• Clinical Research •

Corneal light scattering and anterior segment findings in rheumatoid arthritis patients: a prospective study on disease monitoring

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Abstract

● **AIM:** To evaluate changes in corneal light scattering and anterior segment parameters in newly diagnosed rheumatoid arthritis (RA) patients who achieved remission with systemic treatment, compared to healthy controls.

● **METHODS:** A cross-sectional study was conducted at a tertiary care hospital, in ophthalmology, and rheumatology departments. A total of 42 RA patients (13 men and 29 women) and 56 healthy individuals (23 men 33 women) underwent comprehensive ophthalmologic evaluations, including Scheimpflug corneal densitometry and Pentacam HR measurements. Those who initiated systemic treatment for RA were monitored at first, third, and sixth-month follow-ups. Participants who achieved remission at each follow-up assessment were included.

● **RESULTS:** Significant differences in corneal densitometry were observed, with higher values in RA patients, particularly in the middle and posterior layers. Anterior segment parameters such as anterior chamber volume and angle were significantly reduced in RA patients compared to other groups (P<0.001). Following systemic treatment and achievement of remission, these parameters showed regression toward normal values.

● **CONCLUSION:** The study underscores the potential utility of corneal densitometry and anterior segment analysis as sensitive indicators of subclinical ocular involvement in RA, offering insights into disease progression and treatment efficacy. These findings highlight the importance of early detection and regular monitoring in preventing vision-threatening complications in RA patients.

● **KEYWORDS:** rheumatoid arthritis; corneal light scattering; anterior segment; corneal densitometry; systemic treatment; disease monitoring; remission

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INTRODUCTION

Corneal light scattering can be easily measured through the optical densitometry method, providing rapid results with high reproducibility, ultimately offering objective data about the health of the cornea[1]. Any pathology that can cause changes in the structure of the cornea, such as an abnormal collagen fiber arrangement or the accumulation of molecules that cannot be detected through biomicroscopic examinations, can significantly affect the light scattering. This, consequently, may result in alterations in both visual acuity and contrast sensitivity, impacting overall visual quality.

This technique has gained popularity over the years both to understand the progression of primary eye diseases and to assess the impact of systemic diseases on the cornea. Variable studies have reported changes in corneal densitometry in several diseases such as keratitis, keratoconus, Fuchs endothelial dystrophy, or in systemic diseases such as Wilson's disease, gout, and diabetes mellitus[2-10].

Rheumatoid arthritis (RA) is one of the most common chronic systemic inflammatory autoimmune diseases affecting cornea,

with a prevalence that is steadily increasing and affecting approximately 1% of the population[11-12]. The pathophysiology of RA is characterized by chronic inflammation, which leads to the proliferation of the synovium and, subsequently, causes damage to cartilage and erosion of bone. The disease can also manifest with various extraarticular symptoms, involving the cardiovascular, cutaneous, pulmonary, renal, skeletal, and ocular systems.

Ocular manifestation of RA may present as the initial symptom of the disease. In fact, RA can affect any part of the eye and a rheumatologist must possess a thorough understanding of ocular conditions[13-15]. Among the ocular manifestations, dry eye disease (DED) is the most prevalent, followed by conditions such as episcleritis, scleritis, peripheral ulcerative keratitis (PUK), corneal melting, and ulcers, uveitis, and vasculitis[16-17].

Corneal scattering and other anterior segment structures are of paramount importance for visual prognosis. Analyzing these parameters can play a crucial role in the early diagnosis and monitoring of clinical, structural, and functional changes in RA. Early detection of ocular involvement in RA patients is essential, as it not only provides insights into the progression of the systemic disease but also enables regular monitoring and prevention of complications that could threaten vision. In this context, we aimed to assess the changes in anterior segment findings following the achievement of remission with systemic treatment in newly diagnosed RA patients, who had no clinical corneal involvement at baseline and at 6mo, compared with a healthy control group.

PARTICIPANTS AND METHODS

Ethical Approval This cross-sectional study was conducted between January 2019 and November 2020, at a tertiary care hospital, in Türkiye. The institutional research board approval was acquired before the conductance of study (IRB Number: 57212153-774.01.99-351). The study protocol followed the rules of Helsinki Declaration. The informed consent was obtained from all participants.

