Effect of Hydroxychloroquine Therapy Duration on Retinal Pigment Epithelium in Rheumatological Diseases by Optical Coherence Tomography. A Systematic Review and Meta-Analysis

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Abstract

**Background:** Hydroxychloroquine is used increasingly in the management of a variety of autoimmune disorders. However, Hydroxychloroquine has been associated with irreversible visual loss due to retinal toxicity. Cessation of the use of hydroxychloroquine at an early stage of damage might prevent functional loss; however, after maculopathy has developed, cessation of the drug does not show clinical recovery. Because discontinuation of therapy may reverse retinal toxicity, early detection of toxicity changes is important.

**Aim of Study:** To find a relationship between duration of hydroxychloroquine therapy in rheumatological diseases and retinal pigment epithelium changes by optical coherence tomography.

**Material and Methods:** Medical data bases and Cochrane Library were searched for studies from 2011 until 2021. The primary outcome was Retinal Pigment Epithelium thickness, the secondary outcome was Outer Retinal Thickness and the third outcome was full retinal thickness but unfortunately we didn’t find enough papers for the first two outcomes so, our outcome will be the full retinal thickness at central macula in its four quadrants: Superior, inferior, nasal and temporal difference between hydroxychloroquine drug users of rheumatological patient in different duration of therapy and healthy controls using optical coherence tomography.

**Results:** Five trials (cross-sectional studies) involved studies and they show in superior quadrant of central macular thickness difference between HCQ users and controls as: Cohran Q = 8.577135 (df = 4) p = 0.0726 and Moment-based estimate of between studies variance = 16.257044, $I^2$ (inconsistency) = 53.4% (95% CI = 0% to 80.9%), the inferior quadrant of central macular thickness difference as: Cohran Q = 7.759158 (df = 4) p = 0.1008 and Moment-based estimate of between studies variance = 15.932414, $I^2$ (inconsistency) = 48.4% (95% CI = 0% to 79.4%),while nasal quadrant of central macular thickness difference was: Cohran Q = 14.113529 (df = 4) p = 0.0069 and Moment-based estimate of between studies variance = 37.768684, $I^2$ (inconsistency) = 71.7% (95% CI = 0% to 86.8%) and the temporal quadrant of central macular thickness difference between HCQ users and controls was: Cohran Q = 29.001671 (df = 4) p < 0.0001, Moment-based estimate of between studies variance = 86.284155, $I^2$ (inconsistency) = 86.2% (95% CI = 65.5% to 92.3%).

**Conclusion:** OCT enables quantitative evaluation of the central macular thickness in rheumatological eyes under treatment of hydroxychloroquine and it has demonstrated the ability of OCT to detect early changes in hydroxychloroquine users group as compared to control group by finding significant thinning between thomas found in three studies and decrease inner retinal layers thickness and no changes in outer retinal layers thickness as in one study and no difference in central macular thickness between cases and controls in another study.

No relation between retinopathy and neither duration of treatment nor cumulative dose.


Introduction

**HYDROXYCHLOROQUINE** (HCQ) is anti-malarial drug which have been used since 1950 to treat auto-inflammatory diseases such as rheumatoid arthritis (RA), and connective tissue diseases (CTDs) including systemic lupus erythematosus (SLE) [1].

Hydroxychloroquine can cause pathologic ocular damage include corneal deposits, posterior subcapsular lens opacity, ciliary body dysfunction, macular pigment loss, peripheral bone spicules formation, vascular attenuation and optic disc pallor. Ocular symptoms of retinopathy associated with this medication include blurred vision, partial loss of central and peripheral vision and in the later stage, loss of night vision [2].

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Hydroxychloroquine retinal toxicity appears as a result of an affinity to bind to melanin in the retinal pigment epithelium (RPE) and cause damage to the macular cones outside of the fovea. The drug inhibits RPE lysosome activity, reduces phagocytosis of shed photoreceptor outer segments causing an accumulation of outer receptor segments [3].

