Original Article

Access this article online

Quick Response Code:

Website: www.meajo.org

DOI: 10.4103/meajo.meajo_434_20

Corneal Hysteresis, Central Corneal Thickness, and Intraocular Pressure in Rheumatoid Arthritis, and Their Relation to Disease Activity

Ashraf Ahmed Nossair[1], Mona Kassem Kassem[2], Rasha Mounir Eltanamly[1], Yomna Amr Alahmadawy[1]

Abstract:

PURPOSE: To evaluate biomechanical properties, corneal thickness, and intraocular pressure (IOP) in patients with rheumatoid arthritis (RA) and correlate them with rheumatoid activity.

PATIENTS AND METHODS: Forty RA eyes were enrolled in a cross-sectional study. Clinical Disease Activity Index (CDAI) was used to assess the rheumatoid activity by a rheumatologist. Corneal hysteresis (CH), corneal resistance factor (CRF), and IOP corneal compensated, IOP Goldmann corrected were assessed using ocular response analyzer (ORA), Corneal thickness was measured using optical coherence tomography, and IOP using Goldman applanation tonometer (IOP GAT).

RESULTS: There was a positive correlation between CH and CRF ($P < 0.001$ and $r = 0.818$) and ($P < 0.001$ and $r = 0.714$) in the active and inactive groups respectively, also between CRF and central corneal thickness (CCT) (P value 0.05 and $r = 0.0435$) in Inactive Group only. No correlation was found between CDAI score and ORA parameters. There was a negative correlation between CDAI and CCT in Active Group only ($P < 0.001$ and $r = -0.823$).

CONCLUSION: Corneal biomechanical properties could be affected in rheumatoid patients in both active and remission phases, which may indicate that any corneal changes may be irreversible. These changes are of important significance regarding IOP measurement in rheumatoid patients. CCT may be a new parameter in the follow up of disease activity.

Keywords:

Central corneal thickness, corneal hysteresis, intraocular pressure, ocular response analyzer, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a common joint disorder, in which 1%–2% of the population are affected worldwide, with women more affected two to three times than men.[1]

There are several stages of corneal affection in RA, including stromal inflammation, collagenolysis, marginal guttering, and ulcerative keratitis.[2]

The process of collagenolytic may be explained by the up-regulation of pro-inflammatory cytokines that trigger the production of proteolytic enzymes from the keratocytes, this causes the breakdown of the extracellular matrix.[3]

Corneal hysteresis (CH) is expected to be affected in RA which in turn will affect intraocular pressure (IOP) measurements by standard Goldmann technique. Few studies

[1]Department of Ophthalmology, Faculty of Medicine, Cairo University, Cairo, Egypt, [2]Department of Ophthalmology, Sheikh Zayed Al Nahyan Hospital, Ministry of Health, Egypt

Address for correspondence:
Dr. Yomna Amr Alahmadawy, 3 Montasser Housing, Alharam, Giza 12512, Egypt.
E-mail: dr_y.alahmadawy@yahoo.com

Received: 27-09-2021
Accepted: 30-11-2021
Published: 31-12-2021

How to cite this article: Nossair AA, Kassem MK, Eltanamly RM, Alahmadawy YA. Corneal hysteresis, central corneal thickness, and intraocular pressure in rheumatoid arthritis, and their relation to disease activity. Middle East Afr J Ophthalmol 2021;28:174-9.

have concluded decrease in CH measurements which proves that microscopic corneal changes occur in the active stage and may continue in the remission stage.[4]

The aim of the study was to evaluate the corneal biomechanical properties such as CH, corneal resistance factor (CRF) and IOP corneal compensated (IOPcc), IOP Goldmann corrected (IOPg), by using Ocular Response analyzer (ORA), to measure the central corneal thickness (CCT) as measured by (OCT) pachymetry and IOP by using Goldman applanation tonometer (IOP GAT) in RA patients and correlate them with the disease activity.

Patients and Methods

All participants signed an informed consent to participate in the study and for publication of data before enrollment in this work. The study followed the Declaration of Helsinki and was approved by the Institutional Review Board and Ethical Committee of Cairo University.

Study design

Forty eyes of forty patients were enrolled in a cross-sectional study that was carried at Cairo University Hospital. Approval for the study was obtained from the hospital's ethical committee.

