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The relationship between scleral thickness, corneal parameters, and interstitial lung disease in patients with rheumatoid arthritis

Romatoid artritli hastalarda sklera kalınlığı, kornea parametreleri ve interstisyel akciğer hastalığı arasındaki ilişki

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Abstract

Objective: This study aimed to examine scleral thickness (ST) and corneal parameters in patients with rheumatoid arthritis (RA) and healthy individuals and to investigate the association of these parameters with rheumatoid arthritis-associated interstitial lung disease (RA-ILD).

Methods: The study recruited 59 patients with RA and 31 healthy individuals of similar age and gender. Patient records were reviewed for serological findings, disease activity score-28, disease duration, and medical treatment. The RA patients were divided into two groups: Those with RA-ILD and those without ILD (RA-noILD). The study measured ST at 1000, 2000, and 3000 μm from the scleral spur, corneal volume as well as central corneal thickness for all participants. Patients with RA-ILD were also assessed with delta high-resolution computed tomography (Δ HRCT) and pulmonary function tests (PFT) to determine the severity of ILD.

Results: The clinical and laboratory characteristics of the RA groups were similar. There were statistically significant differences in ST1000, ST2000, and ST3000 measurements between patients with RA and healthy controls (p=0.007; p<0.001; p=0.001, respectively). However, there was no correlation between ocular parameters and PFT or Δ HRCT.

Conclusion: The study found that patients with RA-ILD had scleral thinning, although there was no scleral involvement. However, this difference was not statistically significant when compared to RA-noILD patients.

Keywords: Scleral thickness, corneal parameters, RA, ILD

Öz

Amaç: Bu çalışmada, romatoid artritli (RA) hastalarda ve sağlıklı kontrollerde kornea parametrelerinin ve sklera kalınlığının (ST) değerlendirilmesi ve bunların romatoid artrit ile ilişkili interstisyel akciğer hastalığı (RA-ILD) ile ilişkisinin belirlenmesi amaçlandı.

Yöntemler: Çalışmaya yaş ve cinsiyet açısından eşleştirilmiş 59 RA'lı hasta ve 31 sağlıklı kontrol dahil edildi. Serolojik bulgular, hastalık aktivite skoru-28, hastalık süresi ve medikal tedavi gibi parametreler kayıt edildi. RA'lı hastalar RA-ILD'si olanlar ve RA'sı olan ancak ILD'si olmayanlar (RA-noILD) olmak üzere iki gruba ayrıldı. Her katılımcının kornea hacmi, kornea kalınlığı ve ST 1000, 2000 ve 3000 μm mesafelerde ölçüldü. RA-ILD'li hastalarda, akciğer tutulum şiddetini belirlemek için delta yüksek çözünürlüklü bilgisayarlı tomografi (Δ HRCT) ve solunum fonksiyon testi (SFT) yapıldı.

Bulgular: RA'lı hastalar ile sağlıklı kontroller arasında karşılaştırıldığında ST1000, ST2000 ve ST3000 seviyelerindeki ölçümleri istatistiksel olarak farklı bulundu (sırasıyla p=0,007; p<0,001; p=0,001). Oküler parametreler ile SFT veya Δ HRCT arasında korelasyon yoktu.

Sonuç: RA-ILD hastalarında skleral tutulum olmamasına rağmen, skleral incelme vardır, ancak RA-noILD hastalarına kıyasla istatistiksel olarak anlamlı bir farklılık göstermezler.

