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ORIGINAL PAPER

An assessment of ocular elasticity using real time ultrasound and ocular response analyzer in active or remission rheumatoid arthritis

Mehmet Erol Can · Özlem Unal · Meltem Ece Kars · Sukran Erten · Gamze Dereli Can · Necati Duru · Nurullah Cagil

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Abstract

Purpose To investigate the elasticity of ocular structures in patients with rheumatoid arthritis (RA) without ocular involvement.

Methods The study included 56 RA patients (study group) and 24 healthy volunteers as the control group. The rheumatoid arthritis patients were divided into two subgroups as those in active phase (Group 1, $n = 25$) or in remission phase (Group 2, $n = 31$) according to the disease activity index (DAS 28) score. The elastography values of the ratio of orbital fat-sclera (ROF/S) were measured with real-time US elastography, and corneal mechanical values were measured with the Reichert Ocular Response Analyzer in each eye.

Results The mean ROF/S value was 5.2 ± 1.8 in Group 1, 0.7 ± 0.4 Group 2, and 0.6 ± 0.1 in the control group. There was a significant difference between the Group 1 and control group with regard to ROF/S ($p < 0.001$), but no significant difference was determined between Group 2 and control group ($p > 0.05$). The mean ROF/S value was a significant difference between the Group 1 and 2 ($p < 0.001$). ROF/S was significantly correlated with DAS-28 and C-reactive protein (CRP) ($r = 0.816$, $p < 0.001$ and $r = 0.259$, $p = 0.006$).

Conclusions ROF/S was significantly increased in patients in the active phase of RA. Findings revealed that ocular tissue structural changes may occur in the active phase and these could be related to ocular complications as a prognostic factor.

Keywords Rheumatoid arthritis · Ocular elasticity · Ultrasound elastography · DAS 28

M. E. Can (✉) · G. Dereli Can
Department of Ophthalmology, Yuksek Ihtisas Training and Research Hospital, Mimarsinan Mahallesi Emniyet Caddesi Polis Okulu Karşısı, Bursa, Turkey
e-mail: drm.erolcan@gmail.com

Ö. Unal
Department of Radiology, Yildirim Beyazit University Faculty of Medicine, Ankara Ataturk Training and Research Hospital, Ankara, Turkey

M. E. Kars · N. Cagil
Department of Ophthalmology, Yildirim Beyazit University Faculty of Medicine, Ankara Ataturk Training and Research Hospital, Ankara, Turkey

S. Erten
Department of Rheumatology, Yildirim Beyazit University Faculty of Medicine, Ankara Ataturk Training and Research Hospital, Ankara, Turkey

N. Duru
Department of Ophthalmology, Kayseri Training and Research Hospital, Kayseri, Turkey

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune systemic inflammatory disease of joints and other

tissues [1]. The prevalence of RA is approximately 1% of the world population, with women affected approximately three times more often than men, in whom it tends to develop later in life [1, 2]. RA is much more common after the age of 40, although it can develop at any age [3]. The cause of RA is not known, but abnormal immune system activation plays a key role at pathogenesis [4–6]. The main characteristic of RA is persistent symmetric polyarthritis, and extra-articular manifestations may be observed in addition to the characteristic joint changes [7]. Skin, ocular, oral, gastrointestinal, pulmonary, cardiac, renal, neurological, bone, and hematological involvement are the most common extra-articular manifestations of RA [1, 2].

Ocular findings usually occur in 25–39% of patients [8, 9]. The most common ocular manifestation is keratoconjunctivitis sicca in RA. Episcleritis, scleritis, anterior uveitis, stromal keratitis, sclerosing keratitis, keratolysis, peripheral ulcerative keratitis, and corneal melting are the other common ocular manifestations [8, 10, 11].

Ultrasound elastography is a technique that provides non-invasive assessment of tissue mechanical properties [12]. Ultrasound elastography show changed elasticity of tissues resulting from specific pathological or physiological processes. Elasticity and stiffness measurement of tissues have been used in the differential diagnosis of tumor, inflammation, and normal tissue. Ultrasound elastography has been used to examine breast, thyroid, prostate, cervix, liver, cardiac, musculoskeletal system, and some groups of lymph nodes [12, 13].