Our study consists of three groups. Group 1 represents the healthy control group, group 2 represents newly diagnosed RA patients, and group 3 represents newly diagnosed RA patients who achieved remission after 6mo. Patients diagnosed with RA according to the 2010 Rheumatoid Arthritis Classification Criteria were evaluated by an ophthalmologist before treatment[18]. Patients who initiated systemic treatment for RA were assessed during the first, third, and sixth-month follow-up visits. Patients who were assessed according to the American College of Rheumatology Criteria during the 6th-month follow-up and were reported to be in remission at each visit by the rheumatologist were included in the study[19]. Only the right eyes of the subjects were taken into consideration. Patients with detected any ocular surface pathology during any visit were excluded. The other exclusion criteria are as follows: presence of any corneal pathologies or severe dry eye findings at the initiation, any history of systemic diseases other than RA, having a history of ocular disease, surgery, trauma, or laser treatment, refractive error greater than ±3 diopters, contact lens wear, ocular trauma, uveitis, strabismus, nystagmus, pregnancy, or inability to cooperate with Scheimpflug corneal topography image acquisition.

A comprehensive ophthalmologic evaluation was conducted. This evaluation included best-corrected visual acuity (BCVA) assessment using the Snellen chart, anterior segment examination *via* slit-lamp biomicroscopy, Schirmer's test, tear break-up time, intraocular pressure (IOP) measurement (Goldmann applanation tonometer), and dilated fundus examination. The Scheimpflug densitometry analysis of the cornea was performed using the Pentacam HR (Oculus Optikgerate GmbH, Wetzlar, Germany) for all participants. Anterior and posterior keratometry values, anterior and posterior astigmatism, central corneal thickness (CCT), corneal volume (CV), anterior chamber depth (ACD), anterior chamber angle (ACA), and anterior chamber volume (ACV) were measured and recorded for all participants during the same session.

All measurements were conducted under consistent room illumination conditions, within the same time period of the day (9 *a.m.* to 3 *p.m.*), and administered by the same experienced operator (Yılmaz YC), prior to other ocular examinations such as applanation tonometry. The automatic release mode was employed to minimize operator-induced errors. Corneal densitometry (CD) was performed before pupillary dilation. The degree of backward light scattering was quantified using the Pentacam HR in grayscale units (GSU) ranging from 0 to 100, where 0 indicates minimal light scattering and 100 represents a completely opaque cornea. Additionally, the cornea was divided into four concentric zones by the software. In the analysis, the program located the corneal apex and analyzed four annular areas (0–2, 2–6, 6–10, and 10–12 mm diameter) around the apex. For each concentric zone, CD was measured for three separate layers: anterior (120 μm), middle (space between anterior 120 μm and posterior 60 μm), and posterior layers (60 μm).

Normative CD data reveal a consistent decrease in light backscatter from the anterior to the posterior layers of the cornea. The corneal epithelium is a primary source of light backscattering due to significant differences in refractive indices. In contrast, the middle layer, primarily composed of the corneal stroma, exhibits lower scattering. This reduction is attributed to the precise organization of collagen fibrils and the surrounding extracellular matrix. The posterior stroma, with

Table 1 Comparison of anterior segment parameters between the rheumatoid arthritis patients at baseline and 6mo and control group

Parameters	Control (group 1)		Baseline (group 2)		6mo (group 3)		*P*1	*P*2
	Mean	SD	Mean	SD	Mean	SD		
Anterior Kmean	43.64	1.2	43.74	0.9	43.97	0.9	0.684	0.255
Anterior astigmatism	0.87	0.6	0.74	0.6	0.8	0.6	0.127[a]	0.142[b]
Posterior Kmean	6.35	0.2	6.33	0.1	6.35	0.2	0.277[a]	0.120[b]
Posterior astigmatism	0.29	0.1	0.22	0.1	0.25	0.2	0.007[a]	0.297[b]
CCT	529.75	30.3	532.19	33	526.4	25.3	0.705	0.391
ACD	3.01	0.3	2.99	0.26	2.95	0.3	0.669	0.483
ACV	153.77	31.4	126.79	21.9	152.83	28.3	<0.001	<0.001[b]
ACA	38.76	7.1	33.68	5.1	38.03	4.6	<0.001	<0.001[b]
CV	59.8	3.4	59.48	3.1	58.36	3.7	0.634	0.193

*P*1: *P* value between the groups 1 and 2; *P*2: *P* value between the groups 2 and 3. [a]Mann-Whitney *U* test; [b]Wilcoxon signed-rank test. SD: Standard deviation; K: Keratometry; CCT: Central corneal thickness; ACD: Anterior chamber depth; ACV: Anterior chamber volume; ACA: Anterior chamber angle; CV: Corneal volume.

its highly organized structure and lower keratocyte density, demonstrates the lowest densitometry values. Regarding annular CD values, the highest measurements are typically observed in the 10–12 mm annulus, followed by the 6–10, 0–2, and 2–6 mm annuli. The increased retroreflection in the peripheral region is likely due to the circumferential orientation of peripheral corneal collagen fibers relative to the limbus and the larger diameter of the elastic fibers. Variations in the corneal diameter, as measured white-to-white, could affect CD values in the 10–12 mm region. Specifically, if the corneal diameter is less than 12 mm, the densitometry analysis may include the limbal part of the cornea, where CD tends to be higher. Literature data consistently indicate that the 2–6 mm region of the cornea exhibits the lowest densitometry values across both healthy populations and patient groups. This suggests that the 2–6 mm region is inherently the most transparent area of the cornea and likely the last region to be affected by pathological changes. However, the exact underlying cause of this phenomenon remains unclear[2,10,20-21].

