

# Corneal biomechanical features in patients with ankylosing spondylitis

## *Características biomecânicas da córnea entre pacientes com espondilite anquilosante*

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### ABSTRACT

**Purpose:** To evaluate the corneal biomechanical features and central corneal thickness in ankylosing spondylitis patients and to evaluate correlations of these parameters with disease activity.

**Methods:** The study included 51 patients diagnosed with ankylosing spondylitis (mean age, 40.80 ± 13.15 years; range, 18-72 years) and 34 age- and sex-matched healthy controls (mean age, 42.00 ± 12.32 years; range, 18-60 years). All underwent a complete ophthalmological and physical examination, including visual acuity testing and biomicroscopic anterior and posterior segment examinations. Corneal hysteresis, corneal resistance factor, Goldmann-correlated intraocular pressure, and corneal compensated intraocular pressure were evaluated with an ocular response analyzer, and the central corneal thickness was measured with Sirius® corneal tomography. The Bath Ankylosing Spondylitis Disease Activity Index, Functional Index, and Metrology Index scores were recorded.

**Results:** In the ankylosing spondylitis patients, the mean disease duration was 7.73 ± 6.05 (range, 1-30) years. There was no statistically significant difference between the patients and controls in the corneal biomechanical features. The Goldmann-correlated intraocular pressure and corneal compensated intraocular pressure both showed positive correlations with age (p=0.003 and p=0.001, respectively). There was a negative correlation between corneal hysteresis and disease duration (p=0.002), and between central corneal thickness and the Bath Ankylosing Spondylitis Metrology Index score (p=0.003).

**Conclusion:** This study demonstrated a significant negative correlation between corneal hysteresis and disease duration in ankylosing spondylitis patients. Furthermore, the central corneal thickness value decreased with an increase in Bath Ankylosing Spondylitis Metrology Index score, which may result in an underestimate of intraocular pressure readings and thus an inaccurate risk assessment of glaucoma.

**Keywords:** Spondylitis, ankylosing; Corneal biomechanics; Corneal tomography; Severity of illness index

### RESUMO

**Objetivo:** Avaliar as características biomecânicas da córnea e espessura central da córnea em pacientes com espondilite anquilosante e analisar a correlação destes parâmetros no grupo de estudo com a atividade da doença.

**Métodos:** Foram incluídos no estudo 51 pacientes com diagnóstico de espondilite anquilosante e 34 controles saudáveis com idade e sexo. Todos os sujeitos foram submetidos a um exame oftalmológico e físico completo, incluindo exames de acuidade visual, exames de segmento anterior e posterior biomicroscópicos. Foram avaliados o coeficiente de resistência da córnea, a pressão intraocular correlacionada com Goldmann e a pressão intraocular compensada da córnea com o analisador de resposta ocular, a espessura corneana central com a tomografia corneana pelo Sirius®. Se o índice de atividade da doença de espondilite anquilosante de banho, o índice funcional de espondilite anquilosante de banho, o índice de metrologia de espondilite anquilosante de banho.

**Resultados:** Foram incluídos no estudo 51 pacientes com idade média de 40,80 ± 13,15 (intervalo: 18-72) anos e 34 casos de controle com idade média de 42,00 ± 12,32 (intervalo: 18-60) anos. No grupo espondilite anquilosante a duração média da doença foi de 7,73 ± 6,05 (1,00-30,00) anos. Não houve diferença estatisticamente significativa entre dois grupos quanto às características biomecânicas da córnea. Na análise de correlação, no grupo de estudo; pressão intraocular correlacionada com Goldmann e pressão intraocular compensada da córnea estavam positivamente correlacionados com a idade (p=0,003, p=0,001, respectivamente). Houve uma correlação negativa entre a duração da doença e CH (p=0,002), e entre índice de metrologia de espondilite anquilosante de banho e espessura corneana central (p=0,003).

**Conclusão:** Este estudo demonstrou correlação negativa significativa entre a duração da doença e a histerese corneal em pacientes com espondilite anquilosante. Além disso, com um aumento na pontuação de índice de metrologia de espondilite anquilosante de banho, o valor de espessura corneana central também estava diminuindo o que pode causar uma diminuição nas leituras de pressão intraocular artificialmente e resultar em avaliação de risco imprecisa de glaucoma.

**Descritores:** Espondilite anquilosante; Biomecânica da córnea; Tomografia da córnea; Índice de gravidade de doença

### INTRODUCTION

Ankylosing spondylitis (AS) is a chronic, progressive, inflammatory disease of the sacroiliac joints and the axial skeleton, which can also affect extra-articular parts of the body, such as the intestines, urinary system, and eyes<sup>(1)</sup>. In general, its pathogenesis arises from environmental factors that trigger an abnormal immunological response in predisposed individuals, causing inflammation.