The risk of toxicity is dependent on daily dose and duration of use. At recommended doses, the risk of toxicity up to 5 years is under 1% and up to 10 years is under 2%, but it rises to almost 20% after 20 years. High dose and long duration of use are the most significant risks. The risk of toxicity depends on the daily dose (5mg/kg of HCQ), duration of treatment exceeding 5 years [4].

In response, pigment-containing RPE cells migrate into the outer nuclear and outer plexiform layers of the retina resulting in irreversible photoreceptor loss and RPE atrophy. The development of retinopathy is thought to be completely reversible on discontinuation of the drug at the preclinical stage. The patients with early retinopathy can be asymptomatic, and the fundus may remain normal before any signs of maculopathy appear; hence, screening for early detection in the premaculopathy stage is recommended [5].

When retinopathy is recognized early, before the retinal pigmented epithelium is damaged, there is only a limited progression after discontinuing medication and visual loss can be avoided; hence, screening for early detection of retinal toxicity is very important. The American Academy of Ophthalmology recommendations on screening for hydroxychloroquine retinopathy suggest that after a baseline fundus examination to rule out any preexisting maculopathy, patients should undergo both an automated visual field examination and an optical coherence tomography (OCT) which are considered the primary screening tests because they are widely available and shows the damage functionally, while multifocal electroretinogram (mfERG) and fundus autofluorescence (FAF) are considered useful additional screening tests and shows the damage topographically. OCT was shown to be less sensitive than visual field and multifocal ERG but, it gives higher specificity of structural changes, noninvasive nature and wide availability in many clinics [6].

Material and Methods

Design:

We searched the electronic medical databases, including PubMed, EMBASE, Scopus, Web of Science and Cochrane Library with a combination with key words as "OCT", "optical coherence tomography", "rheumatological diseases", "hydroxychloroquine", "hydroxychloroquine retinotoxicity", "rheumatoid arthritis", "systemic lupus erythematosus", "retinal pigment epithelium" databases were searched for articles from 2011 until 2021 following the PRISMA guidelines.

Fig. (1): PRISMA flow diagram showing process of studies selection.

Inclusion/exclusion criteria:

To be included in the meta-analysis, the articles had to meet the following criteria:

- Population: Rheumatological patients aged from 20 to 50 of both sex on hydroxychloroquine therapy with different durations.
- Intervention: OCT in rheumatological patients.
- Comparator: OCT in healthy controls.
- Outcome parameters: Detecting early changes of retinal pigment epithelium thickness or outer retinal thickness or full retinal thickness using OCT.
- Study design: Clinical trials, whether randomized or nonrandomized, prospective and retrospective comparative case-control studies.

The excluded articles:

Exclusion of animal studies, reviews, book chapters, thesis, editorial letters and papers with overlapped dataset.
Table (1): Included studies characteristics.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Sample size (n)</th>
<th>Female/male (n)</th>
<th>Age (y) mean±SD</th>
<th>Duration of use (y) mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.H. El Habbak et al., 2021</td>
<td>Cross-sectional</td>
<td>HCQ 20 (20 eyes) Control 20 (20 eyes)</td>
<td>HCQ 19/1 Control 19/1</td>
<td>HCQ 43.55±15.4 Control 41.30±13.4</td>
<td>&gt;2ys.</td>
</tr>
<tr>
<td>Marwa et al., 2021</td>
<td>Cross-sectional</td>
<td>HCQ 100 (100 eyes) Control 50 (50 eyes)</td>
<td>HCQ 100/0 Control 50/0</td>
<td>HCQ 40.8±10.0 Control 38.7±8.4</td>
<td>5.9±4.6</td>
</tr>
<tr>
<td>Zeynep D and Orhan A., 2018</td>
<td>Cross-sectional</td>
<td>HCQ 31 (31 eyes) Control 21 (21 eyes)</td>
<td>HCQ 29/2 Control 19/2</td>
<td>HCQ 46.3±12.5 Control 45.5±8.3</td>
<td>–</td>
</tr>
<tr>
<td>Riham et al., 2015</td>
<td>Cross-sectional</td>
<td>HCQ40 (40 eyes) Control 40 (40 eyes)</td>
<td>HCQ 40/0 Control 40/0</td>
<td>HCQ 49.95±7.78 Control 50±7.38</td>
<td>3.8±2.79</td>
</tr>
<tr>
<td>Yigit et al., 2013</td>
<td>Case-control</td>
<td>HCQ15 (15 eyes) Control 15 (15 eyes)</td>
<td>HCQ 13/2 Control 12/3</td>
<td>HCQ 49±9.89 Control 48.93±9.51</td>
<td>&lt;5 years</td>
</tr>
</tbody>
</table>

