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Research article

Effects of hydroxychloroquine on retinal structure and function: A comparative study in a Sri Lankan setting

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Abstract

Objective: *To evaluate the impact of long-term Hydroxychloroquine (HCQ) therapy on visual performance and retinal structure in patients with Rheumatoid Arthritis (RA) in a Sri Lankan cohort.*

Methodology: *This prospective cross-sectional study included 300 participants (150 RA patients on HCQ therapy for over six months and 150 control participants). Visual function assessments included visual acuity (VA), color vision, contrast sensitivity, and foveal sensitivity, along with Optical Coherence Tomography (OCT) measurements to evaluate macular and retinal nerve fiber layer (RNFL) thickness. Group comparisons were conducted using independent samples t-tests, with statistical significance set at $p<0.05$.*

Results: *RA patients on HCQ therapy demonstrated significantly reduced VA, color discrimination, contrast sensitivity, and foveal sensitivity compared to controls ($p < 0.05$). OCT measurements revealed thinning of central foveal and parafoveal regions, correlating positively with HCQ therapy duration. Specifically, central foveal thickness was lower in HCQ patients by an average of 11.1 μm compared to controls ($p=0.03$). Ganglion cell layer (GCL) and RNFL thickness remained largely unaffected by HCQ duration.*

Conclusion: *Long-term HCQ therapy is associated with noticeable declines in visual function and retinal structure changes in RA patients. Regular ophthalmic screening is recommended for early detection and prevention of HCQ-induced retinal toxicity.*

Key words: hydroxychloroquine, retinal toxicity, rheumatoid arthritis, optical coherence tomography, visual function, Sri Lanka

Introduction

Hydroxychloroquine (HCQ) and Chloroquine (CQ) were initially developed as antimalarial drugs but have since gained widespread use in treating autoimmune diseases, particularly Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE). As Disease-Modifying Antirheumatic Drugs (DMARDs), they are valued for their ability to reduce inflammation and disease progression. HCQ is especially favored over CQ due to its relatively lower toxicity profile and effectivity in managing RA symptoms, reducing flares and improving long-term patient outcomes. However, HCQ therapy is not without risks, as prolonged use can lead to severe ocular side effects, including irreversible retinal toxicity.

HCQ-induced retinopathy and mechanism of toxicity

The ocular toxicity of HCQ, first documented in the late 1950s, is primarily associated with its affinity for melanin-containing cells in the retina, particularly the retinal pigment epithelium (RPE). This toxicity typically manifests as a unique pattern of retinal damage described as bull's eye maculopathy, characterized by parafoveal thinning surrounding the central fovea. The mechanism behind this toxicity involves HCQ's binding to melanin, which allows it to accumulate in the RPE and potentially disrupt cellular function over time. This disruption affects the RPE's ability to support photoreceptors, gradually leading to photoreceptor loss, visual impairment, and eventually vision loss if not detected and managed early.

Research suggests that HCQ induces retinal toxicity by interfering with lysosomal activity within RPE cells, causing cellular stress and degeneration. This damage subsequently affects the photoreceptor layer above the RPE, leading to a loss of peripheral and central vision. As these changes initially occur at a subclinical level, patients may remain asymptomatic in the early stages, making routine screening vital to detect retinal toxicity before irreversible damage occurs.

Risk factors: duration, cumulative dose, and genetic susceptibility

The risk of HCQ retinopathy is strongly associated with the cumulative dose and duration of therapy.

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Evidence shows that retinal toxicity is more likely to occur when cumulative doses exceed approximately 1,000 grams or when treatment extends beyond five years, even at standard dosages. Marmor et al. (2016) and the American Academy of Ophthalmology (AAO) emphasize that patients on HCQ therapy for extended periods should undergo regular ophthalmic evaluations to monitor for early signs of toxicity. Additionally, genetic variations in melanin concentration and metabolism could influence susceptibility to HCQ toxicity, justifying further research.

The potential for long-term retinal damage makes it critical for healthcare providers to adhere to recommended HCQ dosing guidelines and conduct regular screenings. Recognizing risk factors such as cumulative dose and therapy duration can enable clinicians to stratify patients by risk and customize follow-up intervals accordingly.

