ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/ophthal.2016-51870

Evaluation of Tear Film Function and Corneal Thickness of Behcet's Disease Patients Without Ocular Involvement

Aktif Göz Tutulumu Olmayan Behçet Hastalarında Gözyaşı Fonksiyonu ve Korneal Kalınlık Değerlendirmesi

Ayşe Aslıhan KARCI,[a]
Nurşad ÇİFCİ ASLAN,[b]
Tuba GÜLER,[c]
Fulya DÖRTBAŞ[d]

Clinics of
[a]Opthalmology,
[b]Dermatology,
[c]Physical Therapy and Rehabilitation,
[d]Romatology,
Kocaeli Derince Training and Research Hospital,
Kocaeli

Geliş Tarihi/*Received:* 27.04.2016
Kabul Tarihi/*Accepted:* 09.01.2017

Yazışma Adresi/*Correspondence:*
Nurşad ÇİFCİ ASLAN
Kocaeli Derince Training and Research Hospital,
Clinic of Dermatology, Kocaeli, TURKEY/TÜRKİYE
nuradaslan@yahoo.com

ABSTRACT Objective: Behcet's disease (BD) is a chronic inflammatory vasculitis characterized by mucocutaneous ulcers and ocular involvement. There are a few studies about the effects of BD on the ocular surface. We aimed to investigate central corneal thickness (CCT) and tear film function in patients without clinically detectable ocular pathology. **Material and Methods:** Eighty nine eyes of 45 BD patients without ocular pathology were examined and compared with 52 eyes of 26 healthy, age and sex matched volunteers. For both groups, after routine opthalmologic examinations, tear film function tests, containing tear break-up time (BUT) and Schirmer test were done. CCT was measured with ultrasonic pachymeter. Schirmer test results, CCT and BUT measurements were compared and p<0,05 was considered statistically significant. **Results:** Mean values of Schirmer tests in patient and control groups were 7.62±5.87 mm and 9.32±3.92 mm, respectively. Difference between groups was not statistically significant (p= 0.06). Mean BUT was significantly lower in the patient group (p= 0.0001). Mean CCT of patient and control groups were 536.13±31.47 µm and 540,90±36,39 µm, respectively. There was no significant difference between the CCT of the groups (p= 0.41). All parameters were similar for patients receiving and not receiving immunosuppressive therapy (p>0.05). **Conclusion:** There may be changes in tear film functions of BD patients without clinically detectable ocular pathology. Since BUT test results were found to be significantly lower in our patient group we concluded that BD patients without ocular pathology must also be evaluated for symptoms of dry eye.

Keywords: Behcet syndrome; cornea; dry eye syndromes

ÖZET Amaç: Behçet Hastalığı (BH) mukokutanöz ülserler ve oküler tutulum ile karakterize kronik inflamatuar bir vaskülittir. Behçet hastalığının oküler yüzey üzerine etkisini bildiren çok az çalışma vardır. Klinik olarak oküler bulguları olmayan Behçet hastalarının gözyaşı fonksiyonlarını ve kornea kalınlıklarını değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** Oküler patolojisi olmayan 45 Behçet hastasının 89 gözü, benzer yaş ve cinsiyette 26 sağlıklı gönüllü bireyin 52 gözü incelendi ve karşılaştırıldı. Her iki gruba rutin oftalmolojik muayeneyi takiben göz yaşı kırılma zamanı (GKZ) ve Schirmer testi içeren göz yaşı fonksiyon testleri yapıldı. Santral kornea kalınlığı (SKK) ultrasonografik pakimetri ile ölçüldü. Grupların Schimer test sonuçları, GKZ ve SKK değerleri istatistiksel analizler ile karşılaştırıldı, p< 0,05 istatistiksel olarak anlamlı kabul edildi. **Bulgular:** Hasta ve kontrol grubunun ortalama Schirmer test değerleri sırasıyla 7,62±5,87 mm ve 9,32±3,92 mm olarak ölçüldü. Gözyaşı fonksiyon değerlendirilmesinde Schirmer testi sonuçları her iki grup için benzerdi (p= 0,06). Göz yaşı kırılma zamanı (GKZ) kontrol grubunda anlamlı derecede yüksek bulundu (p= 0,0001). Hasta ve kontrol grubunun SKK'ları sırasıyla 536,13±31,47 µm ve 540,90±36,39 µm olarak tespit edildi. Grupların SKK'ları arasında anlamlı fark görülmedi (p= 0,4). Bütün parametreler, immunsupressif tedavi alan ve almayan hastalar için benzer bulundu (p> 0,05). **Sonuç:** Klinik açıdan oküler bulguları olmayan Behçet hastalarının, göz yaşı fonksiyonlarında değişiklikler olabilir. Bizim hasta grubumuzda GKZ ölçümleri anlamlı derecede düşük bulunduğundan oküler patolojisi olmayan Behçet hastalarının kuru göz bulguları açısından da incelenmesi gerektiğini düşünmekteyiz.