Eligibility criteria

RA patients with either active or inactive disease presenting to the rheumatology department were recruited in the study. Patients who had any other autoimmune disease, ocular surgery, glaucoma medication, and corneal pathology were excluded from the study.

Forty eyes of 40 RA patients were isolated and divided into two groups by rheumatologist:

- Group A: 20 active RA patients
- Group B: 20 inactive RA patients.

Rheumatologic examination

Rheumatologist calculated the disease activity by using the Clinical Disease Activity Index (CDAI) equation

CDAI = SJC + TJC + PGA + EGA

SJC = swollen joint count; TJC = tender joint count; PGA = patient global assessment; EGA = evaluator global assessment.

SJT and TJC can range from 0 to 28 for each, whereas PGA and EGA can range from 0 to 10 for each making the CDAI value to range from 0 to 76.

Ophthalmic examination

Cases were evaluated by a rheumatologist on the same day of the ophthalmic examination. All patients underwent full medical/ocular history including symptoms of dry eye, with complete ophthalmic examination including best-corrected vision, applanation tonometer, anterior segment examination with special emphasis on the cornea (excluding corneal pathology), lens status, and dilated fundus examination.

Intraocular pressure measurement

Ocular response analyzer

The IOP measurement using ORA was done before GAT. The Reichert ORA (Reichert Ophthalmic Instruments, Buffalo, New York, USA) was used.

At least three measurements were taken; any measurement with a waveform score below 5 was discarded. The software then calculates the most accurate reading and displays it. The reading was then recorded; CRF and CH were also assessed with ORA.

Goldman applanation tonometry

After a resting period of at least 30 min from finishing the ORA measurement, the GAT reading was obtained.

Central corneal thickness

CCT was assessed for all patients by OCT Pachymetry after a resting period of half an hour following ORA examination. Pachymetry Map was obtained: Quantify central corneal thickness within the central 5 mm zone where the minimum thickness is indicated as *. Epithelial map and thickness within central 5 mm zone where the minimum thickness is indicated as *.

Statistical analysis

Data were analyzed statistically in terms of mean, standard deviation (±SD), median, and range. Comparison of numerical data of the study groups was performed using Student *t*-test for independent samples in comparing normally distributed data and Mann Whitney U test for independent samples in comparing non-normal data. Correlation between different variables was performed using Pearson moment correlation equation for linear relation of normally distributed variables and Spearman rank correlation equation for non-normal variables/non-linear monotonic relation. *P* values below 0.05 were considered statistically significant. All statistical calculations were done using the computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

Results

There were 4 males (10%) and 36 females (90%). The average age of the patients included in this study was 52 (±10.7) years old, ranging from 29 to 70.

The average BCVA was 0.875 (±0.10(ranging from 0.6 to 1.0 in the active group (A) and 0.830 (±0.20), ranging from 0.1 to 1.0 in the inactive group (B).

Baseline characteristics

No statistically significant difference was detected among all variables between both groups [Table 1].

We studied the difference between IOP measured by GAT and ORA in both active and inactive groups, and we found that the mean IOP in descending order was IOPcc, IOPg then GAT with its mean 14.24 (±3.0), 12.9 (±3.3), and 12.8 (±2.2) mmHg respectively in the active group A, and 14.90 (±2.5), 13.30 (±2.5) and 12.7 (±2.2) mmHg respectively in the inactive group B. However, there was no statistically significant difference between the two groups (P = 0.4, 0.6, and 0.9).

We studied the correlation between CCT and CH in the two groups, and there was no evident statistically significant correlation between them (P = 0.846 and r = 0.046) and (P = 0.228 and r = 0.282) in active and inactive groups, respectively.

We studied the correlations between IOPcc and IOPg and CH in both groups. A significant negative correlation was found between CH and IOP cc in both groups ($P < 0.002$ and $r = -0.467$) and ($P < 0.003$ and $r = -0.477$) in active and inactive group respectively as displayed in Figure 1a and b, while there was no significant correlation found between CH and IOP g (P = 0.856 and r = 0.03) and (P = 0.441 and r = −0.125) in active and in active group, respectively.

We also studied the correlation between CH and CRF, a positive significant correlation was found in which ($P < 0.001$ and r = 0.818) and ($P < 0.001$ and r = 0.714) in the active and inactive group respectively, as shown in Figure 2a and b.