Advances in screening and imaging for HCQ retinopathy

Technological advances in retinal imaging have improved the early detection of HCQ toxicity. Optical Coherence Tomography (OCT), a non-invasive imaging modality, allows for high-resolution visualization of retinal layers, particularly the macular and parafoveal regions where HCQ toxicity typically manifests. OCT imaging can detect microstructural changes in retinal thickness and cellular integrity, providing a critical tool for early detection of HCQ-related retinal changes. Other modalities, including multifocal electroretinography (mfERG) and adaptive optics (AO), offer further insights into retinal function and cellular structure, though these are less commonly used in routine clinical practice due to accessibility and cost considerations.

The American Academy of Ophthalmology (AAO) and Royal College of Ophthalmologists recommend baseline OCT exams before initiating HCQ therapy, with annual follow-up screenings after five years of treatment or sooner if cumulative dose thresholds are reached. These guidelines have been instrumental in reducing the incidence of severe HCQ toxicity by promoting early intervention and treatment adjustments.

Gaps in knowledge and relevance to the Sri Lankan context

Despite the global consensus on the need for regular screening, limited data exist on HCQ retinopathy in specific populations, including those in Sri Lanka. Genetic, environmental, and healthcare access factors may influence the prevalence and progression of HCQ toxicity across different populations. In Sri Lanka, access to advanced ophthalmic technologies like OCT may be limited, particularly in rural areas, potentially delaying diagnosis and increasing the risk of irreversible vision loss. Moreover, healthcare systems facing resource constraints may not prioritize regular retinal screening, further highlighting the importance of locally relevant studies to inform effective and feasible screening practices.

The present study addresses this gap by examining HCQ-related retinal changes in a Sri Lankan cohort of RA patients. By assessing both structural (OCT-based) and functional (visual acuity, color vision, contrast sensitivity, and foveal sensitivity) metrics, this research seeks to provide insights into the specific manifestations of HCQ toxicity in this population leading to development of tailored screening protocols.

Objectives

The main objective was to evaluate the impact of HCQ therapy on retinal structure and visual function in Sri Lankan RA patients. Additionally, the specific objectives included

1. Comparing visual performance metrics between HCQ-treated patients and a matched control group.
2. Assessing structural changes in the retina, particularly in the macular and parafoveal regions, using OCT imaging.
3. Exploring the relationship between treatment duration and the severity of retinal changes, providing insights into the progressive nature of HCQ toxicity.

This study was designed to bring evidence-based approach to enhance awareness among Sri Lankan clinicians about the importance of early screening and advocate for the integration of HCQ monitoring protocols within local healthcare practices. Ultimately, this study aimed to contribute to improved patient outcomes by mitigating the risk of HCQ-related visual impairment in Sri Lanka.

Methodology

Study design

This study was a prospective, cross-sectional comparative study conducted over one year, from January to December 2019, in Colombo Sri Lanka. The purpose was to assess retinal structural changes and visual performance in Rheumatoid Arthritis (RA) patients on long-term Hydroxychloroquine (HCQ) therapy and compare these parameters with a control group of individuals with no history of HCQ use.

Study population

A total of 300 female participants were recruited for this study. This included 150 RA patients who had been on HCQ therapy (200 mg daily) for a duration of more than six months and 150 age- and sex-matched control participants with no RA diagnosis or history of HCQ therapy. Female participants were exclusively included due to the higher prevalence of RA among women and to create a homogenous sample.

- **Inclusion Criteria for HCQ Group:** Female RA patients on HCQ therapy (200 mg daily) for at least six months, aged between 40 and 70, with no pre-existing ocular conditions affecting visual acuity or retinal health.
- **Exclusion Criteria for Both Groups:** Individuals with optic neuropathy, pre-existing retinopathy, history of chorioretinitis, central visual field defects, neurological impairments, hepatic or renal insufficiency, or history of intraocular surgery were excluded to ensure that visual and retinal measurements would not be influenced by other comorbidities.

Data collection procedures

The assessment involved multiple visual function tests and OCT imaging to measure retinal structure and detect any subclinical or clinical signs of HCQ toxicity.

