ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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The Effect of Duration of Disease on Corneal Biomechanical Properties in Patients with Rheumatoid Arthritis

Romatoid Artritli Hastalarda Hastalık Süresinin Korneanın Biyomekanik Özelliklerine Etkisi

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ABSTRACT Objective: To investigate corneal biomechanical parameters of patients with rheumatoid arthritis (RA) by using ocular response analyzer (ORA) and to detect the influence of duration of disease on these parameters. **Material and Methods:** ORA measurements were performed of 42 patients with RA without any manifest corneal involvement (RA group) and 42 healthy control subjects. Corneal hysteresis (CH), corneal resistance factor (CRF), Goldmann correlated IOP (IOPg) and corneal compensated IOP (IOPcc) values recorded. Central corneal thickness (CCT) measured with ultrasonic pachymeter. RA group categorized into two groups; patients have less than 10 years of duration of disease (Group A, 22 patients) and patients have more than 10 years of duration of disease (Group B, 20 patients). Right eye measurements of all groups were compared. **Results:** There was no statistically significant difference between groups with regard to mean age and gender (p=0.286, p=0.687, respectively). Mean values of IOPcc, IOPg, CRF, CH and CCT measurements were no statistically significant difference between RA and control groups (p>0.05). When compared group A with B, the difference in the IOPcc, IOPg, CH and CCT values were not statistically significant (p>0.05), CRF was statistically significantly lower in group B than group A (p=0.042). There was no statistically significant difference between group A and control group and, group B and control group (p>0.05). IOPcc, IOPg, CRF and CH were negatively correlated with disease duration but this was not statistically significant (p>0.05). **Conclusion:** Corneal biomechanics properties measured with ORA are not significantly different in patients with RA without any manifest corneal involvement when compared to healthy control subjects. CRF was found to be low in RA patients whose disease duration was longer than 10 years.

Keywords: Arthritis, rheumatoid; intraocular pressure; cornea; corneal diseases

ÖZET Amaç: Oküler cevap analizörü (OCA) ile romatoid artritli (RA) hastaların kornea biyomekanik özelliklerini incelemek ve hastalık süresinin bu özelliklere etkisini araştırmak amaçlanmıştır. **Gereç ve Yöntemler:** Herhangi bir kornea tutulumu olmayan RA'li 42 hasta ile sağlıklı 42 birey çalışmaya dahil edildi. OCA ile alınan kornea histerezis (KH), kornea resistan faktör (KRF), Goldmann uyumlu göz içi basıncı (GİBg) ve kornea kompenzatuar göz içi basıncı (GİBkk) ölçümleri kaydedildi. Merkezi kornea kalınlığı (MKK) ölçümü cihazda bulunan ultrasonik pakimetre ile yapıldı. RA hastaları hastalık süresine göre; 10 yıldan az olan (Grup A, 22 hasta) ve 10 yıldan fazla olan (Grup B, 20 hasta) olarak iki gruba ayrıldı. Tüm grupların sağ göz ölçümleri karşılaştırıldı. **Bulgular:** RA ve kontrol grubunda yaş ve cinsiyet bakımından istatistiksel olarak anlamlı fark yoktu. RA ve kontrol grubunda KH, KRF, GİBg, GİBkk ve MKK ölçümleri bakımından istatistiksel olarak anlamlı fark tespit edilmedi (p>0,05). Grup A ve grup B KH, GİBg, GİBkk ve MKK ölçümleri bakımından karşılaştırıldığında aralarında istatistiksel olarak anlamlı fark saptanmadı (p>0,05). Ancak KRF grup B'de grup A'dan istatistiksel olarak anlamlı düzeyde düşük bulundu (p=0,042). Grup A ve grup B'nin kontrol grubu ile karşılaştırılmasında istatistiksel olarak anlamlı fark tespit edilmedi (p>0,05). KH, KRF, GİBg ve GİBkk'nin hastalık süresi ile ters korelasyonunun olduğu ancak bunun istatistiksel olarak anlamlı düzeyde olmadığı saptandı (p>0,05). **Sonuç:** Herhangi bir kornea tutulumu olmayan RA'li hastaların kornea biyomekanik özelliklerinin sağlıklı bireylerden farklı olmadığını tespit ettik. Hastalık süresi 10 yıldan uzun olan RA hastalarında KRF'ün daha düşük olduğu saptanmıştır.