In this study, real time-ultrasound elastography, and ocular response analyzer were used to investigate the ocular and periocular tissues of patients with RA according to disease activity, by comparing it with the elasticity in the eyes of an age and sex-matched healthy control group.

Methods

Study subjects

This prospective, cross-sectional study investigated 56 patients with RA and 24 healthy individuals, as the control group. This study was performed in accordance with the Declaration of Helsinki. Approval for this human study was granted by the Local Ethics Committee of Kecioren Training and Research Hospital. All adult participants provided written informed consent to participate in this study.

The disease activity of the patients with RA was evaluated by a rheumatology specialist using the disease activity score 28 (DAS-28) [14]. The DAS-28 was calculated using the Ritchie Articular Index, a 28-joint swollen joint count, C-reactive protein (CRP), and a general health assessment on a visual analog scale [14].

The RA patients were divided into two subgroups according to the DAS-28 scores as follows: active (DAS-28 > 2.6, Group 1, $n = 25$) and remission (DAS-28 ≤ 2.6, Group 2, $n = 31$). The patients with RA didn't have any history of ocular involvement by inflammatory disease.

Examination protocol and study measurements

Each participant underwent a complete ophthalmological assessment, including best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, intraocular pressure (IOP) measured by Goldmann applanation tonometry, and fundus examination.

The Ocular Response Analyzer (Reichert Ophthalmic Instruments, Buffalo, NY, USA) was used to measure the mechanical features of the cornea in all subjects. The corneal hysteresis (CH), corneal resistance factor (CRF), corneal-compensated IOP (IOPcc), and Goldmann-correlated IOP (IOPg) were measured using the Ocular Response Analyzer. Three serial measurements (Waveform Scores > 7) were acquired in each right eye and the mean was used for analyses. Axial length (AL) was also measured with using a Lenstar LS 900 biometer (Haag-Streit AG, Koeinz, Switzerland). All measurements were taken by an experienced clinician (M.E.K.).

Ocular ultrasound elastography measurement

A freehand real-time elastographic (RTE) examination was performed with a high-frequency linear probe (12–17 MHz) on an Aplio 500 ultrasound machine (Toshiba Medical Systems, Co, Ltd, Otawara, Japan) by a single radiologist (Ö.U.) experienced in B-scan ultrasonography and elastography.

The individuals were investigated in the supine position. After evaluation of the orbit with

conventional ultrasonography, the probe was placed on the eyelid of the patient. Elastography was performed with elasto software. The radiologist compressed the eye by applying a mild vertical pressure to the probe. The gray scale and the elastographic images were displayed side by side for comparison. Elasticity views were produced by moving the probe continuously and obtaining compression and relaxation waveforms. After 8–10 compression and relaxation cycles, the elastographic examination was finalized, and strain rate measurements were obtained. Compression and relaxation waveforms were displayed on the elastography screen, above and below the baseline wave scale.

At a comparatively slow speed, numerous slight compression/release was applied 3–5 times at intervals of 1–2 s and measurements were repeated. Compression/release is examined to be suitable when the velocity profile displayed at the bottom of the display is almost sinusoidal, and the release (lower side) is considered to be closer to the actual strain value than the compression (upper side). At least 10 attempted elastography examinations were made for each eye until the color displayed in the region of interest (ROI) was completely stable to allow reliable measurement results. The strain images were obtained according to a strain color scale, with blue representing hard tissue, green, tissue of average stiffness, and red soft tissue based on the degree of strain in the tissue.

The strain ratios [fat-lesion (sclera) ratio] of the study and control groups were recorded. All images were obtained from the right eyes of both groups.

The ratio of orbital fat to sclera (S) was measured according to the semi-quantitative evaluation of the elastographic images. The region of interest (ROI) of the sclera was drawn, and the corresponding ROI in the adjacent normal fatty tissue was later drawn as a control for the measuring ROF/S (ratio of orbital fat-sclera) (Fig. 1). The analyzed region in the sclera was the same dimension for all subjects and it was placed at a fixed distance from the surface. The radiologist who carried out the US examinations also performed the image analyses.