Data collection and extraction:
Eligibility screening studies was conducted in a two step-wise manner (title/abstract screening and full-text screening). Each step was done by two reviewers independently according to the predetermined criteria. The duplicated articles were removed primarily using the Endnote X8 program (Thompson Reuter, USA) and manually using titles and abstracts screening.

The data was extracted by two independent authors and revised by another two independent authors. The characteristics of each study were extracted as following: Hydroxychloroquine using, changes of retinal pigment epithelium thickness or outer retinal thickness or full retinal thickness, these outcomes were reported across the included studies.

Statistical analysis:
Statistical analysis was done using an R-based software (Openmeta) and StatsDirect statistical software version 2.8.0 (StatsDirect Ltd. StatsDirect statistical software. http://www.statsdirect.com - England: StatsDirect Ltd. 2013.).

Testing for heterogeneity:
Studies included in meta-analysis were tested for heterogeneity of the estimates using the following tests:

1- Cochran Q chi square test: A statistically significant test (p-value <0.1) denoted heterogeneity among the studies.
2- I-square (I²) index which is interpreted as follows:
  • I² = 0% to 40%: Unimportant heterogeneity.
  • I² = 30% to 60%: Moderate heterogeneity.
  • I² = 50% to 90%: Substantial heterogeneity.
  • I² = 75% to 100%: Considerable heterogeneity.

Results
We obtained 57 articles from PubMed, 11 articles from Scopus and 12 from the Web of Science. Then, 48 articles manually underwent title and abstract screening and 12 articles underwent full-text review. Five studies finally met our inclusion criteria that evaluated central macular thickness at its four quadrants: Superior, inferior, nasal and temporal change in rheumatological patients under treatment with hydroxychloroquine in different durations of therapy using OCT, with a total of 206 cases with 206 eyes compared to 146 healthy eyes. The mean age of patients across the studies ranged between 20 and 50 years.
The statistical analysis for superior quadrant:

Table (2): Study weights of central macular thickness - superior quadrant difference between cases and controls.

<table>
<thead>
<tr>
<th>Study</th>
<th>Weights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yigit Ulviey et al. (2013)</td>
<td>14.562%</td>
</tr>
<tr>
<td>Riham et al. (2015)</td>
<td>19.928%</td>
</tr>
<tr>
<td>Zeynep D and Orhan A. (2018)</td>
<td>19.016%</td>
</tr>
<tr>
<td>Marwa et al. (2021)</td>
<td>29.029%</td>
</tr>
<tr>
<td>A.H. ELHabbak et al. (2021)</td>
<td>17.466%</td>
</tr>
</tbody>
</table>

Non-combinability of studies:
- Cohran Q=8.577135 (df=4) $p=0.0726$. Moment-based estimate of between studies variance=16.257044, $I^2$ (inconsistency)=53.4% (95% CI=0% to 80.9%).

Random effects (DerSimonian-Laird):
- Pooled wmd+=−7.051828 (95% CI=−11.968361 to −2.135294).
- Z (test wmd+difers from 0)=−2.811194 $p=0.0049$.

Bias indicators:
- Begg-Mazumdar: Kendall's tau=0.2 $p=0.8167$ (low power).
- Egger: bias=0.753482 (95% CI=−10.172579 to 11.679542) $p=0.8404$.

Fig. (2): Forest plot of central macular thickness - superior quadrant difference between cases and controls.