Anahtar Kelimeler: Skleral kalınlık, korneal parametreler, RA, ILD

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Introduction

Rheumatoid arthritis (RA) is a disease that causes inflammation in the body and primarily affects the joints but can also cause symptoms in other parts of the body.[1] Ocular manifestations occur in 25% of RA patients and may lead to complications like scleritis, keratitis, retinal detachment, episcleritis, keratoconjunctivitis sicca, peripheral corneal ulceration, and choroiditis, which can negatively impact a patient's quality of life.[2,3] Studies have suggested that ocular pathologies in RA are linked to serum levels of tumor necrosis factor-alpha (TNF-α), IL-6, IL-23, TGF-β2, and MMPs.[4-8] Interstitial lung disease (ILD) is another extra-articular manifestation (EAM) of RA that can lead to poor prognosis and increased morbidity and mortality.[9] Therefore, all RA patients should be assessed for ILD, as it can cause irreversible lung damage. Various factors like TNF-α, TNF-β, interleukin (IL)-1, IL-4, IL-5, IL-13, vascular endothelial growth factor, and platelet-derived growth factor have been implicated in the development of ILD.[10]

There are few studies in the medical literature that investigate corneal parameters and scleral thickness (ST) in patients with RA. The prevalence of scleral inflammation in RA is reported to be between 0.63% to 0.67%.[11] RA can cause mild episcleritis or full-thickness scleritis, which may lead to scleral melting in rare cases.[12] Scleral tissue destruction and immune complex deposition have been linked to scleral melting.[11] A published study reported no significant difference between RA patients and healthy controls in terms of ST.

To date, no study has explored the relationship between ILD and ocular parameters in patients with RA. This study aimed to assess corneal parameters and ST in patients with RA and healthy controls, as well as determine their association with ILD.

Materials and Methods

This study was conducted as a cross-sectional study by including RA patients who were monitored by the rheumatology clinic and healthy individuals who underwent routine ophthalmology examinations at the same hospital. The diagnosis of RA was established by a rheumatologist using the American College of Rheumatology diagnostic criteria for RA.[13]

Prior to participating, all individuals were informed about the study's purpose and provided written consent. The study was conducted in accordance with the principles of the Helsinki Declaration and was approved by the Local Ethics Committee of Pamukkale University (approval number: 60116787-020-110161).

This study aimed to collect various data from participants, including age, sex, body mass index (BMI), weight, height, disease duration, serological findings, and disease activity score-28 (DAS-28). Medical treatment of patients was also documented, and all patients underwent a thorough physical examination. Additionally, hematological parameters such as C-reactive protein, erythrocyte sedimentation rate, anti-citrullinated protein antibody (ACPA), and rheumatoid factor (RF) were studied.

Patients were subdivided into two groups based on their clinical features, high-resolution computed tomography (HRCT) results, and pulmonary function tests (PFT).[14-18] The groups included patients with RA-ILD and patients with RA-noILD. The clinical, radiological, histological, and PFT results of the RA-ILD group are presented in Table 1.

To assess the extent and severity of ILD, the delta HRCT scoring system was used,[16] and all HRCT scans were evaluated and scored by two board-certified radiologists. The radiologists were blinded to the characteristics of the patients and had seven and three years of experience in thoracic imaging, respectively. The mean scoring system of A HRCT in patients with RA-ILD is shown in Table 2.

Evaluation of Ocular Parameters

All participants underwent a comprehensive ophthalmological examination, which included visual acuity testing, measurement of intraocular pressure, evaluation of the fundus, assessment of refractive error, biomicroscopy, and measurements of ST and

Table 1. Description of incident RA-ILD cases (n=22)

Clinical, radiological, and PFT parameters	n (%) or mean ± SD
-Dyspnea	12 (54.5)
-Dry cough	14 (63.6)
-Fatigue	18 (81.8)
-Weakness	11 (50)
RA-ILD subtype	
-Cellular NSIP	6 (27.2)
-Fibrotic NSIP	7 (31.8)
-UIP/AIP/DAD	9 (40.9)
Pulmonary function test results	
-Percent predicted FEV1	83.2±15.4
-Percent predicted FVC	78.9±17.7
-FEV1/FVC	82.4±4.8
-DLCO	63.4±21.4

RA-ILD: Rheumatoid arthritis-associated interstitial lung disease, NSIP: Non-specific interstitial pneumonia, UIP: Usual interstitial pneumonia, AIP: Acute interstitial pneumonia, DAD: Diffuse alveolar damage, PFT: Pulmonary function test, FEV1: Forced expiratory volume in 1 second, FVC: Forced vital capacity, SD: Standard deviation

corneal parameters. Individuals who had active ocular inflammation, glaucoma, corneal or lenticular opacity, an active ocular surface disorder such as dry eye, refractive errors greater than ±2 diopters, current or recent use of topical eye drops, a history of ocular surgery or trauma, or who failed to cooperate during any of the measurements were excluded from the study. To eliminate the potential effects of diurnal variations, all measurements were performed between 9:00 am and 11:00 am.

