The Comparison of Corneal Biomechanical Parameters of Cases with Behçet's Disease and Normal Subjects

Behçet Hastalığı Olguları ve Normal Bireylerin, Kornea Biyomekaniği Parametrelerinin Kıyaslanması

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ABSTARCT

Purpose: To compare the corneal biomechanical parameters of cases with Behçet's disease (BD) and normal subjects by ocular response analyzer (ORA).

Material and Methods: Fifty two eyes of 52 cases with BD and 26 eyes of 26 normal subjects were enrolled to our prospective study. Cases with BD were divided into two groups according to the number of uveitis attacks within the last 1 year. Group 1 consisted of 25 eyes of 25 cases who had at least 1 attack under systemic treatment, group 2 consisted of 27 eyes of 27 cases who had no uveitis attack with or without systemic treatment for the last 1 year. Group 3 consisted of 26 eyes of 26 control subjects. None of the cases in the study had glaucoma and taken any anti-glaucoma treatment before. Corneal hysteresis (CH), corneal resistance factor (CRF), corneal-compensated intraocular pressure (IOPcc) and Goldmann-correlated intraocular pressure (IOPg) of the cases were measured by ORA. The comparison of the results was performed by Anova, Shapiro-Wilk, post-hoc tukey and chi-square tests for the statistical analysis.

Results: There were no statistically significant differences in GAT (p=0.1), IOPg (p=0.07), CRF (p=0.11) and IOPcc (p=0.75) between the groups. But the mean CH was found to be significantly higher in control subjects than group 1 and 2 (p=0.04).

Conclusion: Because of the low values of CH of the cases with BD, the changes in corneal biomechanics was thought to be related with relapsing uveitis and/or corticosteroid use.

Key Words: Behçet's disease, cornea, corneal biomechanics, ocular response analyzer.

ÖZ

Amaç: Behçet hastalığı (BH) olgularının oküler cevap analizatörü (ORA) ile ölçülen kornea biyomekaniği parametrelerinin, normal bireylerle kıyaslanması amaçlandı.

Gereç ve Yöntem: Elli iki BH olgusunun 52 gözü ve 26 sağlıklı bireyin 26 gözü geriye dönük çalışmamıza dahil edildi. BH olguları, son bir yıldır üveit ataklarının sıklığına göre iki gruba ayrıldı. Grup 1, sistemik tedavi altında son bir yıldır en az bir atak geçiren 25 olgunun 25 gözünü; grup 2, herhangi bir sistemik tedavi almazken ya da tedavi altında, son bir yıldır hiç atak geçirmemiş 27 olgunun 27 gözünü, grup 3 ise 26 sağlıklı bireyin 26 gözünü içermekteydi. Daha önce hiç bir olgu, glokom ya da göz içi basıncı (GİB) artışı nedeniyle anti-glokomatöz tedavi almamıştı. ORA ile korneal histerezis (KH), korneal rezistans faktör (KRF), korneal-kompanse GİB (GİBkk) ve Goldmann uyumlu GİB (GİBg) ölçümleri alındı. İstatistiksel analizlerde, Anova, Shapiro-Wilk, post-hoc tukey ve ki-kare testleri kullanıldı.

Bulgular: Gruplar arasında, Goldmann applanasyon tonometrisi ile ölçülen GİB (p=0.1), GİBg (p=0.07), KRF (p=0.11) ve GİBkk (p=0.75) açısından anlamlı farklar saptanmadı. Ancak normal bireylerin KH değerleri, BH olgularına oranla anlamlı ölçüde yüksek bulundu (p=0.04).

Sonuç: BH olgularında ortalama KH değerlerinin normal bireylere oranla düşük bulunması nedeniyle, bu olgularda, kornea biyomekaniğindeki değişikliklerin tekrarlayan üveit atakları ve/veya kortikosteroid kullanımı ile ilişkili olabileceği sonucuna varıldı.

Anahtar Kelimeler: Behçet hastalığı, kornea, kornea biyomekaniği, oküler cevap analizatörü.