Exclusion criteria

Ophthalmic exclusion criteria included patients with any history of anterior or posterior scleritis or orbital disease, a best corrected visual acuity (BCVA) worse than 20/20, a refractive error less than − 2 diopters (D) or more than + 2 D, intraocular pressure (IOP) readings greater than 21 mmHg, history of uveitis, retinal disease, corneal disease, corneal or intraocular surgery, pregnancy, or any associated systemic disorders that might affect the eyes (e.g., uncontrolled diabetes, hypertension, or connective tissue diseases).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software version 20.0 (SPSS Inc., Chicago, IL, USA). Ocular parameter measurements of the right eyes were used for the analyses. For the continuous variables, the data were tested for normality by using Kolmogorov–Smirnov test [15]. The Chi-square test was used to define variation in categorical variables [15]. The Independent t test was used to assess differences in scale variables and ANOVA was applied to the comparisons between the control and study subgroups [15]. Pearson correlation analysis was used to evaluate the correlation between each pair of measurements [15]. All the results were stated as mean ± standard deviation (SD). p value less than 0.05 was considered statistically significant.

Results

Demographic characteristics

The study group comprised 45 (80.3%) females and 11 (19.7%) males, and the control group comprised 22 (91.6%) females and 2 (8.3%) males ($p = 0.746$). The mean age was 49.78 ± 9.91 years (range 24–65 years) in the patient group and 47.25 ± 5.16 years (range 37–55 years) in the control group ($p = 0.222$).

The mean values of age, gender distribution, disease duration, and DAS-28 score in the study subgroups (active and remission) and the control group are summarized in Table 1.

Results of US elastography

In the subgroup analysis, the mean ROF/S was 5.2 ± 1.8 in Group 1, 0.7 ± 0.4 in Group 2, and