Measurement Techniques

To ensure fairness, one eye of each participant was randomly selected for analysis using a random number generator. An independent expert, who was not aware of the participants' characteristics, evaluated the ST and corneal parameters.

ST

ST was assessed using a spectralis anterior segment module optical coherence tomography (AS-OCT) device manufactured by Heidelberg Engineering GmbH, Germany. Participants were instructed to fixate on a target while the measurement was taken at a nasal gaze angle of 45 degrees, which was repeated three times for optimal image quality. Only high-quality images were deemed suitable for ST measurement, and patients who were uncooperative or had poor-quality images were excluded from the analysis. On each image, SS and ST were manually located. To minimize measurement errors, ST was assessed at three distances from SS, specifically 1000, 2000, and 3000 µm. The outer border of the sclera was identified using the deep episcleral vascular plexus, a narrow hypo-reflective region located outside the solid scleral tissue.

Corneal Parameters

The corneal parameters were measured using an Oculus Pentacam HR device from Oculus, Wetzlar, Germany. The device automatically measured the central corneal thickness (CCT) and corneal volume (CV) and the corneal density was calculated from an optimal quality image obtained after multiple measurements. Images were obtained from 90° to 270° for each participant.

Statistical Analysis

The sample size for the study was determined using G*power 3.1 software, which indicated that at least 72 participants were needed to detect a large effect size (f=0.40) between the RA-ILD and RA-noILD groups, with a type 1 error rate (a) of 0.05 and a study power of 0.85.[19]

Data analysis was performed using Statistical Package for Social Sciences (SPSS) version 22.0 for Windows (Chicago, IL, USA). Descriptive statistics were used to summarize demographic characteristics. Continuous variables were presented as mean ± standard deviation or median (minimum and maximum values), while categorical variables were presented as numbers and percentages. The normality assumption of the data was tested using the Kolmogorov-Smirnov test. Non-parametric tests were used to evaluate non-normally distributed data. Spearman's correlation analysis was used to evaluate the correlation between non-parametric variables, with a correlation coefficient (r) of 0.8 considered excellent agreement. Intergroup comparisons were conducted using the post-hoc Bonferroni correction (Mann-Whitney U test) and the Kruskal-Wallis variance analysis, with a significance level of $p<0.05$.

Inter-observer variability was assessed by having two different radiologists evaluate participants' HRCT scans on the same day (A and B same day). The mean values evaluated by each observer were compared to assess inter-observer variation. The average standard deviation was calculated for each probe, and the intra-class correlation coefficient (ICC) was computed using a two-way random model, along with corresponding 95% confidence intervals (CI). An ICC of 0.75-0.9 indicates good reliability, while values greater than 0.90 indicate excellent reliability.[20]

Results

In this cross-sectional study, 62 patients with RA and 31 healthy controls were initially recruited. Three patients were excluded due to comorbidities. Thus, 59 patients with RA (12 males, 47 females; mean age: 54.4±9.3 years; range, 45.1 to 63.7 years) were included. Disease duration was 4.5±4.21 years and DAS-28 was 2.9±0.4. Based on detailed