Anahtar Kelimeler: Behçet sendromu; kornea; kuru göz sendromları

Behcet's disease (BD) is a chronic, inflammatory, multi-systemic disease characterized by recurrent attacks. This is an inflammatory, nongranulomatous and obstructive vasculitis affecting mucocutaneous tissue.[1]

Ocular involvement rate of the disease is about 50-70% and it is an important clinical manifestation showing the severity of the disease.[2] Ocular involvement occurs approximately within 2-4 years after the onset of the disease.[3] Anterior segment eye involvement is often seen as severe anterior uveitis and hypopyon.[2,4] On the other hand panuveitis occurs in the vast majority of the patients. Sometimes retinal layers and vitreous may be affected by the disease.[5,6] The involvement of the posterior segment may be sight-threatening, as a result of recurrent retinal vaso-occlusive inflammation.[7,8]

There are a few studies about the effects of BD on the ocular surface.[6,9-12] CCT was reported as higher in BD patients with active ocular pathology whereas not changed in BD patients without ocular pathology.[11] To our knowledge, there is also not enough information about the effects of the disease on the tear film function of patients. In our study, we aimed to investigate tearfilm function and central corneal thickness in patients without clinically detectable ocular pathology.

MATERIAL AND METHODS

This study was performed in Kocaeli Derince Training and Research Hospital. Our study was designed as a prospective case-control study. The study design was approved by the Ethics Committee of Kocaeli University Faculty of Medicine and the study was done in accordance with the Declaration of Helsinki Rules.

Patients, that were diagnosed as complete BD, according to International Study Group criteria for BD and have been followed in, ophthalmology, rheumatology, dermatology and neurology outpatients clinics between January 2014-December 2014, were examined.[13] Among them, 45 BD patients without ocular involvement, between the ages of 18-50 years were included in the study.

Left eye of one patient in the study group was excluded because of the presence of corneal nephelions and 89 eyes of 45 patients were included. Patients' age, gender, full eye examination, duration of illness, and medical treatment that they received were recorded. If there was no story of inflammation attack in the last three months, patients were accepted as inactive in terms of eye involvement.

In 12 of the patients they had previous history of uveitis, but there was no attack in the last year. Thirty three of the patients had no story of uveitis.

In the control group, 26 age and sex matched healthy volunteers between ages of 18-50 years were examined and 52 eyes of them were included in the study.

For control and study groups, individuals who had undergone eye surgery, who had high spherical (> 3 diopters) and high cylendric (> 2 diopters) refraction errors and glaucoma, contact lens wearers, and who had used eye drops in the last 3 months were not included. Individuals that had history of other chronic systemic diseases (rheumatic diseases, diabetes mellitus, hypertension, ischemic heart disease, liver and kidney disease, psychiatric illness) and undergoing systemic therapy were excluded from the study.

Informed consents of the study and control groups were taken, then all routine opthalmological examinations were done. Eye refractive errors were evaluated, slit-lamp and fundus examinations were performed.