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Geliş Tarihi - Received: 08.05.2012
Kabul Tarihi - Accepted: 24.07.2012
Glo-Kat 2012;7:189-193

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INTRODUCTION

Behçet's disease (BD), which was described by a Turkish dermatologist Hulusi Behçet in 1937, is characterized by relapsing uveitis, arthritis, oral and genital aphthous ulcerations and skin lesions such as erythema nodosum.[1-6] It is a chronic multisystem disease related with phenotype HLA B5 and is most commonly seen in the Mediterranean and Far Eastern countries.[1-6]

Recurrent iridocyclitis, retinitis and retinal vasculitis are major ocular manifestations and cataract, secondary glaucoma and optic atrophy are the most devastating complications of the disease.[1-6]

Cornea may also be affected by chronic inflammation with compromised endothelial dysfunction.[7-13] Increased central corneal thickness (CCT) values have been reported in cases with active BD compared with inactive BD and normal subjects.[12-13]

Ocular response analyzer (ORA; Reichert Inc., Depew, NY) is an instrument that measures intraocular pressure (IOP) free from the influence of corneal biomechanical factors.[14-19] It provides measurements of the corneal hysteresis (CH), corneal resistance factor (CRF), Goldmann-correlated IOP (IOPg) and corneal compensated IOP (IOPcc). An air puff indents the cornea to flat shape and then a slight concavity. When the air puff turned off, cornea first becomes flat and then resumes its normal convex shape.

The instrument records the pressure at the two points when the cornea is flat (P1 and P2).[14] CH, the viscous dampening in cornea to a deformation, is the difference of P1 and P2 and is related with viscoelastic properties of the cornea.

IOPg is the average of P1 and P2. IOPcc is the most accurate IOP independent from corneal properties and is derived from the equation P2-(kP1). CRF is related with elastic behavior and stiffness of the cornea.[14]

Chronic inflammation or steroid use may affect the corneal biomechanical parameters like other structures of the eye. In this study, our aim was to compare CH, CRF, IOPg and IOPcc of adult cases with BD and normal subjects by ORA.

MATERIALS AND METHODS

Our study involved 52 eyes of 52 cases with ocular BD who were under control in Uvea department of Ankara Ulucanlar Eye Research Hospital and 26 eyes of 26 normal subjects. All of the cases fulfilled the international criteria for BD. The cases were evaluated prospectively and also their past medical histories were reviewed.

All of the study procedures were conducted in accordance with the Declaration of Helsinki, and informed consents were taken from all of the participants. This study was approved by The Ethical Committee of Ankara University School of Medicine. Cases with Behçet's disease were divided into two groups according to the number of uveitis attacks within the last 1 year. Group 1 consisted of 25 eyes of 25 cases who had at least 1 attack under systemic immunosuppressive and/or anti-inflammatory treatment, group 2 consisted of 27 eyes of 27 cases who had no uveitis attack with or without systemic immunosuppressive and/or anti-inflammatory treatment for the last 1 year. Group 3 consisted of 26 eyes of 26 control subjects. The time of onset of BD, the course, location and characteristics of the ocular involvement, the frequency of uveitic relapses and systemic anti-inflammatory medications used during and prior to this study were recorded for each patient. The eyes of the adult cases ($\geq$17 years old) of BD with inactive uveitis in the eye which was included to study (no history of uveitis within the past 1 month), IOP$\leq$21 mmHg with Goldmann applanation tonometer (GAT) without any anti-glaucomatous agents, were included to our study. Healthy subjects who did not have a history of any systemic disease, family history of glaucoma or ocular problems other than refractive error were included as the control group.

Our exclusion criteria were the eyes with IOP>21 mmHg, glaucomatous optic nerve appearance (cup disc ratio greater than 0.6, vertical cup asymmetry more than 0.2, neuroretinal rim loss or notching with or without a disc hemorrhages and nerve fiber layer defects) or glaucomatous visual field defects (arcuate scotome, nasal step, positive glaucoma hemifield test). Cases that had previous history of any systemic disease other than BD, glaucoma or elevated IOP, corneal disease, aphakia, contact lens use, ocular trauma or ocular surgery within the past 6 months were excluded from the study.