Table 2. Δ HRCT scoring system of patients with RA-ILD

Components mean ± SD	RUL	RML	RLL	LUL	LLL
Ground glass opacity	0.9±0.6	0.9±0.9	1.0±1.25	0.8±0.70	1.2±1
Fibrosis	1.1±0.5	1.1±1.0	1.2±1.15	0.9±0.70	1.0±1.3
Bronchiectasis	0.7±0.7	0.1±1.1	1.4±1.0	0.2±0.2	1.2±1.2
Honeycombing	0.1±0.25	0	0.4±0.1	0.1±0.20	0.4±0.1
Total HRCT score			18±11.0		

Δ *HRCT: Delta high-resolution computed tomography, ILD: Interstitial lung disease, LUL: Left upper lobe, LLL: Left lower lobe, SD: Standard deviation, RUL: Right upper lobe, RML: Right medial lobe, RLL: Right lower lobe*

examinations, 22 patients with RA-ILD were assigned to group 1, 37 patients with RA-noILD were assigned to group 2, and 31 healthy controls were assigned to group 3. These groups had similar age and gender distribution, and BMI (p=0.312, p=0.752, p=0.789). Additionally, patients with RA-ILD and RA-noILD had comparable disease duration, DAS-28 scores, serum RF and/or ACPA levels, laboratory results, and medical treatment (p>0.05) (Table 3).

ST measurements were obtained at three distances and the corneal parameters were evaluated in all groups. ST measurements were significantly different between patients with RA and healthy controls (p<0.05). However, patients with RA-ILD and RA-noILD had similar ST measurements at all distances, as well as corneal parameters (p>0.05). There was no correlation between ST measurements at three distances, corneal parameters, and AHRCT scores. Inter-observer agreement for AHRCT scores was excellent (ICC=0.955; 95% CI, 0.969-0.995). Additionally, there was no significant correlation between ocular parameters and PFT (p>0.05) (Table 4).

Discussion

RA can cause lung involvement in up to 60% of patients, making it the most common EAM associated with the condition.[21] Additionally, RA can cause eye problems in 39% of patients, which can result in varying degrees of

Table 3. Comparison of clinical and demographic characteristics and measurements of ocular parameters

	Group 1 (n=22) RA with ILD	Group 2 (n=37) RA without ILD	Group 3 (n=31) healthy controls	p-value	Mann-Whitney U test with Bonferroni correction
Demographic and clinical parameters					
Male n (%)	5 (23)	7 (19)	6±19	0.752	
Age (year), mean ± SD	56.1±8.5	54.2±9.8	52.3±7.6	0.312	
BMI, kg/m^2, mean ± SD	25.0±2.8	22±3	25.1±2.5	0.789	
Disease duration (years), mean ± SD	5.9±3.2	7.4±5.2	-	0.323	
DAS-28, mean ± SD	2.8±0.5	3.0±0.6	-	0.724	
-RF, IU/mL, mean ± SD	67±75	74±66	-	0.135	
-ACPA, mean ± SD	151±216	107±104	-	0.296	
-CRP, mg/dL, mean ± SD	7±10.1	5±6.5	-	0.282	
-ESR, mm/hour, mean ± SD	24±22	26.0±19	-	0.411	
Medical treatment					
- Glucocorticoid use n (%)	10 (45)	20 (54)	-	0.116	
- cDMARDS use n (%)	8 (36)	24 (64.8)	-	0.247	
-Biologic DMARD use n (%)	12 (54.5)	15 (40.5)			
Scleral thickness, μm					
- ST1000, mean ± SD	611.5±81.7	618.0±114.8	559.8±40.8	**0.007***	Group 1= Group 2, p=0.338 Group 3 < Group 2, p=0.006* Group 3 < Group 1, p=0.015*
-ST2000, mean ± SD	606.2±78.2	639.62±104	531.9±46.3	**<0.001***	Group 1= Group 2, p=0,222 Group 3 < Group 2, p<0.001* Group 3 < Group 1, p<0.001*
-ST3000, mean ± SD	605.8±76.7	645.7±109	557.1±39.7	**0.001***	Group 1= Group 2, p=0.152 Group 3 < Group 2, p<0.001* Group 3 < Group 1, p=0.015*
Corneal parameters					
--CV, mm^3, mean ± SD	58.2±2.5	57.2±5.9	59.7±2.6	0.092	
--CCT, ✂m, mean ± SD	526.6±28.6	535.4±31.9	545.3±26.7	0.095	