To evaluate the tearfilm function, the amount of tear production was measured by Schirmer test. For Schirmer testing, primarily topical anesthesia was done with proparacaine (Alcaine 0.5%), then Schirmer paper was placed in a portion of the outer third of the lower eyelid. The patient was told to close eyes and wait for a periode of 5 minutes. After that, test papers were removed and tear test measurements were recorded. Results higher than 6 mm, were considered as normal.[14]

To assess the tearfilm stability, tear breakup time tests were done. For the measurements of

TABLE 1: Demographic features and mean values of test results in patient and control groups.

	Patient group	Control group	P value
Sex F/M	20/25	15/11	0.101
Mean age (mean ±SD) (year)	35.3±8	35.6±10	0.86
Central corneal thickness (mean ±SD)	536±31µm	540±36µm	0.4
Schirmer test	7.6±5 mm/5min	9.3±3 mm/5min	0.06
Break-up time	6.4±3seconds	13.2±4seconds	0.0001

SD: Standart deviation.

BUT, patient eyes were stained with a fluorescein strip. The patients were told to blink their eyes for 2 or 3 times. Then patients were asked to look without blinking their eyes. Time of formation of the first dry spots on the cornea was detected by biomicroscopy under the light of cobalt blue and results were recorded. Results that were higher than 10 seconds, were considered as normal.[14]

Central corneal thickness measurements were done by ultrasonic pachymetry method.[15] After topical anesthesia with proparacaine (Alcaine 0.5%), CCT was measured by pachymetry probe.

Demographic features of groups were analyzed by using descriptive statistics. We used crosstabulation for comparison of sex of groups. Among the different groups, we used independent t-test to compare variables. A two-sided P-value lower than 0.05 were considered statistically significant. Statistical analysis was performed by using SPSS 17 (Chicago, IL) pack program.

RESULTS

Age and sex distribution, Schirmer test results, BUT test results and the average corneal thickness values of patients and control group are shown in Table 1.

In the study group, 20 (44.4%) of them were female and 25 (55.6%) of them were male. In control group, 15 (57.6%) of them were female and 11 (42.4%) of them were male. The average age of the patient and control groups were 35.34±8.18 years, 35.61±10.08 years respectively. Age and sex distributions of groups were statistically similar (p>0.05). The average pachymetry values of patient group and the control group were 536.13±31.47 µm, 540.90±36.39 µm respectively. There was no significant difference between two groups (p= 0.40). Schirmer test results in the patient group and the control group were 7.62±5.87 mm, 9.32±3.92 mm, respectively. The mean values of BUT in patient group and control group were found as 6.40±3.44 seconds, 13.21±4.06 seconds, respectively (Figure 1). Schirmer test results revealed no significant differences between two groups (p= 0.06). Whereas BUT test results were significantly different between two groups (p= 0.0001).

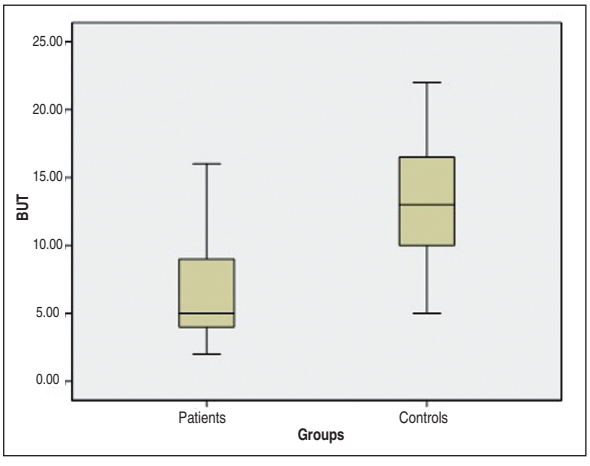

FIGURE 1: BUT (Break-up time) results of groups.

The patient group was divided into two subgroups. Patients who had history of previous eye involvement and who had no history of eye involvement were compared with each other. Schirmer test results were found to be 7.37±6.88 mm, 7.72±5.50 mm respectively. The mean values of BUT were 6.91±4.51 seconds, 6.21±2.97 seconds, respectively and CCT measurements were found to be 538.20±24.23 µm, 535.36±33.89 µm, respec-

TABLE 2: BUT and CCT results of patient subgroups.