All the patients underwent detailed ophthalmologic examinations, including best-corrected visual acuities with Snellen charts, slit-lamp anterior chamber examinations, dilated fundus examinations, gonioscopy with Goldmann three-mirror lens, CCT measurements by ultrasonic pachymeter, visual field examinations with Humphrey automated perimeter and IOP measurements with GAT. IOP measurements were performed between the 9 am and 11 am by two independent and masked observers. Corneal biomechanical parameters were performed by the same experienced physician (ES) according to normal clinical practice and manufacturer's guidelines. ORA measurements were performed at least 30 minutes before GAT which was performed by the same physician (UE).

The eyes with inactive inflammation or the eyes with better visual acuity in the case of bilateral inactive inflammation or the right eyes in the case of same visual performance and bilateral inactive inflammation were included to the study.

Statistical Analysis: Shapiro-Wilk test was used in order to check the concordance of the data of the study with the normal distribution curve for each group. After the observation of the presence of the concordance of the data of the study with the normal distribution curve, chi-square test was used for the sex distribution of the groups, Anova and post-hoc tukey tests were used for the other data of the groups in statistical analysis. Statistical significance was set as $p<0.05$. All statistical analyses of the study were performed by using SPSS for Windows (SPSS Inc., Chicago, IL, USA) software.

RESULTS

The mean age of the 25 cases in group 1 which consisted of 6 female (24%) and 19 male (76%) cases, was 32.2±8.4 years (19-54 years); the mean age of the 27 cases in group 2 which consisted of 9 female (33,3%) and 18 male (66.4%) was 42.8±9.4 years (30-61 years) and the mean age of the 26 cases the control group which consisted of 10 female (38.5%) and 16 male (61.5%) cases, was 34.5±7.4 years (19-46 years).

The difference between the sex of the three groups was not statistically significant (p=0.53). The cases in group 2 were significantly older than the cases of the other groups (p<0.001) but the difference between the age of the group 1 and 3 was not statistically significant (p=0.63) (Table 1).

The mean age at the time of the diagnosis of BD in group 1 was 26.3±8.05 years (range, 12 to 44 years) and in group 2 was 28.6±7.8 years (range, 14 to 46 years). Thee mean period between the diagnosis of BD and the study was 8.3±5.5 years (range, 1 to 17 years) in group 1 and 8.2±5.9 years (range, 1 to 29 years) in group 2. All the eyes had chronic recurrent uveitis secondary to BD and all of the eyes were free of active inflammation for at least 1 month prior to the time of the study. 6 eyes in group 1 and 3 eyes in group 2 were pseudophakic. All 25 cases in group 1 were under systemic immunosuppressive agents like corticosteroids, cyclosporine A, azathioprine or interferon. In group 2, 12 cases were under systemic immunosuppressive agents, 11 cases were under colchicum treatment and the remaining 4 cases didn't use any systemic medications during the study.

The mean IOP by GAT was 13.2±2.6 mmHg (9-17 mmHg) in group 1, 14.2±2.6 mmHg (9-19 mmHg) in group 2 and 14.6±1.9 mmHg (10-18 mmHg) in control group.

Table 1: *Summary table of the ours and other studies about glaucoma after pediatric cataract surgery.*

	Group 1	Group 2	Group 3 (Control)	P value
Number of case	25	27	26	
Age (years) (mean±SD-range)	32.2±8.4 (19-54)	42.8±9.4 (30-61)	34.5±7.4 (19-46)	p<0.001
Male, n (%) Female, n (%)	19 (76%) 6 (24%)	18 (66.4%) 9 (33.3%)	16 (61,5%) 10 (38,5%)	p=0.53
Age at the diagnosis of BD (years) (mean±SD -range)	26.3±8.05 (12 to 44)	28.6±7.8 (14 to 46)	Ø	Ø
Presence of BD(years) (mean±SD -range)	8.3±5.5 (1-17)	8.2±5.9 (1-29)	Ø	Ø

BD: Behçet's Disease.