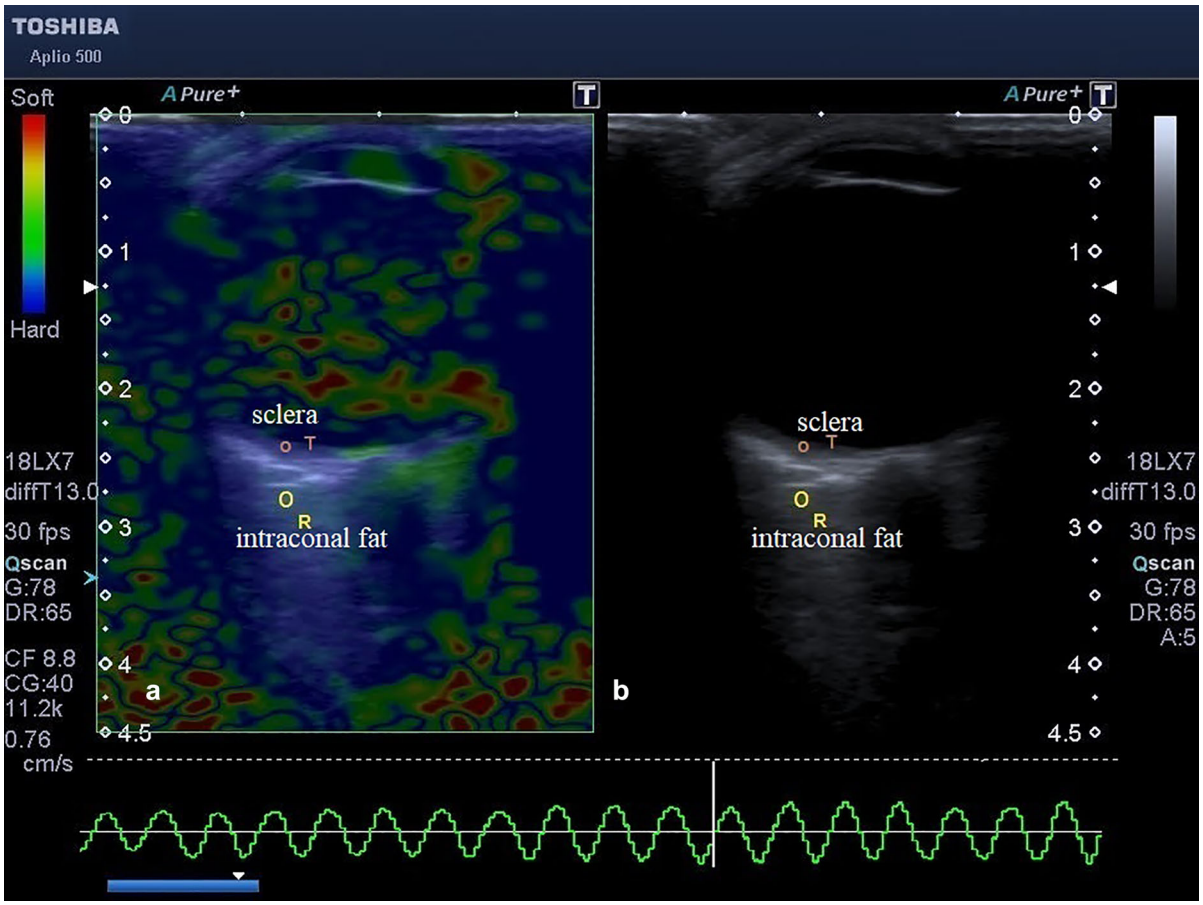

Fig. 1 B-mode ultrasonography image (**b**) and the related elastography image (**a**) of scleral tissue (*T*) versus intraconal fat (*R*). The circles (*T* and *R*) indicate where the elastographic measurements were taken. *R* intraconal fat, *T* sclera tissue

0.6 ± 0.1 in the control group ($p < 0.001$). The mean ROF/S was significantly higher in Group 1 than in Group 2 and the control group. The ANOVA analysis of the ROF/S measurements was summarized in Table 2.

The correlation analyses of the DAS-28, CRP, age, CH, CRF, IOPcc, IOPg, and ROF/S values are shown in Table 3. In the RA group, ROF/S was significantly correlated with DAS-28 and CRP ($r = 0.816$, $p < 0.001$ and $r = 0.259$, $p = 0.006$, respectively). Age, CH, CRF, IOPcc, and IOPg were not correlated with the ROF/S value in the study or the control group ($p > 0.05$).

Results of ORA and AL examinations

The mean CH and CRF values in the control group (10.52 ± 1.36 mmHg and 10.81 ± 1.5 mmHg) were higher than in the study group (9.65 ± 1.37 mmHg and 9.8 ± 1.79 mmHg) ($p < 0.05$).

IOPcc mean value in the study group (16.96 ± 3.41 mmHg) was higher than in the control group (15.49 ± 2.44 mmHg) ($p < 0.05$).

The ANOVA analysis of the ORA measurements between the study and control groups is summarized in Table 2. In the subgroup analysis, the mean CH was 9.8 ± 1.3 mmHg in Group 1, 9.5 ± 1.5 in Group 2, and 10.5 ± 1.4 in the control group. The mean CRF was 10 ± 1.7 mmHg in Group 1, 9.7 ± 2 in Group 2, and 10.8 ± 1.5 in the control group. The difference between the control group and the study subgroups was observed to be significant with the analysis of variance test ($p \leq 0.05$). The mean IOPcc was 15.49 ± 2.45 mmHg in the control group, 16.91 ± 3.35 mmHg in Group 1, and 17 ± 3.48 mmHg in Group 2. In the control group,

Table 1 Patient demographics and characteristics of each group

	Rheumatoid arthritis group (n = 56)	Control group (n = 24)	p[a]	Rheumatoid arthritis subgroups		
				Remission (DAS-28 $\leq$ 2.60) (n = 31)	Active (DAS-28 > 2.60) (n = 25)	p[a]
Age (years)						
Mean ± SD	49.78 ± 9.91	47.25 ± 5.16	0.222	49.87 ± 9.61	49.67 ± 10.15	0.210
Range	24–65	37–55		24–65	28–64	
Gender						
Female	45 (80.3%)	22 (91.6%)	0.746[b]	25 (80.6%)	22 (88%)	0.462[b]
Male	11 (19.7%)	2 (8.3%)		6 (19.4%)	3 (12%)	
Disease duration (years)						
Mean ± SD	7.59 ± 7.80	NA	–	8.82 ± 8.77	6.04 ± 6.09	0.062
Range	1–38	NA	–	1–38	1–25	
DAS-28 score						
Mean ± SD	3.05 ± 1.13	NA	–	2.12 ± 0.37	4.17 ± 0.63	< 0.001
Range	1.46–5.71	NA	–	1.46–2.59	3.21–5.71	

DAS-28 disease activity score-28, *NA* not applicable, *SD* standard deviation

[a]Independent samples t test

[b]Chi-square test

Table 2 Comparison of the US elastography and mean ocular response analyzer measurements in the active RA, remission RA, and control groups