To help manage patients with AS, clinical scoring systems that define the disease activity and its effects on the quality of life have been developed. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) reflects the entire spectrum of disease, with higher

BASDAI scores indicating greater disease activity<sup>(2)</sup>. The Bath Ankylosing Spondylitis Functional Index (BASFI) is an approach to defining and monitoring the functional ability of patients with AS<sup>(3)</sup>. The Bath Ankylosing Spondylitis Metrology Index (BASMI) is a metrological index that is used to measure spinal mobility, with higher BASMI scores indicating greater limitation of movement due to the AS<sup>(4)</sup>.

Extra-articular involvement is commonly reported in AS patients; among these, the most common form of eye involvement is anterior uveitis, which has been reported in up to 30% of AS cases and is usually associated with HLA-B27 positivity<sup>(5,6)</sup>. In general, anterior uveitis is unilateral and recurrent in AS cases. If it is not treated properly, it can

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cause many complications, such as synechia, cataract, glaucoma, and macular edema, with the possible consequence of visual loss.

Glaucoma is a major cause of blindness and is associated with progressive damage to the optic nerve. Increased intraocular pressure (IOP) is the most important risk factor for glaucoma and also the main target of therapy aimed at controlling the disease<sup>(7)</sup>. It is widely accepted that central corneal thickness is a predictive factor for the risk of glaucoma progression<sup>(8)</sup>. IOP tends to be underestimated in thin corneas; as a result, patients with this condition may not receive treatment<sup>(9,10)</sup>. Recent evidence shows that using biomechanical properties, such as corneal hysteresis, to adjust IOP may be less biased by corneal thickness and better associated with glaucoma status<sup>(11)</sup>.

The biomechanical properties of the cornea may change during the course of some chronic inflammatory diseases, such as rheumatoid arthritis or systemic lupus erythematosus<sup>(12-14)</sup>. Although a decrease in central corneal thickness (CCT) was found in AS patients in recent studies<sup>(15,16)</sup>, changes in corneal biomechanical properties have not previously been studied in detail. The aim of this study was to evaluate corneal biomechanical features and CCT in AS patients and to evaluate correlations of these findings with disease activity.

## METHODS

In total, 51 patients diagnosed with AS who attended the Physiotherapy and Rehabilitation Department of Bagcilar Education and Research Hospital, Istanbul, Turkey, between January 2015 and July 2015 were included in the study. The mean age was  $40.80 \pm 13.15$  years (range, 18-72 years); there were 36 men and 15 women. The diagnosis of AS was made according to the modified New York criteria<sup>(17)</sup>, and the disease duration was defined as the time since onset of AS-specific symptoms<sup>(18)</sup>. Physical and locomotor system examinations were performed for all patients, and their medical history and medications were recorded. Routine laboratory tests, including for HLA-B27, were performed and the patients' BASDAI, BASFI, and BASMI scores were recorded.

The control group included 34 age- and sex-matched healthy controls free from any history of rheumatic or ocular diseases. The mean age was  $42.00 \pm 12.32$  years (range, 18-60 years); there were 21 men and 13 women. Anyone with a history of intraocular surgery, corneal disease, glaucoma, contact lens wear, refractive errors >1 diopter, uveitis, or any other ocular disease, or who was using systemic steroids, was excluded from the study. The study was approved by the local ethics committee (Ethics number: 2015-401). Informed consent was obtained from all participants.

All participants underwent a complete ophthalmological examination, including visual acuity testing, assessment of the intraocular pressure (IOP) with an ocular response analyzer (ORA®, Reichert Inc., Depew, NY), tomography, and biomicroscopic anterior and posterior segment examinations. The ORA reports two IOPs: Goldmann-correlated IOP (IOPg) and corneal compensated IOP (IOPcc)<sup>(19)</sup>; it was also used to evaluate corneal hysteresis (CH) and corneal resistance factor (CRF). CH, which is an indicator of corneal viscosity, was measured as the difference between two bidirectional (inward and outward) applanation pressure measurements recorded by the ORA<sup>(20)</sup>. The CRF is considered to be an indicator of the overall resistance of the cornea and is mainly associated with the cornea's elastic properties<sup>(20)</sup>. The mean values of four measurements, for which all the signals had a waveform score >6.0, were used in the analysis<sup>(20,21)</sup>. Single eye of each patient having higher waveform score is included in the study.

The central corneal thickness was measured using a Sirius® topography system (Costruzione Strumenti Oftalmici, Florence, Italy), which consists of a combination of two rotating Scheimpflug cameras and a Placido disk. All measurements were made by the same trained examiner following the manufacturer's guideline.