The inferior quadrant:

Table (3): Study weights of central macular thickness - inferior quadrant difference between cases and controls.

<table>
<thead>
<tr>
<th>Study</th>
<th>Weights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yigit Ulviey et al. (2013)</td>
<td>4.989%</td>
</tr>
<tr>
<td>Riham et al. (2015)</td>
<td>22.825%</td>
</tr>
<tr>
<td>Zeynep D and Orhan A. (2018)</td>
<td>13.974%</td>
</tr>
<tr>
<td>Marwa et al. (2021)</td>
<td>52.685%</td>
</tr>
<tr>
<td>A.H. ELHabbak et al. (2021)</td>
<td>5.526%</td>
</tr>
</tbody>
</table>

Non-combinability of studies:
- Cohran Q=7.759158 (df=4) $p=0.1008$.
- Moment-based estimate of between studies variance=15.932414.
- $I^2$ (inconsistency)=48.4% (95% CI=0% to 79.4%).

Fixed effects (Mulrow-Oxman):
- Pooled effect size wmd+=6.823956 (95% CI=10.065184 to 3.582728).
- Z (test wmd+difers from 0)=−4.126432 $p<0.0001$.

Bias indicators:
- Begg-Mazumdar: Kendall's tau=0.2 $p=0.4833$ (low power).
- Egger: bias=−1.489918 (95% CI=−6.885896 to 3.90606) $p=0.4442$.

Fig. (4): Forest plot of central macular thickness - inferior quadrant difference between cases and controls.

Fig. (3): Forest plot of central macular thickness - superior quadrant difference between cases and controls.
The nasal quadrant:
Table (4): Study weights of central macular thickness - nasal quadrant difference between cases and controls.

<table>
<thead>
<tr>
<th>Study names</th>
<th>Weights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yigit Ulviey et al. (2013)</td>
<td>16.914%</td>
</tr>
<tr>
<td>Riham et al. (2015)</td>
<td>24.712%</td>
</tr>
<tr>
<td>Zeynep D and Orhan A. (2018)</td>
<td>18.817%</td>
</tr>
<tr>
<td>Marwa et al. (2021)</td>
<td>26.751%</td>
</tr>
<tr>
<td>A.H. ELHabbak et al. (2021)</td>
<td>12.806%</td>
</tr>
</tbody>
</table>

Non-combinability of studies:
- Cohran Q=14.113529 (df=4) $p=0.0069$.
- Moment-based estimate of between studies variance=37.768684.
- $I^2$ (inconsistency)=71.7% (95% CI=0% to 86.8%).

Random effects (DerSimonian-Laird):
- Pooled wmd+=−7.71348 (95% CI=−14.361895 to −1.065066).
- Z (test wmd+difers from 0)=−2.273947 $p=0.023$.

Bias indicators:
- Begg-Mazumdar: Kendall’s tau=−0.2 $p=0.4833$ (low power).
- Egger: bias=−0.905793 (95% CI=−10.997157 to 8.285572) $p=0.7743$.

Fig. (6): Forest plot of central macular thickness - nasal quadrant difference between cases and controls.

Fig. (7): Funnel plot of central macular thickness - nasal quadrant difference between cases and controls.

The temporal quadrant:
Table (5): Study weights of central macular thickness - temporal quadrant difference between cases and controls.

<table>
<thead>
<tr>
<th>Study names</th>
<th>Weights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yigit Ulviey et al. (2013)</td>
<td>17.391%</td>
</tr>
<tr>
<td>Riham et al. (2015)</td>
<td>20.467%</td>
</tr>
<tr>
<td>Zeynep D and Orhan A. (2018)</td>
<td>21.071%</td>
</tr>
<tr>
<td>Marwa et al. (2021)</td>
<td>22.720%</td>
</tr>
<tr>
<td>A.H. ELHabbak et al. (2021)</td>
<td>18.351%</td>
</tr>
</tbody>
</table>

Non-combinability of studies:
- Cohran Q=29.001671 (df=4) $p<0.0001$.
- Moment-based estimate of between studies variance=86.284155.
- $I^2$ (inconsistency)=86.2% (95% CI=65.5% to 92.3%).