	Rheumatoid arthritis subgroups		Control	p[a]		
	Active RA	Remission RA		Control versus active	Control versus remission	Remission versus active
ROF/S	5.2 ± 1.8	0.7 ± 0.4	0.6 ± 0.1	< 0.001	0.234	< 0.001
CH (mmHg)	9.8 ± 1.3	9.5 ± 1.5	10.5 ± 1.4	0.025	0.006	0.386
CRF (mmHg)	9.9 ± 1.6	9.7 ± 2	10.8 ± 1.5	0.05	0.017	0.432
IOPcc (mmHg)	16.91 ± 3.35	17 ± 3.48	15.49 ± 2.44	0.119	0.096	0.886
IOPg (mmHg)	15.94 ± 3.90	15.60 ± 4.1	14.63 ± 2.59	0.143	0.286	0.662
AL (mm)	22.82 ± 0.66	22.8 ± 0.66	22.95 ± 0.61	0.538	0.810	0.932

ROF/S ratio of orbital fat-sclera, *CH* corneal hysteresis, *CRF* corneal resistance factor, *IOPcc* corneal-compensated intraocular pressure, *IOPg* Goldmann-correlated intra-ocular pressure, *AL* axial length, *RA* rheumatoid arthritis

[a]ANOVA test

the mean IOPcc was significantly lower than in Groups 1 and 2, but no significant difference was determined between Groups 1 and 2 ($p > 0.05$). The ORA measurements of both control and study subgroups are summarized in Table 2. The mean values of AL were not statistically significantly different between the RA and the control groups ($p > 0.05$). The AL measurements of both control and study subgroups are summarized in Table 2.

Table 3 Correlation analyses between ROF/S and other parameters in Rheumatoid arthritis and control groups

	ROF/S			
	Rheumatoid arthritis group		Control group	
	r	*p*[a]	*r*	*p*[a]
DAS-28	0.816	< 0.001	–	–
Disease duration (years)	− 0.136	0.156	–	–
CRP (mg/L)	0.259	0.006	–	–
Age (years)	0.039	0.684	− 0.269	0.204
CH (mmHg)	0.036	0.706	− 0.177	0.409
CRF (mmHg)	0.044	0.645	0.033	0.879
IOPcc (mmHg)	0.012	0.901	0.098	0.650
IOPg (mmHg)	0.040	0.680	0.039	0.857

ROF/S ratio of orbital fat-sclera, *DAS-28* disease activity score-28, *CRP* C-reactive protein, *CH* corneal hysteresis, *CRF* corneal resistance factor, *IOPcc* corneal-compensated intraocular pressure, *IOPg* Goldmann-correlated intraocular pressure

[a]Pearson correlation

Discussion

Our study evaluated the mechanical features and elasticity of the eye in active and remission phases of RA patients. The results indicated that RA patients in the active phase had higher ROF/S values compared with the healthy participants and RA patients in the remission phase. The ROF/S values did not demonstrate any variation between the healthy participants and RA patients in the remission phase. In addition, RA patients were observed to have lower CH and CRF values compared with the control group.

Rheumatoid arthritis commonly involves multiple organ systems, including the eye. Pathogenetically, rheumatoid arthritis affects the microvasculature in these organs [16–18]. B- and T-cells, and inflammatory cytokines (TNF-α, interleukin 1, 6, and 17) play key part in the disease processes of RA [19, 20]. Inflammation and proliferation lead to the havoc of various tissues, including cartilage, bone, ligaments, tendons, and blood vessels [21]. Extra-articular manifestation in RA is more often seen in patients with active disease and is related to elevated mortality [22]. Ocular involvement can potentially lead to vision-threatening disease and indicate systemic involvement. The most widespread manifestations in RA are keratoconjunctivitis sicca, anterior uveitis, episcleritis, scleritis, corneal changes (keratolysis, corneal melting, stromal, and sclerosing keratitis, and peripheral ulcerative keratitis) [8, 10, 11].