Statistical Analysis The Statistical Package for the Social Sciences (SPSS) software version 22 (SPSS Inc., Chicago, IL, USA) was utilized for statistical analysis. The Kolmogorov-Smirnov test was employed to determine the data distribution. Descriptive statistics were presented as mean±standard deviation. The independent *t*-test or Mann-Whitney *U* test was employed for intergroup analyses, depending on the normality of the data distribution. For the analysis of dependent groups, the paired sample *t*-test and Wilcoxon signed-rank test were used for normally and non-normally distributed data, respectively. The statistical significance level was set at $P<0.05$.

RESULTS

Fifty-six newly diagnosed RA patients were evaluated at the initial examination. Fourteen patients who did not achieve remission by the sixth month or did not regularly attend follow-up appointments were excluded. Thus, 42 RA patients and 56 healthy individuals were included in the study. The mean ages of the patients and the control group were 43.07±8.62 and 40.54±8.09y, respectively. The RA group consisted of 13 men and 29 women, while the control group included 23 men and 33 women. There were no significant differences in age and gender distribution between groups ($P=0.084$ and 0.304, respectively). The mean BCVA was 20/20 in both examinations. Throughout the follow-up period, no ocular adverse drug reactions were observed as a result of treatment. All participants had clear corneas and crystalline lenses. The mean IOP was measured as 15.98±3.32, 14.26±4.2, and 16.44±3.2 mm Hg for groups 1, 2, and 3, respectively ($P<0.001$ for groups 1 and 2 and groups 2 and 3, respectively).

When comparing anterior segment parameters, no significant differences were found between the groups except in ACA and ACV parameters. The ACA and ACV values were significantly lower in group 2 compared to the other groups. The anterior segment findings were summarized in Table 1.

In both examinations, the CD values decreased from anterior to posterior as shown in Table 2. Significantly higher CD values were observed in group 2 compared to the other groups in the anterior layer at the 6–10 and 10–12 mm zones. In the middle layer, group 2 had higher values compared to group 1 in all zones, but had higher values only in the 6–10 and 10–12 mm zones compared to group 3. In the posterior layer, group 2 had higher values compared to group 1 in all zones, and higher values in the 2–6, 6–10, and 10–12 mm zones compared to group 3.

DISCUSSION

RA, a systemic autoimmune disease, is associated with a chronic inflammatory process that has the potential to damage both joints and extraarticular organs[22]. Beyond mobilizing additional cells for joint attacks, these cytokines trigger a systemic cascade, potentially establishing a connection

Table 2 Comparison of the corneal densitometry measurements (gray scale units) between the rheumatoid arthritis patients at baseline and 6mo and control group

Layer	Annulus, mm	Control (group 1)		Baseline (group 2)		6mo (group 3)		*P*1	*P*2
		Mean	SD	Mean	SD	Mean	SD		
Anterior	0–2	21.27	1.4	21.56	2.0	21.46	1.5	0.399	0.797
	2–6	19.67	2.0	19.80	2.4	19.65	1.6	0.763	0.709
	6–10	23.19	3.0	28.45	4.5	25.25	5.2	<0.001[a]	0.006[b]
	10–12	30.47	4.8	35.44	6.9	31.95	6.9	<0.001	0.020
Middle	0–2	15.61	1.1	17.13	2.3	16.97	1.3	<0.001[a]	0.871[b]
	2–6	15.26	1.0	16.76	1.7	16.36	2.4	<0.001[a]	0.249[b]
	6–10	20.60	3.9	24.37	3.9	22.39	5.6	<0.001[a]	0.016
	10–12	22.05	4.3	27.76	4.4	24.37	4.7	<0.001	<0.001[b]
Posterior	0–2	12.63	1.0	14.48	1.1	14.31	1.8	<0.001[a]	0.629
	2–6	11.38	0.8	16.28	1.4	14.23	2.5	<0.001[a]	<0.001
	6–10	15.30	3.0	18.56	2.9	16.64	4.1	<0.001[a]	0.010
	10–12	17.13	3.6	24.28	3.4	21.78	4.2	<0.001	0.002