However, when we studied the correlation between CCT and CRF in both groups, we found a positive statistically significant correlation between CRF and CCT in inactive Group (B ((P = 0.05 and r = 0.0435), but no significant correlation between them in the active group (A) (P = 0.328 and r = 0.231).

We studied the correlation between CDAI score, ORA parameters (CH, CRF, IOPcc, and IOP g), and IOP GAT in both groups. No statistically significant correlation was found.

However, we found a highly negative significant correlation in which was ($P < 0.001$ and $r = -0.823$)

Table 1: Comparison of subjects' demographics and ocular response analyzer data, central corneal thickness measured by optical coherence tomography pachymetry and intra ocular pressure Goldman applanation tonometer Goldmann applanation readings tonometry of both groups

Variable	Active group (n=20)		Inactive group (n=20)		P
	Mean±SD	Range	Mean±SD	Range	
Age (years)	52.6±10.7	30-70	46.6±12.3	29-70	0.107
Disease duration (years)	14.4±9.7	4-35	13.8±7.7	1-30	0.830
CH (mmHg)	9.9±1.3	7.3-12.1	9.3±1.6	6.7-12.1	0.217
CRF (mmHg)	9.2±1.5	7.1-12.8	8.8±1.6	6.1-12.9	0.373
IOPcc (mmHg)	14.2±3.0	8-18	14.9±2.5	10-20	0.425
IOPg (mmHg)	12.9±3.3	7.0-18.9	13.3±2.5	9.1-18.8	0.676
CCT (µm)	517.0±22	472-563	509.5±19.6	477-566	0.265
IOP (mmHg)	12.8±2.2	10-16	12.7±2.2	10-18	0.943

SD: Standard deviation, CH: Corneal hysteresis, CRF: Corneal resistance factor, IOP: Intraocular pressure, IOPcc: IOP corneal compensated, IOPg: IOP Goldmann corrected, CCT: Central corneal thickness

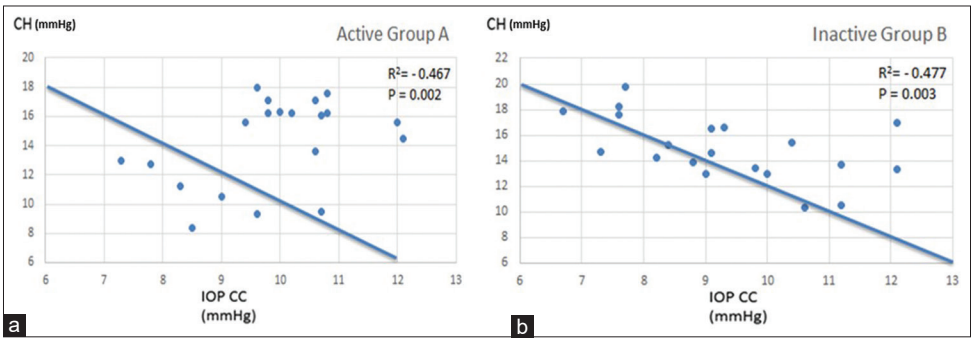

Figure 1: (a) Correlation between corneal hysteresis and intraocular pressure corneal compensated in active group (A). (b) Correlation between corneal hysteresis and intraocular pressure corneal compensated in inactive group (B)

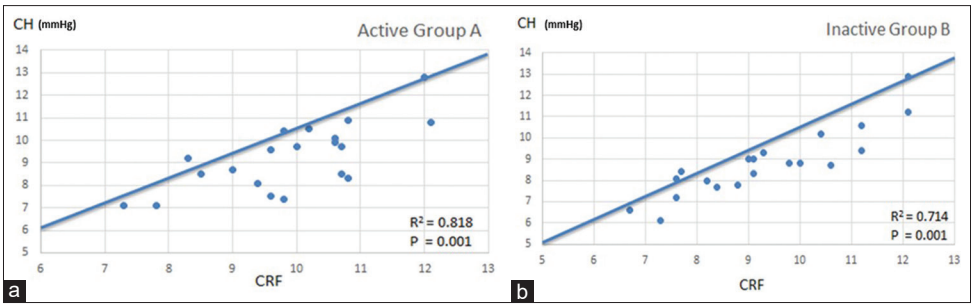

Figure 2: (a) Correlation between corneal hysteresis and corneal resistance factor in active group (A). (b) Correlation between corneal hysteresis and corneal resistance factor in inactive group (B)

between CDAI and CCT in Active Group (A) as shown in Figure 3 while no such correlation between them in the inactive group (B) ($P = 0.816$ and $r = 0.102$).

