-test.
IOP : Intraocular pressure.
GAT : Goldmann applanation tonometry.
No. : Number.
Sig : Significance,
S : Significant.

Table (6): Comparison between the study and the control groups regarding posterior segment examination.

Examination of posterior segment	Study group No.=30	Control group No.=30	Test value	*p*-value	Sig.
Normal	25 (83.3%)	30 (100.0%)	5.455*	0.065	NS
Abnormal foveal reflex	3 (10.0%)	0 (0.0%)			
Tilted disc	2 (6.7%)	0 (0.0%)			

p-value >0.05: Not significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
*: Chi-square test.
No: Number.
Sig: Significance.
NS: Not significant.

Table (7): Comparison between the study and the control groups regarding errors of refraction.

BCVA	Study group No.=30	Control group No.=30	Test value	*p*-value	Sig.
Sphere:					
Mean ± SD	–0.53±1.35	–0.97±0.89	–1.872≠	0.061	NS
Range	–3.5-3	–2.5-0			
Cylinder:					
Mean ± SD	–0.52±0.82	–0.22±0.41	–1.863≠	0.063	NS
Range	–3.25-0	–1.5-0.5			
Axis:					
Mean ± SD	85.26±55.99	91.36±34.86	–0.259≠	0.795	NS
Range	5-175	35-180			

p-value >0.05: Not significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
≠: Mann-Whitney test.
BCVA: Best corrected visual acuity.
No: Number.
Sig: Significance.
NS: Not significant.

There was a negative correlation between CCT and sphere with *p*-value=0.010 and *r*=–0.462. There was no correlation between CCT and the other parameters (Table 8).

Table (8): Correlation between CCT and other studied parameters in the study group.

	CCT	
	r	*p*-value
CD	0.017	0.927
CV	–0.266	0.155
HEX %	0.194	0.304
Age	–0.188	0.503
Duration of HCQ intake (years)	0.120	0.671
BCVA	0.178	0.346
IOP measured by GAT. (mmHg)	0.100	0.599
Sphere	–0.462*	0.010
Cylinder	–0.153	0.419
Axis	0.012	0.962

p-value >0.05: Not significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
* : Spearman correlation coefficient.
CCT : Central corneal thickness.
CD : Cell density.
HEX% : Percentage of hexagonal cells.
HCQ : Hydroxychloroquine.
BCVA : Best corrected visual acuity.
IOP : Intraocular pressure.
GAT : Goldmann applanation tonometry.

There was a negative correlation between CD and CV with *p*-value=0.007 and *r*=–0.480 (Table 9). Also, there was a negative correlation between CD and age with *p*-value=0.017 and *r*=–0.605 (Table 9). While there was no correlation between CD and the other parameters in the study group.

Table (9): Correlation between CD and other studied parameters in the study group.

	CD	
	r	*p*-value
CCT	0.017	0.927
CV	–0.480**	0.007
HEX %	–0.258	0.169
Age	–0.605*	0.017
Duration of HCQ intake (years)	0.187	0.504
BCVA	0.134	0.480
IOP measured by GAT. (mmHg)	–0.237	0.208
Sphere	0.308	0.097
Cylinder	0.090	0.635
Axis	–0.161	0.510

p-value >0.05: Not significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
* : Spearman correlation coefficient.
CCT : Central corneal thickness.
CD : Cell density.
HEX% : Percentage of hexagonal cells.
HCQ : Hydroxychloroquine.
BCVA : Best corrected visual acuity.
IOP : Intraocular pressure.
GAT : Goldmann applanation tonometry.

There was a negative correlation between CV and CD with *p*-value=0.007 and *r*=–0.480 (Table 10). Also, there was a negative correlation between CV and HEX % with *p*-value=0.022 and *r*=–0.417 (Table 10). There was no correlation between CV and the other parameters.

Table (10): Correlation between CV and other studied parameters in the study group.

	CV	
	r	*p*-value
CCT	–0.266	0.155
CD	–0.480**	0.007
HEX %	–0.417*	0.022
Age	0.357	0.191
Duration of HCQ intake (years)	–0.060	0.831
BCVA	–0.148	0.436
IOP measured by GAT. (mmHg)	0.292	0.117
Sphere	0.072	0.706
Cylinder	–0.242	0.197
Axis	0.180	0.461

p-value >0.05: Not significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
* : Spearman correlation coefficient.
CCT : Central corneal thickness.
CD : Cell density.
HEX% : Percentage of hexagonal cells.
HCQ : Hydroxychloroquine.
BCVA : Best corrected visual acuity.
IOP : Intraocular pressure.
GAT : Goldmann applanation tonometry.