Table 2: *Corneal biomechanical parameters of cases with Behçet's disease (BD) in group 1, group 2 and control group.*

	Group 1	Group 2	Control group	P Value:
CH (mean±SD), (mmHg):	9.6±1.4	9.1±1.4	10.1±1.4	p=0.04*
CRF (mean±SD), (mmHg):	9.3±2.0	8.6±2.0	9.8±1.8	p=0.11
IOPg (mean±SD), (mmHg):	13.3±2.8	14.2±2.5	14.8±1.8	p=0.07
IOPcc (mean±SD), (mmHg):	15.1±2.3	14.8±2.6	15.3±2.4	p=0.75

*BD: Behçet's Disease, CH: Corneal Hysteresis, CRF: Corneal Resistance Factor, IOPg: Goldmann Correlated Intraocular Pressure, IOPcc: Corneal-compensated Intraocular Pressure. *statistically significant.*

The difference between the mean IOP by GAT of the groups was not statistically significant (p=0.1). The mean CCT measured by ultrasonic pachymeter of the eyes was 538.9±17.8 µm (range: 509 to 582 µm) in group 1, 540.8±18.7 µm (range: 505 to 585 µm) in group 2 and 541.9±15.7 µm (range: 503 to 578 µm) in control group but the difference was not statistically significant (p=0.37).

The corneal biomechanical parameters of the groups are summarized in table 2. The mean CH values of in group 1 and group 2 were lower than normal subjects and this result was statistically significant (p=0.04). The differences between CRF, IOPg and IOPcc of the groups were not statistically significant (p=0.11, p=0.07, p=0.75 respectively), (Table 2).

DISCUSSION

Visual function impairment is frequent in BD related with the complications of panuveitis like cataract, glaucoma, persistent vitreous opacity, macular degeneration or retinal and optic atrophy.[1-6] Recurrent ocular inflammations may also compromise corneal endothelial dysfunction and affect the biomechanics of cornea.[7-9] According to our knowledge, it is the first report that compares the corneal biomechanics of the cases with BD and normal subjects with ORA.

Over the past years, ORA has become one of the most important instruments for both research and clinical evaluation of cases with corneal diseases and glaucoma.[14-19] Although GAT is still the gold standard method for measuring IOP, the well-recognized effects of CCT, corneal curve and most importantly corneal biomechanical behavior led to the development of new tonometric methods designed to minimize these effects, like ORA.

In addition to the most accurate IOP (IOPcc), it can also provide CH and CRF measurements, which are the most important parameters about corneal biomechanics. Low CH and high CRF is strongly associated with glaucoma.[15-17]

In Shah et al's study, CH has been reported to be lower in normal-tension glaucoma (NTG) than primary open-angle glaucoma (POAG) and ocular hypertension (OHT). Cases with OHT were found to have the highest CH values. Low CH is also associated with glaucoma progression.[15]Anand et al have reported that POAG patients with asymmetric visual fields had lower CH in their eyes with worse visual field.[16]

CH can increase when IOP is reduced to normal levels after medical and surgical treatment of glaucoma. [17] So, CH could be a useful tool in the diagnosis, follow-up and treatment of glaucoma. Corneal edema may also affect corneal biomechanical behavior.[18-19]

Hager et al found CH to be diminished with significantly increased CCT related with postoperative corneal edema 1 day after clear corneal cataract surgery.[18] But in Lu et al's study, CH was not found to be associated with corneal swelling induced by soft contact lens wear.[19]