1. **Visual Acuity (VA):** VA was measured using the Snellen chart for distance vision, with results recorded as visual acuity fractions (e.g., 6/6, 6/9) and 'N' notation for near vision.
2. **Visual Field Sensitivity:** A Humphrey Field Analyzer (10-2 perimetry) was used to evaluate central visual field sensitivity. The 10-2 perimetry specifically tests the central 10 degrees of vision, which is critical for detecting early changes in patients on HCQ therapy.
3. **Contrast Sensitivity**: The LEA contrast sensitivity test was administered to assess participants' ability to perceive contrast, with measurements recorded as a percentage. This test is valuable in assessing subtle visual changes that may indicate early toxicity.
4. **Color Vision:** Ishihara's color plates (34 plates) were used to evaluate color discrimination ability, an essential aspect of visual performance that is often impacted in HCQ toxicity.
5. **Optical Coherence Tomography (OCT) Imaging:** Spectral Domain OCT (SD-OCT) was performed using the Cirrus 5000 system to measure macular thickness, retinal nerve fiber layer thickness (RNFL), and ganglion cell layer thickness (GCLT). OCT imaging provided detailed measurements of:
    - **Central Foveal Thickness (CFT):** The thickness of the central fovea, known to be effected in HCQ toxicity.
    - **Parafoveal Thickness:** The thickness of the retina in the parafoveal region across four quadrants (superior, inferior, nasal, and temporal).
    - **Perifoveal Thickness:** Thickness measurements of the perifoveal region to assess for any peripheral changes.

Participants received an information sheet and informed written consent was obtained prior to data collection. The study ensured autonomy by allowing participants to withdraw at any time and maintained confidentiality by collecting data anonymously. Data was stored securely in password-protected digital formats, with no paper-based data collected.

Data Analysis

Data were analyzed using statistical software (SPSS). Descriptive statistics were calculated for baseline characteristics, and differences in visual function and OCT measurements between the HCQ and control groups were assessed using independent samples t-tests. Statistical significance was set at $p<0.05$ for all comparisons. Additionally, within the HCQ group, correlations between the duration of therapy (in number of years) and retinal measurements were compared to evaluate the cumulative impact of HCQ on retinal structure and function.

Results

Participant characteristics

The study included 300 female participants, evenly divided between the HCQ-treated RA group (n=150) and control group (n=150). The mean age for the HCQ group was 53.6 ± 9.8 years, while the control group had a mean age of 51.4 ± 8.1 years. Among the HCQ-treated group, 82.6% had been on therapy for over two years, with 40% having used HCQ for more than four years, highlighting a relatively high proportion of long-term HCQ users in the study.

Visual function tests

1. **Visual Acuity (VA):** Participants in the HCQ group exhibited a significantly lower average VA (6/9) compared to the control group (6/6). Long-term HCQ therapy was associated with further reductions in VA, with patients on HCQ for over four years showing a mean VA of 6/12.

2. **Color Vision:** HCQ-treated participants had a significantly lower mean Ishihara color discrimination score (33.8 ± 0.9) compared to controls (34.6 ± 1.2) (p=.02). Duration analysis indicated that color vision declined progressively with extended HCQ use. Patients on therapy for more than four years scored 32.2 ± 1.1, while those on therapy for less than two years had higher scores (36.0 ± 1.3).
3. **Contrast Sensitivity:** The HCQ group had a mean contrast sensitivity score of 5.5% ± 3.8, which was significantly lower than the control group's mean of 2.8% ± 1.6 (p=0.05). A trend of decreased contrast sensitivity was observed with increasing therapy duration, with scores declining to 5.8% ± 0.8 in participants on HCQ for more than four years.
4. **Foveal Sensitivity:** HCQ-treated participants had reduced foveal sensitivity (mean 30.6 dB ± 1.3) compared to the control group (33.8 dB ± 0.8) (p=0.01). Long-term HCQ exposure correlated with further reductions, with participants on therapy for over four years showing a mean sensitivity of 30.3 dB ± 0.8.

Retinal thickness measurements (OCT Findings)

OCT imaging revealed significant thinning in the macular and parafoveal regions in the HCQ group compared to controls, particularly in patients with extended HCQ therapy.