The statistical analyses of the results were performed using SPSS Statistics, version 21 (IBM Corp., Armonk, NY). Results are presented as mean  $\pm$  SD for continuous variables and as proportions (%) for cate-

gorical variables. Student's *t*-test or the chi-square test was used for comparisons between the patient and control groups. Correlations were calculated using Pearson correlation analysis. Statistical significance was set as  $p < 0.05$ .

## RESULTS

The demographic characteristics and corneal biomechanical features of study participants are summarized in table 1. In the AS group, the mean disease duration was  $7.73 \pm 6.05$  years (range, 1-30 years). The mean values (ranges) of the BASFI, BASDAI, and BASMI scores were  $1.46 \pm 1.34$  (0-5.10),  $2.15 \pm 1.27$  (0.10-4.60), and  $2.33 \pm 1.56$  (0.40-7.20), respectively. HLA B27 was positive in 41 (80%) of the AS group. Correlation analysis revealed positive correlations of IOPg and IOPcc with age in the AS group ( $r=0.30$ ,  $p=0.03$  and  $r=0.36$ ,  $p=0.01$ , respectively), and negative correlations between CH and disease duration ( $r=-0.32$ ,  $p=0.02$ ) and between CCT and BASMI ( $r=-0.31$ ,  $p=0.03$ ) (Table 2). Correlation analysis was applied to the control group to assess how corneal biomechanical features were associated with age. This showed a positive correlation between IOPcc and age ( $r=0.45$ ,  $p=0.005$ ) (Table 3).

## DISCUSSION

In this study, we compared corneal biomechanical features and CCT between patients with AS and healthy controls. This did not reveal any differences between the groups in IOPg, IOPcc, CH, CRF, or CCT, but IOPcc showed a positive correlation with age in both the AS and the control group. In patients with AS, there were negative correlations between CH and the disease duration and between CCT and the patients' BASMI scores<sup>(22)</sup>.

Ocular involvement is one of the most common extra-articular findings in AS patients. Although the pathogenesis of eye disease in AS has yet to be clearly identified, it has been suggested that environmental triggers and the activation of both innate and adaptive immunological systems may be implicated in genetically susceptible individuals<sup>(23,24)</sup>. Acute anterior uveitis has been reported in about 30%-40% of individuals with AS and is strongly associated with HLA-B27 positivity<sup>(25)</sup>. Furthermore, it has been observed that AS patients with uveitis had worse BASDAI and BASFI scores<sup>(26)</sup>. Because the effects of uveitis may be the topic of a future study, we did not include two patients with active uveitis and six patients with a previous history of uveitis in this study.

Data about corneal changes in AS patients are limited. A recent study evaluated the corneal parameters of 57 patients with AS by Scheimpflug imaging and compared the results with 57 healthy control cases, observing that the mean CCT and corneal volume were reduced significantly in AS patients along with the Schirmer test

**Table 1. The demographic features and corneal biomechanical features of study participants**

	Ankylosing spondylitis (n=51)	Control (n=34)	p
Sex (M/F)	36/15	21/13	0.48
Age (years)	$40.80 \pm 13.15$	$42.00 \pm 12.32$	0.67
IOPg (mmHg)	$15.30 \pm 3.52$	$15.97 \pm 4.02$	0.43
IOPcc (mmHg)	$16.59 \pm 3.56$	$16.56 \pm 3.43$	0.97
CH (mmHg)	$9.69 \pm 1.58$	$10.07 \pm 1.37$	0.25
CRF (mmHg)	$9.75 \pm 1.79$	$10.25 \pm 1.88$	0.22
CCT ( $\mu$ m)	$539.78 \pm 38.81$	$544.35 \pm 34.49$	0.58

M= male; F= female; IOPg= Goldmann-correlated intraocular pressure; IOPcc= corneal compensated intraocular pressure; CH= corneal hysteresis; CRF= corneal resistance factor; CCT= central corneal thickness. The p values were determined using Student's *t*-test.