CCT can be affected by many ocular diseases, contact lens use, surgeries or trauma primarily associated with compromised corneal endothelial functio.[7-12] Pillai et al examined morphological changes in corneal endothelial cells by specular microscopy in anterior uveitis cases. Inflammation may compromise the barrier integrity of corneal endothelium and lead clinical or subclinical corneal edema.[11] Similar with Pillai et al, Miyanaga et al found a significant correlation between CMV-associated iridocyclitis and corneal endothelial cell loss.[12] The measurement of CCT is the most important indirect method for determining the health of cornea.[7-12,13] Evereklioğlu et al.,[12] found thicker CCT in BD cases with active ocular involvement than the once with no ocular involvement at the time of the study and normal subjects. They observed CCT of cases with active ocular involvement returned to nearly normal after treatment stated that CCT should be taken into account in managing the treatment of BD. Ozdamar et al found similar findings in their study with BD cases and concluded that recurrent uveitis did not lead to a permanent change in CCT in BD.[13]

In our study we compared the corneal biomechanics of the cases with BD and normal subjects with ORA. We divided our cases of BD into two groups according the frequency of attacks of uveitis. Although our cases had ocular BD with relapsing panuveitis, none of them had active uveitis in their eyes which were included to the study. We especially excluded the eyes with active inflammation at the time of the study in order to eliminate the effect of active inflammation on corneal biomechanics parameters.

Our main purpose was to examine the chronic permanent effects of relapsing uveitis on corneal biomechanical behavior related with inflammation and/or steroid use. Although Evereklioğlu et al.,[12] and Ozdamar et al.,[13] have stated that recurrent uveitis did not lead to a permanent change in CCT, there should be some detectable small changes in CH and CRF without a significant increase in CCT. CH and CRF is not correlated with CCT.[14] CH is lower than normal levels in keratoconus, congenital glaucoma and Fuchs endothelial dystrophy while CCT is thin in keratoconus and very thick in the other two conditions. Independent from CCT, we expected some changes in corneal biomechanical parameters related with relapsing inflammation in BD and our main purpose was to detect these.

Only 9 eyes in our study were pseudophakic and all had cataract surgery at least 6 months before the study. Kamilya et al.,[20] reported that cataract surgery could affect corneal biomechanical parameters only in postoperative few days. So pseudophakia was thought to not affect our results.

Corticosteroids are known to be a modulating factor of the biomechanical properties of the cornea.[21] Spoerl et al.,[21] investigated the change in biomechanical properties of the cornea induced by high-dose hydrocortisone in their study. They observed increased CCT values and reduced corneal stiffness in porcine corneas after high-dose hydrocortisone injection. Because corticosteroids are the main agents in the treatment of uveitis, cases with frequent attacks should use steroids in higher doses and/or long periods. In addition to the effects of inflammation itself, steroid use might cause some changes in our cases with BD.

The mean CH values of cases with BD in both group 1 and 2 were found to be statistically significantly lower than the control subjects and this was the main finding in our study. But there were no significant differences in CRF, IOPcc and IOPg between the three groups. A strong association between relapsing inflammation and/or steroid use and glaucoma or elevated IOP is well-known. Also, low CH is known to be associated with glaucoma.[15-17] But none of our cases had glaucoma or high IOP at the time of the study or before. In our opinion, uveitis and/or steroid use might cause the changes in corneal biomechanic in our cases with BD. But there was no significant difference in CH of the cases in group 1 and 2 in which the severity of the disease differed. We expected CH should have been lower in group 1 than group 2 because of higher frequency of uveitis attack.

In our study we found an evidence of the relationship between corneal hysteresis and relapsing uveitis in cases with BD with inactive uveitis at the time of the study and no history of glaucoma or elevated IOP before. Our study demonstrates that monitoring the corneal biomechanical parameters should be important in cases with BD with active uveitis or the patients with history of elevated IOP. The major limitation of our study was thought to be the inadequacy of the number of the cases. Further investigations for the usage of ORA should be encouraged in uveitis to detect the relationship of the changes in corneal biomechanic behavior and active uveitis. In that case, the quantitative measurements obtained by ORA could provide important information about the corneal health affected by the course of uveitis in BD. Also the risk for glaucoma should be kept in mind especially in BD cases with lower values of CH.

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