There was a negative correlation between HEX % and CV in the study group with *p*-value=0.022 and *r*=–0.417 (Table 11). There was no correlation between HEX % and the other parameters.

Table (11): Correlation between HEX % and other parameters in the study group.

	HEX%	
	r	*p*-value
CCT	0.194	0.304
CD	–0.258	0.169
CV	–0.417*	0.022
Age	0.009	0.974
Duration of HCQ intake (years)	0.110	0.696
BCVA	0.144	0.447
IOP measured by GAT. (mmHg)	–0.124	0.513
Sphere	–0.193	0.307
Cylinder	0.196	0.298
Axis	–0.021	0.933

p-value >0.05: Not significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
* : Spearman correlation coefficient.
CCT : Central corneal thickness.
CD : Cell density.
HEX% : Percentage of hexagonal cells.
HCQ : Hydroxychloroquine.
BCVA : Best corrected visual acuity.
IOP : Intraocular pressure.
GAT : Goldmann applanation tonometry.

Case (1): A 40-year-old female patient is under hydroxychloroquine therapy 400mg per day for 4 years. Her BCVA in RT eye was 6/6 by a refraction of – 0.50X180 and in Lt eye 6/6 unaided. Her CD in the Rt eye (2925 cells/mm^2) and in the Lt eye (2748) are normal according to her age **[6,7,8]**. Her CV, HEX% and CCT in the Rt eye are 29%, 63% and 557 [illegible] respectively. Her CV, HEX% and CCT in the Lt eye are 33%, 68% and 564 [illegible] respectively. All these parameters in both eyes are normal (Fig. 1) **[7,9]**.

CV values >40% are abnormal, HEX% <50% is considered clinically significant pleomorphism and the mean value of CCT in normal eyes is 554.78±32.61.

Control (1): A 27-year-old female has no significant medical or surgical history. Her unaided VA was 6/6 in both eyes. Her CD in the Rt eye (2832 cells/mm^2) and in the Lt eye (2766) are normal according to her age **[6,7,8]**. Her CV, HEX% and CCT in the Rt eye are 28%, 67% and 555 [illegible] respectively. Her CV, HEX% and CCT in the Lt eye are 25%, 71% and 565 [illegible] respectively All these parameters in both eyes are normal (Fig. 2). **[7,9]**.

CV values >40% are abnormal, HEX% <50% is considered clinically significant pleomorphism and the mean value of CCT in normal eyes is 554.78±32.61.

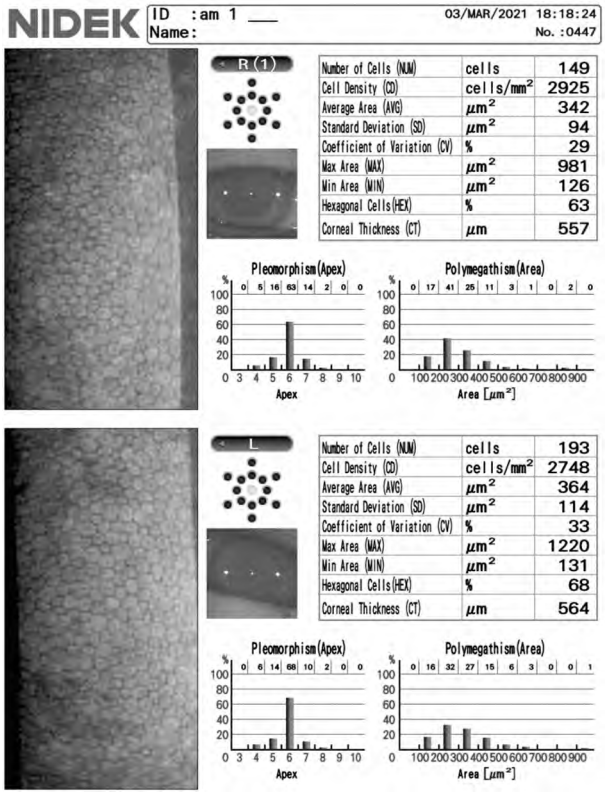

Fig. (1).