1. **Central Foveal Thickness (CFT):** HCQ-treated participants exhibited a mean CFT of 236.2 ± 16.6 μm, significantly lower than the control group's 247.3 ± 13.1 μm (p=0.03). CFT decreased with therapy duration, highlighting a cumulative effect of HCQ on central foveal structure.
2. **Parafoveal Thickness:**

   Superior Quadrant: HCQ group had a mean thickness of 315.2 ± 12.1 μm, while the control group averaged 324.6 ± 10.8 μm (p=0.04).

   Inferior Quadrant: HCQ-treated patients showed significant thinning in the inferior parafoveal region (312.3 ± 13.3 μm) compared to controls (320.1 ± 10.5 μm, p=0.02).

   Nasal Quadrant: Nasal parafoveal thickness was reduced in the HCQ group (316.6 ± 12.3 μm) compared to the control group (324.0 ± 11.0 μm, p=0.02).

   Temporal Quadrant: Temporal thinning was pronounced in the HCQ group (314.8 ± 16.8 μm) vs. controls (323.6 ± 10.2 μm, p=0.01), supporting the characteristic temporal involvement in HCQ toxicity.
3. **Perifoveal Thickness:** No significant differences were observed between the HCQ and control groups in perifoveal thickness.
4. **Retinal Nerve Fiber Layer (RNFL) and Ganglion Cell Layer Thickness (GCLT):** No significant alterations were detected in RNFL or GCLT between HCQ-treated and control groups.

Duration-Based Analysis within the HCQ Group

1. **Central Foveal Thickness (CFT):** The Pearson correlation coefficient between therapy duration and CFT was –0.92with a p-value of 0.030, indicating a strong negative correlation.
2. **Parafoveal Thickness (Superior Quadrant):** For parafoveal thickness in the superior quadrant, the correlation coefficient was ?0.88 with a p-value of 0.040, also demonstrating a strong negative association.
3. **Visual Acuity Score:** The correlation between therapy duration and visual acuity score was 0.91 with a p-value of 0.02, indicating a strong positive correlation.

Discussion

The findings of this study highlight significant associations between the duration of Hydroxychloroquine (HCQ) therapy and both retinal structural changes and declines in visual performance in patients with Rheumatoid Arthritis (RA). These results contribute to a growing body of literature underscoring the risk of HCQ-induced retinopathy, particularly in long-term users.

Structural impact on central foveal and parafoveal thickness

Our study revealed a strong negative correlation between therapy duration and central foveal thickness (CFT), with a Pearson correlation coefficient of -0.92 (p=0.03). This aligns with the well-documented impact of HCQ on the macular region, which observed that HCQ's toxic effects on the retina are dose-dependent and progressively increase with cumulative exposure[1,2]. Marmor et al.'s work, which provides the foundation for current screening guidelines, emphasizes that structural changes in the macula, including CFT reduction, are early indicators of HCQ toxicity, detectable even in asymptomatic patients through OCT imaging[1]. Our findings thus reinforce the importance of CFT as a primary screening parameter in patients on long-term HCQ therapy.

The parafoveal region, particularly the superior quadrant, also demonstrated significant thinning with increased HCQ exposure (correlation coefficient = -0.88, p=0.04). This pattern of parafoveal involvement is consistent with the findings of Chen et al, who reported that parafoveal thinning often precedes other visual symptoms and is a hallmark of HCQ-induced toxicity[3]. Our study supports the view that targeted OCT scanning of the parafoveal area, particularly the superior and temporal quadrants, should be a routine component of screening protocols for patients undergoing extended HCQ therapy. The characteristic vulnerability of the parafoveal region is likely due to the selective affinity of HCQ for melanin in retinal pigment epithelial (RPE) cells, which may lead to localized damage that initially affects parafoveal photoreceptors before spreading centrally[4].

Functional decline in visual acuity and contrast sensitivity

The correlation between HCQ duration and visual acuity decline (correlation coefficient =0.91, p=0.02) in our study is a critical finding, as it indicates that functional visual deficits occur alongside structural changes. Similar to Wolfe and Marmor's findings, our results suggest that even in cases where structural changes are subclinical, prolonged HCQ exposure is likely to manifest as measurable declines in visual acuity[5]. This functional decline has important implications for patients' daily lives, particularly in activities that require fine visual discrimination, such as reading and driving. Our study also observed decreased color vision and contrast sensitivity in HCQ-treated patients, which aligns with the findings of Lyons and Severns[6]. Their research highlights that functional tests assessing contrast sensitivity and color discrimination are valuable adjuncts to structural OCT measurements, providing a more comprehensive assessment of HCQ toxicity.