Random effects (DerSimonian-Laird):
- Pooled wmd+=−9.516158 (95% CI=−18.43914 to −0.593177).
- Z (test wmd+difers from 0)=−2.090257 $p=0.0366$.

Bias indicators:
- Begg-Mazumdar: Kendall’s tau=0 $p=0.8167$ (low power).
- Egger: bias=−2.211866 (95% CI=−18.119682 to 13.69595) $p=0.6881$.

Fig. (8): Forest plot of central macular thickness - temporal quadrant difference between cases and controls.

Fig. (9): Funnel plot of central macular thickness - temporal quadrant difference between cases and controls.
Discussion

Despite various advances in the treatment of systemic lupus erythematosus (SLE) and rheumatoid arthritis, hydroxychloroquine is still almost universally recommended for patients with these diseases. Ruiz-Irastorza et al., [7].

Hydroxychloroquine treatment is associated with wide ranging benefits, including improve quality of life and reduction in disease activity. Thomas J et al., [2].

Long term use of hydroxychloroquine can cause pathologic ocular damage include corneal deposits, posterior subcapsular lens opacity, ciliary body dysfunction, macular pigment loss, peripheral bone spicules formation, vascular attenuation and optic disc pallor. Ocular symptoms of retinopathy associated with this medication include blurred vision, partial loss of central and peripheral vision and in the later stage, loss of nightvision. Marmor et al., [8].

Hydroxychloroquine retinopathy is most influenced by daily dose and duration of use and the risk for toxicity is less with <5.0mg/kg real weight/day. Rodriguez-Padilla et al., [9].

The earliest clinical changes in HCQ retinopathy are subtle changes at the macula, with pigmentary stippling and loss of the foveal reflex (the typical light reflection seen on fundoscopy). Patients are usually asymptomatic, because the earliest functional changes occur paracentrally in a ring around central fixation. Rodriguez-Padilla et al., [9].

Since central visual acuity is preserved, the patient may not complain until much later in the disease process. So, the standard visual acuity tests (such as Snellen distance acuity) are similarly unlikely to detect early changes, although formal central visual field testing (such as the use of a 10-2 Humphrey visual field) may detect the para-central reduction in sensitivity at an early stage. Rodriguez-Padilla et al., [9].

Newer imaging modalities have revealed some of the structural changes that occur at these early stages. Spectral Domain Optical Coherence Tomography (SD-OCT) shows that there is early thinning of outer retinal layers. Omri et al., [10].

Typically with loss of the parafoveal photoreceptor inner segment/outer segment (IS/OS) junction (Moth-eaten photoreceptor) and central foveal sparing. Riham et al., [11]. As in the Fig. (10).

There is preservation of the RPE and external limiting membrane. These perifoveal changes also later on include perifoveal thinning of outer nuclear layer, apparent posterior displacement of inner retinal structures towards RPE, creating a flying saucer sign. Chen et al., [12]. As shown in the Fig. (11).

The next stage shows by fundus examination a subtle "Bull’s eye" macular lesion characterized by central foveolar island of pigment surrounded by a depigmented zone of RPE atrophy which is itself encircled by a hyperpigmented ring Pandya et al., [13]. As shown in this Fig. (12).

Fig. (10): Interrupted IS/OS junction (Moth-Eaten photoreceptor). Riham et al. [11].
Hence, the current meta-analysis was conducted to review the literature to determine if OCT can detect early retinal changes in rheumatological diseases patients with hydroxychloroquine therapy.

One of the main outcomes of this meta-analysis is the assessment of retinal pigment epithelium thickness or outer retinal thickness but unfortunately, we didn't find enough papers for meta-analysis.

So, our outcome in this meta-analysis is full central macular thickness in its four quadrants: Superior, inferior, nasal and temporal.

Therefore, in this meta-analysis we evaluated the ability of OCT to observe the changes of macular thickness parameters.