CCT: Central corneal thickness, CD: Cell density, CV: Coefficient of variation, HEX%: Percentage of hexagonal cells, BCVA: Best corrected visual acuity.

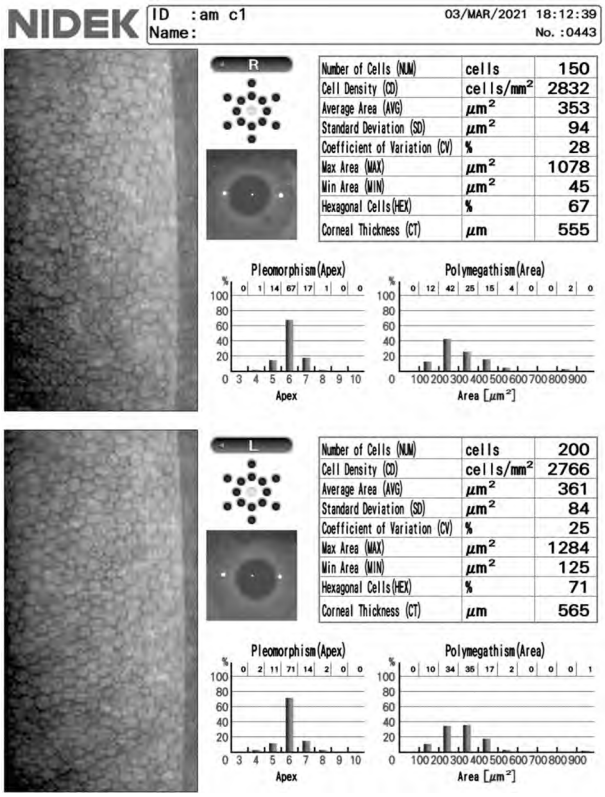

Fig. (2): Control (1).

CCT: Central corneal thickness, CD: Cell density, CV: Coefficient of variation, HEX%: Percentage of hexagonal cells.

Discussion

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 [10].

Ocular side effects of HCQ include lens opacities, ciliary body involvement, retinopathy, and consequent permanent visual loss. It has also been associated with keratopathy [11].

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 [5]. 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 [5,12].

Corneal deposits are one of the first signs of HCQ toxicity. These deposits are composed of antimalarial salts limited to the corneal epithelium [5,13]. 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 [14,15].

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 [16].

This study included 30 eyes of patients with rheumatological diseases representing the study group and 30 eyes of normal healthy individuals representing the control group. We evaluated the CCT, CD, CV and HEX % of the corneal endothelium with noncontact specular microscopy.

The highly statistically significant difference between the study and the control groups regarding mean BCVA (p-value=0.006) can be explained by presence of tilted discs and abnormal foveal examination in 5 cases of the study group.

A statistically significant increase in IOP was found in patients (mean ± SD 15.47±2.10) who used HCQ compared with healthy subjects (Mean ± SD 14.40± 1.77). This can be explained by concurrent use of oral steroids in their protocols of treatment.

A negative correlation between CD and CV in the study group was found with p-value=0.007 and r=–0.480. Also, there was a negative correlation between CD and age with p-value=0.017 and r= –0.605. These results are due to decreased CD with aging and pleomorphism (increased CV) occurs as cells try to compensate for cell death to maintain their barrier function.

The negative correlation between CV and HEX% in the study group occurs as cell death leads to decreased HEX% and pleomorphism (increased CV) occurs as cells try to compensate for cell death by increasing their sizes.

A statistically significant increase in CV was found in patients (mean ± SD 30.73±5.48) who used HCQ compared with healthy subjects (Mean ± SD 26.90±3.72). Different values of CV in both groups may be due to the preservation of cellular migration and enlargement of physiologically stressed endothelial cells in the patients taking HCQ. Polymegathism is the first sign of physiologically stressed endothelial cells.

There was no significant difference between the two groups regarding mean HEX% with mean HEX% 65.57±5.53% and 66.77±4.42% for the study and control groups respectively. Also there was no statistically significant difference between the two groups regarding mean CCT with mean CCT 534.80±38.14 and 545.60±36.76 for the study and control groups respectively. There was no statistically significant difference between the two groups regarding mean CD with mean CD 2850.87 ±298.35 and 2961.67±303.66 for the study and control groups respectively. All these results can be explained by physiological stress of endothelium that is still viable and maintain its barrier function so, CCT, CD and HEX% are still within normal range.