Anahtar Kelimeler: Artrit, romatoid; intraoküler basınç; kornea; kornea hastalıkları

Rheumatoid arthritis (RA) is a common and chronic systemic inflammatory disease of unknown etiology that primarily involves joints, recurring in most cases with quiescent phases alternating with relapses.[1-3] The ocular surface is one of the regions frequently affected by this disease. Different terms are used in RA those describe various stages of ocular involvement and extent of inflammation such as stromal keratitis, sclerosing keratitis, keratolysis, marginal furrowing or guttering and peripheral ulcerative keratitis (PUK).[1-3] However the most common ocular manifestation of RA is keratoconjunctivitis sicca in association with or without secondary Sjogren's syndrome.[2]

Since ocular response analyzer (ORA) is created in 2005 and provides information about biomechanics of cornea in vivo rather than experimental methods, there has been an increasing interest in clinical use of ORA in various diseases especially in glaucoma and refractive sur gery.[4-8] ORA measures viscous damping capacity (viscosity) of the ground substance which gives information of corneal microstructure.

Villani et al. observed significantly higher number of hyper reflective stromal cells in the corneas of RA patients when compared to healthy individuals.[9] They stated that those keratocytes were in a specific stage of metabolic activation induced by proinflammatory cytokines, such as IL-1 and IL-6. They also demonstrated an increase in basal epithelial cells, anterior and posterior stromal cells. These stromal and superficial corneal changes could cause the alteration of corneal biomechanical parameters, especially CH and CRF. We hypothesized that corneal biomechanical properties of RA patients can be altered in the absence of haze or scar due to changes in cellular components of cornea and subclinical inflammation. There are very few studies evaluating corneal biomechanical properties in patients with rheumatoid diseases.[10-13] In this study we compared corneal biomechanical properties of the patients with RA with healthy control subjects. Besides that, a comparison is made after RA patients categorized into two groups according to the duration of disease.

MATERIAL AND METHODS

Informed consent was obtained from all patients and the study was carried out with approval from the Institutional Review Board/Ethics Committee. This research was carried out in accord with the Declaration of Helsinki. Forty two eyes of rheumatoid arthritis patients (RA Group) and 42 healthy control subjects were forty two recruited for the study. RA group categorized into two groups; patients have less than 10 years of duration of disease (Group A, 22 patients) and patients have more than 10 years of duration of disease (Group B, 20 patients).

Both groups underwent a full ophthalmological examination including best-corrected visual acuity with Snellen charts, biomicroscobic and fundus examination by slit lamp.

The patients with corneal opacity, severe dry eye (Schirmer's test <4 mm/5 minutes), glaucoma, any inflammatory ocular disorder or infection including blepharitis, conjunctivitis, meibomitis and dacryocystitis, central or peripheral thinning evident in slit lamp examination along with the patients with a history of ocular surgery, trauma, contact lens use and the ones who use of any topical medication other than artificial tears were excluded from the study.

The ocular response analyzer (Reichert Ophthalmic Instruments, Buffalo, NY) was used to measure the biomechanical properties of the cornea. ORA measurements were performed before any contact procedures and pupillary dilatation to eliminate the possible effect that appla nation and dilatation may have on the corneal biomechanical properties. To reduce the effects of corneal diurnal variation, all examinations were performed between 9 am and 1 pm. No eye drops were used before ORA measurements and the interval between the measurements was approximately 10 to 15 minute. Three to four ORA readings were obtained consecutively and only the best quality readings according to the best Waveform Score were selected for the analysis. Good-quality profiles required relatively equal, well-defined force-in and force-out applanation signal

peaks that were located above the pressure curve and relatively smooth raw applanation signals. All subjects had Waveform Score of more than 4.0. ORA calculated and then displayed the corneal hysteresis (CH), corneal resistant factor (CRF) and IOP both as corneal compensated (IOPcc) and as Goldmann correlated (IOPg) on the computer screen attached to the ORA.

After this, the CCT was measured using a handheld ultrasonic pachymeter within the ORA after reinstilling a drop of the topical anesthetic into the eye before performing pachymetry. Right eye measurements of all groups were compared.

Statistical analyses were performed by using Statistical Package for the Social Sciences 21.0 version for Windows software (SPSS Inc., Chicago, IL, USA). Normality of the data distribution was evaluated using the Kolmogorov-Smirnov test. Independent sample t-test was used to compare quantitative data and chi-squared analysis was used for qualitative data. The Pearson correlation was used to assess the strength of the correlation between the ORA parameters with duration of disease. Descriptive statistics were expressed as frequency and percentage for categorical variables whereas quantitative data were expressed as mean±standard error of mean for normally distributed variables and median (minimum-maximum) for non-normally distributed data. $p<0.05$ was considered statistically significant.

RESULTS

Demographic data of the groups are summarized (Table 1). There was no statistically significant difference between groups with regard to mean age and gender (p=0.286, p=0.687, respectively).

Mean values of IOPcc, IOPg, CRF, CH and CCT measurements are shown detail (Table 2). There was no statistically significant difference between RA and control groups in these parameters ($p>0.05$).

The duration of the disease was less than 10 years (Group A) in 22 patients and more than 10 years (Group B) in 20 patients. The mean age of Group A was 47.1±12.1 years and Group B was 54.3±7.4 years ($p<0.002$). The mean duration of disease for all patients was 88.2 months (range 1-252 months).