*P*1: *P* value between the groups 1 and 2; *P*2: *P* value between the groups 2 and 3. [a]Mann-Whitney *U* test; [b]Wilcoxon signed-rank test.

between RA and various organs, notably eyes. It is well-known that RA is one of the most prevalent autoimmune diseases affecting the cornea, and the literature frequently highlights patient series with active corneal pathology and their corresponding outcomes[23-27]. Detecting subclinical changes secondary to inflammation during the early stages, which might be considered normal in ophthalmological examinations, can prevent subsequent complications, thus averting both time and economic losses in the management. In line with this objective, our study aims to assess the CD and anterior segment parameters, identifying subclinical changes that correlate with the regression of systemic inflammation in patients with RA.

In DED, the most common ocular manifestation of RA, the desired smoothness of the ocular surface is compromised, leading to alterations in light scattering and reflections due to secondary corneal changes. In this context, Koh *et al*'s[28] study demonstrated increased CD values in the anterior layer in eyes diagnosed with DED. In another study, an increase in CD was observed among the patients with RA, specifically within the same layer[29]. Both the studies conducted by Chen *et al*[30] and Kanellopoulos and Asimellis[31] demonstrated an increase in epithelial thickness in patients with DED. Liang *et al*[32] also investigated corneal epithelial cell thickness in individuals with moderate DED. They stated that, in the limbal region, responsible for corneal epithelial cell turnover, DED patients exhibited a significantly lower epithelial cell thickness. Infiltration of this region by inflammatory cells and increased cytokine levels in tears may inhibit stem cell metabolism. Consequently, epithelial deterioration becomes noticeable in the peripheral region over time, whereas a similar situation is not detected in the central part of the cornea. In the current study, significantly higher CD values were found in the anterior layer except 0–2, and 2–6 mm zone in group 2. When considering our study results and a comprehensive review of the literature, asserting that changes in the cornea and the treatment response in DED both originate from the peripheral cornea in the anterior layer would not be surprising.

The susceptibility of the anterior peripheral cornea to inflammatory infiltrate may be attributed to its dependence on nearby capillary beds for nutrient supply. This vulnerability is observed not only in DED but also in conditions such as PUK, where inflammatory cells accumulate at the corneal stroma's periphery, adjacent to the corneal limbus. In RA, corneal biopsies from the peripheral region in scleritis predominantly reveal lymphocytes. Studies involving biopsies of necrotizing scleritis demonstrate T-cells implicated in the pathogenesis of RA[33-35].

On the other hand, the aqueous humor is the most accessible form of the ocular microenvironment and naturally contains soluble factors that inhibit the activation/proliferation of lymphocytes. During the early stages of uveitis, immunopotentiating cytokines may be released into the anterior chamber, disrupting immunosuppression and leading to the development of inflammatory/autoimmune ocular disease. Hence, it has been hypothesized that in anterior uveitis, changes in the composition of the aqueous humor occur first, followed by lymphocyte infiltration, exacerbating the disease[36-37]. In this context, worsening of endothelial cells secondary to increased inflammation is also an expected outcome in anterior uveitis. Previous studies on Fuch's uveitis have also demonstrated an increase in posterior densitometry values[38-39]. Our study aligns with existing literature, revealing a marked increasing in the CD values in the posterior layer in group 2. This observation serves as compelling evidence for the existence of cellular-level pathology in the anterior

chamber, and the regression of this pathology with treatment, as detected through densitometry, even in the absence of clinical detection in the newly diagnosed RA patients.

Villani *et al*[40] conducted an assessment of corneal microstructural changes in the patients with RA using *in vivo* confocal microscopy. In their study, the RA group exhibited a lower density of superficial epithelial cells. However, notable increases were observed in the basal epithelium, anterior and posterior stromal cell densities compared to the control group. These elevated levels of formations are indicative of metabolic activation in the keratocytes among patients with ocular surface inflammation. In that study, an increased cell density was observed not only in the epithelium layer but also in the stromal layer. This suggests that there is an elevation in the CD values in RA, and it would not be incorrect to assume that this correlates with the duration and severity of the disease. Studies have reported an increase in subbasal dendritic cells in inflamed eyes and a decrease in dendritic cell density in the same layer after systemic treatment[41-42]. The change in corneal backscattering values with treatment in our study was found to be consistent with the literature, except for not involving the central part of middle and anterior layer.