We studied the correlations between the (IOPcc, IOPg) and IOP GAT in both groups. A highly significant positive correlation was found ($P < 0.001$) ($r = 0.768$ and 0.932 respectively) and ($P < 0.001$) ($r = 0.905$ and 0.951) in active and inactive group respectively

However, when we studied the correlations between IOP GAT and CCT in both groups, the correlation was insignificant between both groups ($P = 0.08$ and $r = 0.280$) and ($P = 0.4478$ and $r = 0.124$) in active (A) and inactive (B) group respectively.

Correlation between IOP GAT and CH was insignificant ($P = 0.975$ and $r = -0.005$) and ($P = 0.193$ and $r = -0.210$) in the active and inactive group, respectively.

Discussion

RA is an autoimmune disease with periods of activity and remission. The ocular inflammatory signs can be observed in active periods, yet subtle tissue changes might occur in the remission phase as detected by ORA.[4]

Some reports have proved that other autoimmune connective tissue disorders, as systemic lupus erythematosus and scleroderma, can change the corneal biomechanical properties as assessed by the ORA.[5,6]

In the current study, we studied the biomechanical properties, CCT and IOP in RA and correlated them with the activity of the disease.

In the current study, 20 active (group A) and 20 inactive (group B) patients of RA were included. The mean values of CH were 9.8 (±1.3) and 9.3 (±1.6) in active and inactive group respectively which is lower than the normal Egyptian population values as compared to the work of Allam and Khalil in 2015, who studied 350 eyes of 350 normal people (half of them were men) using the ORA to measure corneal biomechanical properties. They found the mean CH in men was 9.69 (±2.05) mmHg and in women 10.41 (±1.65) mmHg with a significant *P* value.[7]

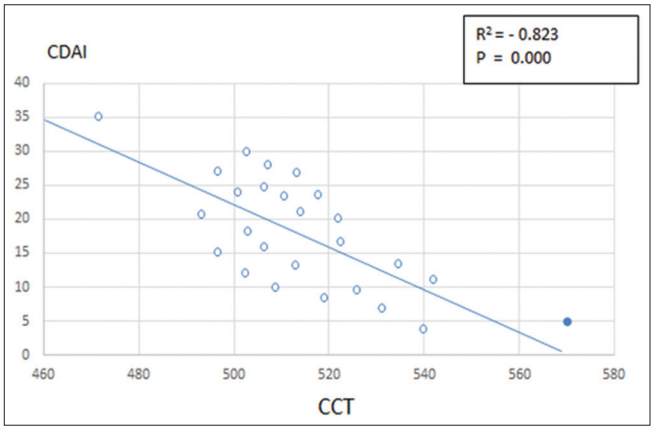

Figure 3: Correlation between Clinical Disease Activity Index and central corneal thickness in active group (A)

Another study was published in May 2017 by Ali *et al*., in which CH and CRF were measured in 195 Egyptians, healthy people. The mean CH value was 10.25 ± 0.12 mmHg, and the mean CRF was 10.25 ± 0.15 mmHg which also was higher than the values of the current study. A possible explanation for the lower CH found in our study would be less CCT due to irreversible stromal changes and epithelial thinning due to dryness which is a common occurrence in RA.[8]

Prata *et al*.'s results matched the current results, as they studied twenty eyes of eleven female RA patients and compared them to 36 eyes of 20 female healthy controls. Hysteresis had lower values in the RA eyes than in the healthy ones. No significant difference was found between the RA patients and healthy subjects as regarding the IOP. They did not classify the RA patients according to the activity of the disease.[9]

Similarly, Atalay *et al*. in 2015 investigated the pattern of corneal biomechanics in RA patients after classifying them into mild, moderate, and severe considering the disease activity using a Disease Activity Score (DAS)-28

and compared it with normal healthy controls. They determined a decrease in the mean CH measurements in all groups, indicating the ultra-structural corneal changes in the active stage that may remain in the remission phases.[10]

In our study, we found no relation between CH and the activity of the disease as measured by CDAI. Each parameter was compared in both groups, and no significant difference was found among them; these results were matching previous studies. Can and his coworkers in 2015, revealed that there was no significant difference between CH in both active and inactive phases. The low CH parameters in the remission stage confirm the ultra-structural corneal changes that occur which are irreversible and persistent, despite disease inactivity. So, there was no relation between CH and the activity of the disease as measured by CDAI.