Another study was done by Tevfik et al., [17] Both studies used sample of population with females representing the main bulk of the study. This can be explained by high prevalence of autoimmune diseases among females.

However, regarding CV, Tevfik et al., [17] showed no statistically significant difference between the study and the control groups.

Tevfik et al., [17] showed no statistically significant difference between the two groups with mean HEX% 46.06±7.12% and 45.37±6.70% for the study and control groups respectively but the absolute values are much lower than that obtained in our study. This can be explained by high mean

age of study and control groups in the this study with mean age 50.10±10.91 years and 50.53±10.67 years for study and control groups respectively.

A statistically significant difference in this study regarding CD and CCT between the two groups was explained by long duration of hydroxychloroquine intake with long term physiological stress of endothelium and eventual cell loss with decreased cell density. Decreased CD and impaired endothelial function may be the cause of increased CCT. Despite longer mean duration of HCQ intake in our study compared to the other study, CD showed no statistically significant difference. Also, there is no change in CCT.

This discrepancy of results makes the role of HCQ in these changes unclear.

Limitation of the study is the selection of a heterogenous 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 CV 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. There is another limitation which is concurrent use of other immunosuppressives. Further studies are required for the possible association between HCQ and corneal changes.

Conclusion:

The present study revealed that there was a highly significant change in coefficient of variation (CV) in patients who used HCQ for at least 3 years. The study revealed a new ocular adverse effect of long-term use of HCQ on corneal endothelium.

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دراسة الاثار الجانبية المحتملة لعقار الهيدروكسى كلوروكين نتيجة استخدامه لفترة ثلاث سنوات أو أكثر على الطبقة المبطنة للقرنية

أن الهدف من هذا العمل هو دراسة الأثار الجانبية المحتملة لعقار الهيدروكسى كلوروكين نتيجة استخدامه لفترة ثلاث سنوات أو أكثر على الطبقة المبطنة للقرنية.

الهيدروكسى كلوروكين هو عقار مضاد للملاريا ولكن يتم استخدامه كعقار معدل للمنا عة لعلاج الأمراض المناعية ومنها الروماتيزمية حيث يعمل على منع انتكاسات المرض وتقليل معدل الوفيات يتسبب هذا العقار فى آثارجانبية على شبكية العين والغشاء الطلائى للقرنية بالإضافة لأثار جانبية محتملة على الطبقة المبطنة لقرنية العين وهو ما تسعى الدراسة لإثباته نتيجة استخدام العقار لمدة ثلاث سنوات أو أ كثر.

الهيدروكسى كلوروكين كما اسلفنا عقار له العديد من الاثار الجانبية على العين مثل ترسبه فى الغشاء الطلائى للقرنية لكن هذا التأثير محدود فى تأثيره على النظر ويذهب مع توقف تناول الدواء. التأثير الهام لهذا العقار يكمن فى تأثيره على شبكية العين نتيجة الاستخدام لمدة طويلة ولذلك هناك العديد من الاختبارات لإكتشاف هذا التأثير قبل أن يتفاقم. ليس هناك علاج لهذا الأثر الجانبى سوى توقف تناول الدواء.

لقد بنى البحث على دراسة ٣٠ عيناً لمرضى الأمراض الروماتيزمية الذين يتناولون عقار الهيدوركسيكلوروكين كجزء من برنامجهم العلاجى لفترة ثلاث سنوات أو أكثر ومقارنة نتيجة تلك الدراسة بنتيجة دراسة ٣٠ عيناً لأشخاص بيعين يمثلون الحالات المحكمة. يتم إخضاع كل المشتركين فى البحث لفحص عيون إكلينيكى شامل بجانب تصوير القرنية بإستخدام الجهاز المبنى على ظاهرة انعكاس الضوء. يتم مقارنة النتائج والتعبير عنها باستخدام الوسائل الإحصائية المعبرة. لقد سجلت الإحصاءات من واقع سجلات المرضى ارتفاع معدل الأختلاف فى حجم الخلايا المبطنة للقرنية Cooefficient of variation فى المرضى عنها فى الحالات المحكمة مع عدم وجود إختلافات تذكر فى باقى النتائج.