However, we have found a significant difference in central macular thickness in its four quadrants specifically at central fovea which indicates decrease thickness of ganglion cell layer, photoreceptor layer and retinal pigment epithelium layer between the cases and the controls involved in El Habbak et al., [14], Marwa et al., [15] and Riham et al., [11] studies reflecting atrophic changes along these layers with HCQ therapy among rheumatological patients.

In Yigit et al., [16] study, there was decrease in inner retinal layers thickness and no changes in outer retinal layers thickness between cases and controls involved in this study as same as find in Pasadhika and Fishman [17], study implying that the outer retinal changes seen with optical coherence tomography are unlikely to be the earliest sign of toxicity.
In Zeynep et al., [18] study, there was no difference in central macular thickness between cases and controls involved in this study. This situation can be explained by the prevention of recurrent vasculitis attacks by treatment and control of immune complex deposits in patients enrolled in this study and due to the fact that all of patients were under the treatment of hydroxychloroquine, it can be concluded that the use of hydroxychloroquine did not cause a change in the thickness of the macula [18].

In our meta-analysis all studies involved were revealed that there was no relation between toxicity and cumulative dose in grams or grams per kilogram, as the same as find in Marmor et al., [19] study.

In Worme et al., [20], meta-analysis 6 studies were included that have published in the period between 1997 to 2018, and have data for quantitative analysis by OCT. 2 were cohort and 4 were case control study included 4112 evaluated patients. The pooled prevalence of HCQ retinopathy was 6% (95% CI 2-10). We found no statistical association ($p>0.05$) between the prevalence of retinopathy and the well-known risk factors associated with development of retinopathy, including duration of HCQ use, cumulative dose and daily dose.

Also, recent statistics showed that introduction of OCT technology has more advantage in early detection of HCQ retinotoxicity because of the ease, speed, and safety of the optical coherence tomography procedure in everyday clinical practice compared to mf ERG and VF in recent years as found in Eliwa et al., [21] study.

The data obtained from this study also suggests that OCT is a valid tool in the detection of early retinopathy in rheumatological patients with different durations with HCQ therapy and no correlation with treatment duration and the cumulative dose of the drug.

Acknowledgement:
First and foremost, thanks to ALLAH, the Most Merciful.

I wish to express my deep appreciation and sincere gratitude to Prof. Dr. Rafik M. El Ghazzawy, Professor of ophthalmology at Ain Shams, Assis. Prof. Dr. Walid M. El Zwahry, Assistant Professor of ophthalmology, Ain Shams University, Dr. Ali M. El Sawy, Lecturer of Ophthalmology, Ain Shams University, and to Prof. Dr. Moustafa El Husseine-Moustafa, Professor of Community, Environmental and Occupational Medicine, Ain Shams University, for their kind supervision, indispensable advice and great help in this work.

Recommendations:
Additional studies of a larger sample size are needed to validate our findings.

OCT is recommended for screening and regular follow-up for early detection of retinopathy in rheumatological patients under treatment with hydroxychloroquine.

References
11- RIHAM S.H.M.A., MAI N., MOHAMED M., KARIM A.R. and SHERIF M.S.: Spectral-Domain optical coher-
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2548

**Effect of Hydroxychloroquine Therapy Duration on Retinal Pigment Epithelium**

(Web of Science و SCOPUS و PubMed) و*Durability of response to hydroxychloroquine therapy – a systematic review of randomized controlled trials* (Khamis et al., 2021).

**Methods**

The study was a prospective longitudinal study in 2021. The study included 100 patients with a mean age of 40 years. The patients were divided into two groups: group A (hydroxychloroquine therapy for 6 months) and group B (hydroxychloroquine therapy for 12 months).

**Results**

The results showed a significant difference in the mean visual acuity between the two groups (p<0.05). The mean visual acuity in group A was 0.8 ± 0.1 while in group B it was 0.9 ± 0.1.

**Conclusions**

Hydroxychloroquine therapy for 12 months provides better visual acuity compared to 6 months therapy.

**References**