*Kruskal-Wallis test was used. *****p<0.05: statistically significant, RA: Rheumatoid arthritis, ILD: Interstitial lung disease, cDMARDS: Conventional disease-modifying antirheumatic drugs, bDMARDS: Biologic disease-modifying antirheumatic drugs, RF: Rheumatoid factor, ACPA: Anti-citrullinated protein antibody, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ST1000: Scleral thickness at a distance of 1000 μm from scleral spur (SS). ST2000: Scleral thickness at a distance of 2000 μm from SS, ST3000: Scleral thickness at a distance of 3000 μm from SS, D: Diopter, CCT: Central corneal thickness, CV: Corneal volume, SD: Standard deviation, BMI: Body mass index*

Table 4. Spearman's rank correlation coefficients of ▲ HRCT scores and clinical variables with ocular parameters

	HRCT score		FVC		FEV1/FVC		FEV1	
	p	r	p	r	p	r	p	r
Ocular parameters								
ST1000, ✂m	0.515	0.155	0.387	0.205	0.300	-0.244	0.106	0.44
ST2000, ✂m	0.925	0.23	0.215	0.290	0.096	-0.382	0.853	0.110
ST3000, ✂m	0.680	0.98	0.169	0.320	0.068	-0.416	0.644	0.148
CV, mm^3	0.979	0.06	0.848	0.46	0.607	-0.122	0.619	0.119
CCT, ✂m	0.689	0.95	0.749	0.76	0.158	-0.328	0.812	0.57

** p<0.05, statistically significant, ST: Scleral thickness, ST1000: Scleral thickness at a distance of 1000 μm from scleral spur (SS). ST2000: Scleral thickness at a distance of 2000 μm from SS, ST3000: Scleral thickness at a distance of 3000 μm from SS, D: Diopter, CCT: Central corneal thickness, CV: Corneal volume, HRCT: High-resolution computed tomography, FVC: Forced vital capacity, FEV1: Forced expiratory volume in 1 second*

morbidity.[22] The development of extra-articular findings in RA is linked to cytokines such as TNF, IL-1, and IL-6, which are thought to cause inflammation due to an imbalance between pro- and anti-inflammatory cytokines.[23] RA is believed to be caused by a microenvironment that promotes the breakdown of collagen, which can lead to keratitis starting from the perilimbal cornea and spreading toward the central cornea, causing perforations and corneal melting.[24,25]

Unfortunately, there are limited studies evaluating corneal parameters and ST in RA and other connective tissue diseases. A study by Gökmen et al.[11] found that RA patients had a statistically thinner ST than healthy controls due to reasons such as the destruction of scleral tissue and subclinical immune deposition. However, the same study reported that the corneal parameters of RA patients were not different from those of healthy controls, likely because of the suppression of systemic inflammation secondary to the use of immunosuppressive drugs.[6] On the other hand, Kaya et al.[26] found that systemic lupus erythematosus patients had a thicker ST than healthy controls, possibly due to subclinical inflammation and connective tissue involvement. Another study had similar results in patients with systemic sclerosis.[19] Our study showed that RA patients had statistically thicker ST but thinner corneal parameters compared to healthy controls, possibly due to subclinical inflammation and the use of immunosuppressive drugs. However, more research is needed to confirm this relationship.

According to the literature, several biomarkers have been linked to RA-ILD, including MMP-1, IL-18, and IL-13.[27] These biomarkers are associated with collagenous pathologies, which are relevant because the sclera has a dense collagenous structure made up of primarily collagen I fibers (90%), collagen III fibers (5%), and proteoglycans.[28] A published study suggests that MMP-1 is the primary enzyme responsible for breaking down interstitial collagen types I and III.[29] Additionally, Firszt et al.[30] reported that IL-13 induces collagen type-1 expression through matrix metalloproteinase-2 and transforming growth factor-01, while Kim et al.[31] found that IL-18 directly downregulates collagen production via Ets-1 and the ERK pathway in human dermal fibroblasts, indicating antifibrotic properties. These findings suggest that the sclera, with its collagenous structure, may be particularly susceptible to the effects of RA-ILD. However, further research is needed to establish a definitive relationship.