**Table 2. The results of the correlation analysis for the AS patients**

	IOPg (mmHg)	IOPcc (mmHg)	CH	CRF	CCT ( $\mu\text{m}$ )
Age					
<i>p</i>	<b>0.03</b>	<b>0.01</b>	0.28	0.67	0.69
<i>r</i>	<b>0.30</b>	<b>0.36</b>	-0.15	0.06	-0.06
Disease duration					
<i>p</i>	0.77	0.16	<b>0.02</b>	0.12	0.11
<i>r</i>	0.04	0.20	<b>-0.32</b>	-0.22	-0.23
BASFI					
<i>p</i>	0.70	0.40	0.34	0.58	0.66
<i>r</i>	0.05	0.12	-0.14	-0.08	-0.06
BASDAI					
<i>p</i>	0.56	0.29	0.29	0.61	0.30
<i>r</i>	0.08	0.15	-0.15	-0.07	-0.15
BASMI					
<i>p</i>	0.77	0.74	0.24	0.28	<b>0.03</b>
<i>r</i>	-0.04	0.05	-0.17	-0.15	<b>-0.31</b>
HLA B27 positivity					
<i>p</i>	0.33	0.10	0.14	0.59	0.71
<i>r</i>	-0.14	-0.23	0.21	0.08	0.05

BASFI= Bath Ankylosing Spondylitis Functional Index; BASDAI= Bath Ankylosing Spondylitis Disease Activity Index; BASMI= Bath Ankylosing Spondylitis Metrology Index; IOPg= Goldmann-correlated intraocular pressure; IOPcc= corneal compensated intraocular pressure; CH= corneal hysteresis; CRF= corneal resistance factor; CCT= central corneal thickness. The correlation coefficients (*r*) and *p* values were determined with Pearson correlation analysis, *r*= Pearson's correlation coefficient.

**Table 3. The results of correlation analysis performed for the control group**

	IOPg (mmHg)	IOPcc (mmHg)	CH	CRF	CCT ( $\mu\text{m}$ )
Age					
<i>p</i>	0.07	0.005	0.46	0.41	0.87
Coefficient	0.31	0.450	-0.13	0.14	0.03

IOPg= Goldmann-correlated intraocular pressure; IOPcc= corneal compensated intraocular pressure; CH= corneal hysteresis; CRF= corneal resistance factor; WS= waveform score; CCT= central corneal thickness. The *p* values were determined with Pearson correlation analysis.

scores (disease duration, 60.0 months; range, 25.5–156.0 months; BASDAI,  $3.68 \pm 2.66$ )<sup>(15)</sup>. Another study included 68 AS patients and 61 age-matched controls and reported that CCT was significantly decreased in the AS group (disease duration, 5.42 years; range, 1–25 years)<sup>(16)</sup>. In our study, we also observed a decrease in CCT values in the AS group although the difference between the two groups was not statistically significant.

In the present study, we observed a positive correlation between IOPcc and age in both the AS and the control groups. Similarly, another recent study reported a significant association of both IOPg and IOPcc with older age in a large cohort<sup>(27)</sup>. This association of increased IOP with older age should be kept in mind for both healthy individuals and patients with AS, especially during patient screening.

CH reflects the ability of the corneal stromal tissue to absorb and disperse energy<sup>(11)</sup>. In this study, CH decreased with longer durations of AS. Although the exact pathogenesis is not clearly understood, this decrease in CH may be associated with structural changes in proteoglycans and glycosaminoglycans, that preserve the elasticity and rigidity of the corneal stroma<sup>(28)</sup>. The mean disease duration for the patients in the present study was  $7.73 \pm 6.05$  years; these results suggest that, in later periods of the disease, CH would change

further, resulting in significant differences with the healthy controls. Glaucoma is a chronic progressive disease that increases with age<sup>(29)</sup>. Decreased CH has been defined a risk factor for all types of glaucoma and for progressive glaucomatous optic neuropathy<sup>(30)</sup>. Comprehensive studies are warranted to determine whether decreased CH is associated with glaucoma in the later stages of AS.

BASFI, BASDAI, and BASMI are the three main determinants of function, disease activity, and metrology in AS. In this study, only CCT was negatively correlated with BASMI scores, with no other associations found between corneal biomechanical features and the clinical activity index scores. The negative association between CCT and BASMI scores may be related to the findings of previous studies that also reported decreased CCT in AS patients. Clearly, if more severe AS cases are involved in a study, more diminished CCT values would be expected, which would result in a significant difference between AS patients and healthy controls. CCT is especially important when evaluating IOP, and a decreased CCT value may be associated with a lower IOP readings. When evaluating patients at an advanced stage of AS, clinicians should be aware of this condition and the increased risk of glaucoma being overlooked<sup>(31)</sup>.

The main limitation of this study was the low number of patients. Determining the disease duration as "from the beginning of the first AS-related symptoms" could potentially have resulted in inaccuracy. For the patients in this study, the disease durations were generally not long and their disease severity scores were not very high, which may also have influenced the results.

In conclusion, we showed a significant negative correlation between CH and disease duration in AS patients. CCT decreased with higher BASMI scores, which could result in an underestimate of IOP readings and thus in an inaccurate risk assessment for glaucoma.

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