Contrast sensitivity, which was significantly lower in HCQ-treated patients than in controls (mean 5.5% vs. 2.8%, p=0.05), is particularly susceptible to early toxic effects. Stepien et al. documented that reductions in contrast sensitivity often appear before patients report subjective visual changes, underscoring the value of incorporating this test into regular HCQ toxicity screening[2]. Our study found that participants on HCQ for more than four years exhibited the greatest declines, supporting the need for more intensive monitoring of patients with extended therapy duration.

Comparative insights from other imaging modalities

While this study relied on SD-OCT for structural assessments, there is an emerging consensus in the literature on the potential benefits of using advanced imaging modalities, such as adaptive optics (AO) and OCT angiography (OCT-A), to detect early subclinical changes in HCQ toxicity. Studies by Fingler et al. and Melles and Marmor suggest that AO, with its capacity for cellular-level resolution, may reveal microstructural disruptions in photoreceptor arrangement before they become apparent on standard OCT[7,8]. Additionally, OCT-A offers the ability to assess retinal and choroidal microvasculature, which could help identify early vascular changes associated with HCQ toxicity. Although such techniques were beyond the scope of this study, future research using these tools could provide further insights into HCQ's effects on retinal microstructure and offer additional markers for early toxicity detection.

Clinical implications and recommendations

An analysis of retinal thickness and visual performance parameters within the HCQ group showed a significant correlation between therapy duration and severity of retinal changes. Patients on HCQ for more than four years exhibited more substantial thinning across all parafoveal quadrants, as well as greater deficits in visual acuity, color vision, contrast sensitivity, and foveal sensitivity. This duration-based analysis supports the cumulative impact of HCQ on retinal health and reinforces the need for time-sensitive screening protocols.

The strong correlations found between HCQ duration and both structural and functional retinal changes underscore the importance of routine, comprehensive screening for RA patients on HCQ therapy. Current guidelines by the American Academy of Ophthalmology advocate baseline retinal exams followed by annual screenings after five years of therapy, or sooner if cumulative dose thresholds are reached[9]. Our study supports these recommendations, with a particular emphasis on OCT-based CFT and parafoveal measurements, which appear to be sensitive indicators of early retinal changes in HCQ users. Additionally, we recommend incorporating functional tests, such as contrast sensitivity and color vision assessments, into routine screening, especially for patients on therapy exceeding four years, as these may reveal functional declines even when structural changes are subtle.

Given the limited availability of advanced imaging techniques in resource-constrained settings like Sri Lanka, we suggest that healthcare providers prioritize OCT and functional vision tests as part of a simplified yet effective HCQ screening protocol. Our findings advocate for increased awareness and vigilance among clinicians, as early intervention remains the only

effective measure to prevent irreversible HCQ-induced visual impairment.

Limitations and future directions

This study's cross-sectional design limits its ability to establish causality, and the exclusive focus on female participants may affect the generalizability of findings to a mixed-gender population. Future longitudinal studies could provide more definitive evidence on the progression of HCQ toxicity and the specific dose-response relationship. Additionally, exploring alternative imaging methods such as OCT-A and AO could enhance our understanding of HCQ's impact on retinal health and potentially reveal early vascular or microstructural changes not visible on conventional OCT.

Conclusion

In conclusion, this study highlights a strong association between HCQ therapy duration and both structural and functional retinal changes in Sri Lankan RA patients. Our results suggest that OCT-based structural assessments, combined with functional visual tests, offer a practical and sensitive approach for monitoring HCQ-induced toxicity. Implementing these screening measures in routine clinical practice could significantly reduce the risk of irreversible vision loss in patients undergoing long-term HCQ therapy. By adopting targeted screening protocols tailored to local healthcare settings, clinicians can better protect RA patients from the adverse ocular effects of a widely prescribed medication.

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