Mean values of IOPcc, IOPg, CRF, CH and CCT measurements of RA patients in Group A and Group B are shown (Table 3). There was no statistically significant difference between these groups in IOPcc, IOPg, CH and CCT ($p>0.05$). CRF was statistically significantly lower in Group B when compared to Group A (p=0.042).

Four ORA parameters IOPcc, IOPg, CRF and CH were inversely correlated with duration of dis-

TABLE 1: Demographic data of patients.

	n	Age ± SEM (Year)	Gender (Male/Female)
Rheumatoid arthritis group	42	50.55 ± 1.17 (19-67)	7/35
Control Group	42	48.98 ± 0.88 (32-60)	8/34
p		0.286*	0.687**

* Independent samples t test,
**Chi square test, $p<0.05$ was considered statistically significant
SEM, standard error of mean.

TABLE 2: Mean values of ORA measurements and CCT measurements at rheumatoid arthritis group and control group

	n	IOPcc (mmHg) ±SEM	IOPg (mmHg) ±SEM	CRF (mmHg) ±SEM	CH (mmHg) ±SEM	CCT (µm) ±SEM
Rheumatoid Arthritis Group	42	17.63 ± 0.46	16.57 ± 0.49	10.22 ± 0.19	9.81 ± 0.15	550.48 ± 3.91
Control Group	42	16.98 ± 0.33	15.82 ± 0.39	9.94 ± 0.19	9.73 ± 0.14	547.80 ± 3.88
p*		0.258	0.239	0.305	0.731	0.628

* Independent samples t test, $p<0.05$ was considered statistically significant,
ORA: Ocular response analyzer; IOPcc: Corneal compensated IOP; IOPg: Goldmann correlated IOP; CRF: Corneal resistance factor;
CH: Corneal hysteresis; CCT: Central corneal thickness; SEM: Standard error of mean.

TABLE 3: The comparison of ORA parameters between patients with rheumatoid arthritis for group A (disease duration less than 10 years) and group B (disease duration more than 10 years).

Duration of disease	n	IOPcc (mm/Hg) ±SEM	IOPg (mm/Hg) ±SEM	CRF (mm/Hg) ±SEM	CH (mm/Hg) ±SEM	CCT (µm) ±SEM
Group A (Less than 10 years)	22	17.52±0.63	16.72±0.67	10.51±0.26	10.10±0.19	553.45±5.40
Group B (More than 10 years)	20	17.25±0.75	15.82±0.76	9.72±0.26	9.49±0.24	544.41±6.30
p*		0.780	0.381	0.042	0.052	0.278

* Independent samples t test, p<0.05 was considered statistically significant,
ORA: Ocular response analyzer; IOPcc: Corneal compensated IOP; IOPg: Goldmann correlated IOP; CRF: Corneal resistance factor;
CH: Corneal hysteresis; CCT: Central corneal thickness; SEM: Standard error of mean.

ease in RA patients but this correlation was not statistically significant (Table 4).

TABLE 4: Correlation analysis between ORA parameters and duration of disease.

	IOPcc	IOPg	CRF	CH
Pearson Correlation Coefficient (r)	-0.091	-0.115	-0.148	-0.054
p	0.430	0.318	0.196	0.636

*Pearson Correlation test, p<0.05 was considered statistically significant,
ORA, Ocular response analyzer; IOPcc, Corneal compensated IOP;
IOPg, Goldmann correlated IOP; CRF, corneal resistance factor; CH, corneal hysteresis; CCT, central corneal thickness.

DISCUSSION

It is a well-known entity that RA associated corneal inflammation may cause serious problems such as corneal melting that needs prompt autoimmune suppression therapy to protect integrity of globe.[14] This process may be due in part to the upregulation of pro-inflammatory cytokines; these molecules subsequently trigger corneal cells to produce a number of proteolytic enzymes that can effectively degrade the extracellular matrix and initiate collagen breakdown.[15,16]

In our study none of patients present apparent corneal involvement. There are very few studies that histopathologically show subtle inflammation in corneas of patients with rheumatoid diseases without obvious corneal involvement other than dry eye.[9] Villani et al. observed significantly higher number of hyper reflective stromal cells in the corneas of RA patients when compared to healthy individuals.[9] They stated that those keratocytes were in a specific stage of metabolic activation induced by proinflammatory cytokines, such as IL-1 and IL-6. They also demonstrated an increase in basal epithelial cells, anterior and posterior stromal cells. These stromal and superficial corneal changes could cause the alteration of corneal biomechanical parameters, especially CH and CRF. The ORA utilizes a rapid air pulse to indent the cornea and uses two applanation pressure measurements to give the parameters CH, CRF, IOPg, and IOPcc.[17] CH is believed to be a reflection of the viscoelastic or damping properties of the cornea and CRF is defined as overall "resistance" of the cornea.[18]