The only study comparing CD in RA patients and healthy participants was Anayol *et al*[29]. Contrast to our results, higher densitometry values were observed only in the anterior 0–2 and 2–6 mm zones, as well as in the middle and posterior 10–12 mm zones in the RA group. The differing results among studies could be associated with differences in patient age and sample size. Additionally, factors directly impacting densitometry measurements, such as disease duration, receipt of systemic treatment, and disease activity or remission status, were not addressed in that study.

In the literature, no statistically significant difference has been found in the keratometric values of RA patients[43-45]. However, Özkaya *et al*[46] and Gurlevik *et al*[47] reported significantly higher keratometric values across all zones in RA patients. Contrary to these findings, we did not observe a significant difference in keratometric values. It has been hypothesized that peripheral corneal involvement in RA could lead to steeper curvature, but our study did not identify similar findings. Instead, we observed a decrease in posterior astigmatism in the treatment-naive group, which disappeared after the treatment. We attribute this effect to the potential deterioration of endothelial pump function caused by immunopotentiating cytokines in the anterior chamber, leading to temporary edema and a reduction in astigmatism in the posterior cornea.

It has been demonstrated that CCT in individuals with RA is thinner compared to the healthy control group, irrespective of the presence of Sjögren's syndrome[40,48]. This thinning may be attributed to the activity of matrix metalloproteinases and collagenases[40]. In RA, corneal morphology is affected by increased apoptotic and proteolytic activity in corneal stromal changes. However, we did not find a significant change in CCT between the groups. There is no definitive consensus on this issue in the literature. Gunes *et al*[44] and Özkaya *et al*[46] reported a significant decrease in CCT, while Özcura *et al*[45] and Can *et al*[49] found no difference in CCT between RA eyes and control eyes. Similar to CCT, another parameter expected to be affected by disease activity is total CV. Contrary to studies indicating a negative impact of the disease on CV, we could not found the same result[43-44,46]. In the current study, CV did not differ significantly among the three groups. Some studies have reported similar findings regarding the CV value[47,49]. Previous studies have indicated that RA negatively affects corneal endothelial cells[36-37,50]. Chronic inflammation is thought to result in changes in endothelial and stromal morphology, causing stromal and epithelial edema, and increased CV due to the deterioration of endothelial pump function. Considering the diverse results in the literature, we believe that CV and CCT parameters in RA are affected by multifactorial mechanisms (limbal involvement, proteolytic activity, and endothelial cell damage), leading to varied outcomes.

The number of studies evaluating the anterior chamber in RA patients is limited. It has been reported that patients with RA have similar anterior segment parameters to the healthy population[29,43,49]. Can *et al*[49] found no significant difference in ACD and ACV in active or remission RA patients compared to the control group. Gurlevik *et al*[47] also found no significant difference in ACD and ACA values between RA patients and the control group. However, Tasli *et al*[50] reported a decrease in ACD in the RA group, which showed a negative correlation with disease duration. In our study, we detected significant changes in ACA and ACV parameters between groups 1 and 2, as well as between groups 2 and 3. Our results showed that the posterior layer is the most affected part of the cornea, as indicated by densitometry values, highlighting the impact of the inflammatory process in the anterior chamber in RA. Therefore, we believe that in RA, particularly in the early stages, there might be involvement of the ciliary body, where vascularization is likely the highest compared to other parts of the ocular system. This can lead to a reduction in aqueous humor production and consequently a decrease in ACV and ACA values. We clearly observed significant changes in these values after treatment, supporting our hypothesis. Based on these findings, we may conclude that anterior segment parameters other than ACA and ACV may not serve as significant prognostic indicators in the early diagnosis and treatment monitoring of RA.

The small sample size, resulting from our inclusion criteria,

which focused solely on patients newly diagnosed and remaining in remission throughout the follow-up period, could be considered a limitation of our study. Furthermore, the absence of confocal microscopy and specular microscopy analyses may limit the comprehensiveness of our findings, as these modalities could provide additional insights into corneal and anterior segment changes in RA patients. Despite these challenges, it is noteworthy that our study holds the distinction of being the first in the literature to investigate changes in anterior segment parameters in newly diagnosed RA patients who achieved remission following systemic treatment.

In conclusion, CD and anterior segment parameters such as ACA and ACV are sensitive indicators of subclinical ocular involvement in RA. Achieving remission with systemic treatment led to significant improvements in these parameters, suggesting their potential utility in monitoring disease progression and treatment efficacy. These findings highlight the importance of early detection and management of ocular manifestations in RA to prevent long-term visual complications. Further studies with larger cohorts are warranted to validate these findings and establish these parameters as diagnostic and therapeutic markers in RA and potentially other systemic autoimmune diseases affecting the eye.

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