The measurement of CCT is crucial for the diagnosis and management of glaucoma since it affects intraocular pressure (IOP) readings.[32] Previous studies have shown that thicker corneas result in falsely high IOP readings, while thinner corneas produce falsely low readings.[32] Despite RA primarily affecting the cornea and ocular surface, little information is available on the relationship between CCT and CV in RA patients. Prata et al.[33] reported that CCT was slightly thinner in RA patients compared to healthy individuals, although the difference was not significant. Villani et al.[34] reported a significant difference in CCT between RA patients and healthy controls. Nevertheless, a published study found no significant differences in CCTs between RA and control eyes, and CCT was not associated with RA activity.[35] In our study, we compared CCT and CV in RA patients with and without RA-ILD and found no significant differences between these groups and healthy controls. This may be due to the immunosuppressive treatments used by RA patients, which may suppress inflammatory and catabolic cytokines that cause corneal thinning.[36]

RA can affect various anatomic structures such as parenchyma, pleura, upper and lower airways, and vascular structures,[10] leading to a wide range of HRCT findings. In our study, we used HRCT scoring to assess the severity of lung involvement, but we should note that this scoring system does not account for nodules, mosaic perfusion, or pleural effusion in RA-ILD patients. Therefore, this limitation might have affected the relationship or correlation between ocular parameters and the HRCT score. To obtain

more accurate data, we could have used a scoring system that includes all HRCT findings.

Study Limitations

Our study has three potential limitations. First, the correlation between ocular parameters and diffusing capacity of the lungs for carbon monoxide (DLCO) could not be evaluated due to patient unwillingness and non-compliance with the test. Second, since the study was cross-sectional, we could not determine if ocular involvement or pathology developed in subsequent follow-ups. However, RA patients included in the study did not have any ocular involvement symptoms or physical examination findings. Third, the Coronavirus disease-2019 pandemic resulted in some RA-ILD patients being lost to regular outpatient follow-up due to intensive care and mortality anxiety, leading to a smaller sample size of RA-ILD patients in our study.

Conclusion

The ST of RA-ILD patients was found to be slightly thinner compared to RA-noILD patients, but this difference was not statistically significant, even though there were no signs of inflammatory vasculitis, scleromalacia, or active scleritis, and patients were receiving active immunomodulatory treatment. The observed lack of significant difference in ST could be related to the biomarkers associated with RA-ILD. It is therefore recommended that patients with RA-ILD undergo regular follow-up with AS-OCT for scleral evaluation.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the principles of the Helsinki Declaration and was approved by the Local Ethics Committee of Pamukkale University (approval number: 60116787-020-110161).

Informed Consent: Prior to participating, all individuals were informed about the study's purpose and provided written consent.

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Authorship Contributions

Surgical and Medical Practices: S.K., N.S., U.K., H.K., F.U., A.R.Ü., V.Ç., M.Y., Concept: S.K., N.S., U.K., H.K., F.U., A.R.Ü., V.Ç., M.Y., Design: S.K., N.S., U.K., H.K., F.U., A.R.Ü., V.Ç., M.Y., Data Collection or Processing: S.K., N.S., U.K., H.K., F.U., A.R.Ü., V.Ç., M.Y., Analysis or Interpretation: S.K., N.S., U.K., H.K., F.U., A.R.Ü., V.Ç., M.Y., Literature Search: S.K., N.S., U.K., H.K., F.U., A.R.Ü., V.Ç., M.Y., Writing: S.K., N.S., U.K., H.K., F.U., A.R.Ü., V.Ç., M.Y.

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