In the current study, we found a highly significant negative correlation between CH and IOPcc ($P < 0.002$ and 0.003), respectively, in active and inactive groups. So the higher the IOPcc, the lower the CH. These results were the same as previous reports, Can *et al*. suggested that the IOPcc values were higher with ORA because of the change in CH values. However, no significant correlation was detected between CH and IOPg or IOP GAT.[4]

Yazici *et al*. studied the corneal biomechanics in systemic lupus erythematosus (SLE) in comparison to controls of the same age group and showed that CH and CRF values are lower in the SLE group.[6]

In this study, the authors found the mean CCT parameters were 517.0 (±22.0) mm and 509.5 (±19.6) mm in active and inactive groups, respectively. This is much less than the average normal health CCT which is 542 mm.[8,11] The difference between groups regarding CCT was not statistically significant ($P = 0.263$); these results were in accordance with Atalay *et al*.'s previous results.[10]

There wasn't any significant correlation between CH and CCT; normally CH and CCT should be related as was suggested by different studies,[11] so that less CCT means less CH and is associated with more glaucoma damage. Our different results may be attributed to the small sample, so that's why we couldn't elicit a relation)

Statistically significant positive correlation between CCT and CRF in the inactive group ($P = 0.05$) was found in this study, which was in accordance to previous studies in which the higher the CCT, the higher the hysteresis (visco-elasticity) and CRF (elasticity) and vice versa.[12]

CDAI score was used to assess the activity of the disease in this study, we found a statistically significant negative correlation with the CCT in the active group ($P < 0.001$ and $r = -0.823$), meaning that the higher the activity score, the lower the CCT. This may open a new era between rheumatology and ophthalmology as this may show that CCT can be taken in consideration as a parameter to measure the activity of the disease. To our knowledge, this is the only study that correlates the CDAI score with other ocular parameters. Other studies using DAS-28 score activity to measure the activity of RA did not mention such correlation.[4]

DAS-28 score needs more investigation and is more time-consuming when compared to CDAI.[13]

As regarding the mean IOP, it was found to be 14.24 (±3.0), 12.9 (±3.3), and 12.8 (±2.2) mmHg as measured by IOPcc, IOPg, and GAT respectively in the active group (A), and 14.90 (±2.5), 13.30 (±2.5) and 12.7 (±2.2) mmHg respectively in the inactive group (B). However, there was no significant difference between the active and inactive groups. Since IOPcc measurements were always higher than IOP GAT, the possibility of a false low IOP GAT measurement should be considered in patients with RA, especially in glaucomatous patients. This could be explained by the fact that in RA, both corneal epithelium and corneal stroma show pathological changes. Some authors examined stromal ultra-structural changes in RA and revealed that there were changes in both the corneal extracellular matrix and collagen, which resulted in a structural weakening.[14] These stromal and superficial corneal changes may be the cause of the low CH and CCT values that we found.

The limitation of the current study was the deficient evaluation of dryness severity. Most of our cases reported symptoms of dryness as corneal thinning might be due to dry eye. Also, the lack of normal control for this study was another limitation, but we relied on data from normal Egyptian studies to compare our results to.

Conclusion

We found in this work that corneal biomechanical properties change in RA patients in active stage and that these changes may persist through the remission phases. This may indicate that any corneal changes would be irreversible and persistent. These changes are of utmost significance regarding IOP measurement in rheumatoid patients; CCT may be a new parameter in the follow-up of disease activity.

Furthermore, the current exponential spread of corneal refractive procedures necessitates a deeper

understanding of the pathological and biomechanical corneal properties in RA patients for proper evaluation.

Acknowledgement

We would like to thank Dr Mervat Eissa the associate professor of rheumatology at Kasr Alaini hospital for her outstanding help during this work.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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