About 16% of patients with rheumatoid vasculitis have ocular manifestations [11, 23, 24]. These include iritis, retinal and choroidal vascular involvement, scleritis and episcleritis [11, 17, 25, 26]. Vascular involvement, which is a supplementary part of RA pathogenesis is immune complex microangiopathy, and type III hypersensitivity reaction in episcleral and scleral capillaries [27]. Depending on the location and size of the affected vessels, redness, pain, and vision loss might be signs of ocular disease [28]. In RA, the disease duration induces scleral tissue alterations which can lead to scleral destruction [11]. In our study, the patients did not have any history of rheumatoid vasculitis manifestations.

Ultrasound elastography measures elastic features of tissues [29], which is based on the differences between the elasticity of normal and diseased tissues [30]. In the RA inflammation status of body is variable. In active phase, many of tissue changes occur and many of them are irreversible. This irreversible changes are related to diseases duration. ROF/S demonstrate tissue variable in RA. The difference of ROF/S between in active and remission is related to reversible ocular involvement. However, ROF/S could be same values in the late stages of the disease.

The ocular response analyzer measures corneal mechanical features including CH and CRF that rely on corneal viscoelasticity [31]. The CH provides the corneal tissue features that result from viscous damping and the CRF shows overall corneal resistance to any applied force. The ORA also provides intraocular pressure (IOPg) and corneal-compensated IOP (IOPcc). IOPcc is a pressure measurement based on data supplied by the CH.

Many recent studies have indicated that corneal mechanical features change in autoimmune or systemic diseases, some corneal diseases, or hormonal undulations determined by the CH and CRF measured by the ORA method. In RA patients, a few research studies have reported corneal mechanical properties. Tas et al. [32] documented a reduction in both CH and CRF levels in RA patients. Prata et al. [33] documented that CH measured by ORA was significantly lower in RA patients compared to healthy controls. Can et al. [34] also documented lower CH in RA patients, but reported that CH did not demonstrate any changes between RA patients in the active or remission stage.

Previous studies have demonstrated the elastographic characteristics of ocular tissue [35]. Pekel et al. [36] reported decreased elasticity of the retina-choroid-sclera complex in argon laser panretinal photocoagulation. Unal et al. [37] evaluated optic nerve head biomechanics in primary open angle glaucoma and found increases with glaucoma. Agladioglu et al. [38] studied the correlation between primary open angle glaucoma and ocular elasticity in adults and demonstrated that anterior vitreous/posterior vitreous strain ratio increases in glaucoma patients.

To the best of our knowledge, our study is the first to compare the mechanical properties and elasticity of the eye at the same time in active or remission phase RA patients. RA is an inflammatory autoimmune disease that also causes complications in many organ systems and tissues throughout the body in the active stage. Many complications and tissue damage become permanent in the remission stage. In RA, the disease duration induces ultrastructural tissue changes both in the cornea and the sclera. In the current study, RA patients were determined to have lower CH and CRF values than the control group. In this regard, previous studies have found similar results to ours. However, no significant difference was found between RA patients in the active or remission stage in respect of CH and CRF. A possible reason for lower CH and CRF is the irreversible and persistent ultrastructural changes in the stroma of the cornea due to the disease activity of RA.

This study demonstrated that DAS-28 score is significantly related to scleral elasticity. Our results demonstrated a statistically significant difference in ROF/S values between the control group and RA patients. The mean ROF/S values were significantly increased in patients with active RA as compared to remission RA and the control group. The mean ROF/S values did not show any difference between RA patients in remission and the control group. A possible reason for same ROF/S is the reversible ultrastructural changes in sclera due to the disease activity of RA. However, these changes may not be reversible like other tissue changes in the disease progresses. This could be as prognostic value in the disease duration. The higher ROF/S values in the active phase indicate that the ocular tissue alterations that occur in the sclera increase as disease activity increases. A possible reason for this higher ROF/S can be considered to be the vascular involvement of RA. Immune complex vessel deposition and cell-mediated immune responses cause narrowing in scleral vascular structures, with a resulting decrease in scleral elasticity. Another reason for higher ROF/S is edema and inflammation in scleral tissue due to ischemia. As a result of ischemia, loss of tissue and scleral thinning can occur.

In conclusion, the mean CH and CRF values were significantly lower in patients with RA. The mean ROF/S value was significantly higher in patients with active RA when compared with those in remission and the healthy control group. It was also shown in this study that the scleral elasticity could have been affected in the active disease phase of RA. There is a need for further studies to support these findings.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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