When we compared RA patients with control group by means of CH and CRF we found no statistically significant difference. CRF was significantly lower in Group B than in Group A. Although CH was also lower in Group A, but this decrease did not reached to statistically significant level (p=0.052). But there was no significant difference when group A and B were compared to control group. It has been shown that CH and CRF decreases with age so the difference between group A and B in terms of CH and CRF may be associated with older age of the group B than group A.[19]

Prata et al. found decreased CH and CCT in a small group with RA (n=11).[10] But there is no information about IOPcc, IOPg and CRF values of groups. A more comprehensive study has been reported by Tas et al. with 39 patients with RA in which duration of disease was not mentioned.[11] They also found lower CH and CRF and higher

IOPcc values than control group. In their study 2 of the patients had a history of corneal involvement and 5 had episcleritis. In our study none of our patients had corneal involvement. RA may not effect corneal biomechanics in the absence of manifest corneal involvement. But conversely found decreased CH in their group of 53 patients with RA, none of them had corneal scar or active corneal inflammation.[13] They evaluated biomechanical properties of the cornea in RA patients active or remission phases by using disease activity score which uses Ritchie Articular Index, erythrocyte sedimentation rate, besides a general health assessment on a visual analog scale. They found decreased CH, increased IOPcc and no difference in CRF in RA patients when compared to control group. There was no significant difference between active and remission phases so they criticized this change was not due to with the disease activities itself.

CH, CRF, IOPcc and IOPg are found inversely correlated with duration of disease but not statistically significant. This may be because of increasing age.

The precise meanings of CH and CRF are not completely understood.[20] Although all the variables that can influence these parameters are not known totally and two main variables have been proven to have important effect, real IOP (measured manometrically or by Pascal tonometry) and CCT.[20] 40% of the variability can be attributed to CCT and IOP.[21] Some authors believe different CH values between groups result from different IOP and CCT values.[22-24] Studies providing the reliable formulas that will be widely accepted for calculating the corrected CH and CRF values according to CCT and IOP and to other variables that maybe will be discovered in the future, would help standardization of ORA results in studies. In our study change of CH and CRF did not seem to be related to CCT and IOP differences because there were no significant differences in CCT and IOPcc values between groups.

We found no statistical difference by means of IOPcc, IOPg between RA and control groups. These findings are unlikely to those previous studies reported by Prata et al., Tas et al. and Can et al. found RA patients have higher IOPcc measurements when compared to control group.[10,11,13] There may be an association between autoimmunity and glaucoma but we did not find increased IOP in RA patients in our study. Large groups are necessary to evaluate whether RA patients have higher IOP measurements according to their age with considering their systemic therapy.

CCT was lower in RA group than control group and Group A than Group B but not statistically significant. CCT was reported as decreased in RA in previous studies reported by Villani et al., Prata et al. and Tas et al. Can et al found no difference between RA patients and control group similar to our study.[9,10,11,13]

In our study dry eye tests were not taken into consideration when comparing groups so we do not know how many patients have dry eye which may affect CCT as some studies show lower CCT in dry eye patients.[25,26]

One of the limitations of this study is that the systemic therapy of patients are unknown. We do not know medications that patients currently use or used in the past that may have an effect on ORA parameters directly or indirectly by influencing IOP and CCT. Although there is a study show that dry eye does not affect biomechanical measurements with ORA.[27] The second limitation of this study is the absence of assessment of dry eye test results when comparing groups. In further studies the effect of dry eye could be taken into consideration to more properly interpret the results.

In conclusion, corneal biomechanics properties measured with ORA has not significantly different in patients with RA without any manifest corneal involvement when compared to healthy control subjects. CRF found to be decreased in patients with RA with a disease duration of more than 10 years when compared to the patients with the disease duration of less than 10 years. But this difference may be related to higher age instead of disease duration itself. Further studies are needed considering the effect of age, disease duration, dry eye and systemic therapy on ORA measurement in RA patient.

Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

Idea/Concept: *Mustafa Alpaslan Anayol;* ***Design:*** *Mustafa Alpaslan Anayol;* ***Control/Supervision:*** *Pelin Yılmazbaş;* ***Data Collection and/or Processing:*** *Mehmethan Doğan;* ***Analysis and/or Interpretation:*** *Mustafa Alpaslan Anayol;* ***Literature Review:*** *Mehmet Hakan Tırhış;* ***Writing the Article:*** *Meltem Özgül Yılmazoğlu, Mustafa Alpaslan Anayol;* ***Critical Review:*** *Mehmet Ali Şekeroğlu;* ***References and Fundings:*** *Mustafa Alpaslan Anayol;* ***Materials:*** *Mustafa Alpaslan Anayol.*

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