	Colchicine	Colchicine+ immunosupressive drugs	P
Schirmer (mm/5 min) (mean±SD)	8.2±5	6.2±6	0.14
BUT (sec) (mean±SD)	6.8±3	5.5±3	0.09
CCT (µm) (mean ±SD)	534.4±32	539.8±29	0.4

BUT: Break- up time; CCT: Central corneal thickness; SD: Standart deviation.

tively. All test results were found to be statistically similar for both groups (p> 0.40).

Twenty-seven of our BD patients were using only treatment of colchicine and 18 of them were using immunosuppressive therapy (corticosteroids, azathioprine, cyclosporine, methotrexate) in addition to colchicine. Ocular findings of patients that were using only colchicine treatment were compared with patients that were using immunosuppressive drugs in addition to colchicine. Schirmer test results in these two sub-groups were 8.24±5.56 mm, 6.28± 6.39 mm, respectively, the mean values of BUT were 6.81±3.46 seconds, 5.50±3.29 seconds, respectively and CCT measurements were found to be 534.40±32.60 µm, 539.89±29.07 µm, respectively, and all test results were found to be similar for both subgroups (Table 2).

DISCUSSION

It is known that immune mechanisms play an important role in pathogenesis of BD. Neutrophils and inflammatory cytokines causes changes in endothelial cells of vascular structures and clinical findings arise because of this inflammation.[1-12] In BD patients with active eye involvement, cytokines have been reported to increase in the aqueous liquid as it is in circulation. This immuno-inflammatory response may cause tissue damage in the conjunctiva and the cornea of the BD patients.[16-18]

In a previous study, the mean flare of anterior chamber of BD patients without active inflammation were evaluated and the mean flare in these eyes that were in remission were found to be significantly higher.[19] Based on this study, we designed our research, in order to identify what type of changes could happen in the eyes of BD patients without active inflammation.

It is important to measure the cornea thickness to monitor the progression of glaucoma and for determination of suitability for refractive surgery. Higher intraocular pressure can be measured in thick cornea, whereas lower intraocular pressure can be measured in thin cornea.[15] Therefore, it is important for us how BD affects corneal thickness.

When there is ocular inflammation in BD, this disrupts the endothelial cell function and causes increase in corneal thickness.[2,11,20,21] But in BD patients without ocular pathology, CCT test results were reported as similar with control group.[11,21] In accordance with these two studies, in the current study which is wider than others, CCT values of BD patients without active ocular inflammation were found to be similar with the control group.

In our study, we were also able to evaluate the effect of immunosuppressive treatment on the CCT of BD patients and CCT of patients that receiving and not receiving immunosuppressive therapy were found to be statistically similar. We believe that broader researches investigating the effect of immunosuppressive treatment on the ocular surface need to be done.

Depending on the vascular and inflammatory pathology, conjunctival involvement in BD could be expected. In Behcet's disease patients with ocular surface lesions, besides vascular abnormalities, inflammatory cells in the conjunctiva have been previously shown.[12,22-25]

Ocular surface plays a major role in the stabilization of the tearfilm layer. This is supported by mucin release from goblet cells.[26-28] Flammer et al. reported that, in the etiology of BD, vasospasm also plays a role and it leads to ischemic symptoms.[23] This vasospasm, is also effective in the conjunctival blood vessels and can cause conjunctival ischemia. Ischemia during acute attacks, causes permanent damage to the conjunctival goblet cells and epithelial cells. The number of goblet cells decreases as a result of these attacks. Therefore, ocular surface changes may be seen, even in BD patients that are in remission.

Gunduz et al. compared Schirmer test and BUT test results between inactive BD patients and control group and they found that these tests were significantly lower in BD patients.[12] In the same study, dry eye findings were also identified in BD patients that never had ocular pathology in their medical history.

In our study, in BD patients without clinically detectable ocular pathology, BUT test results in BD patients were significantly lower than the control group. So like Gunduz et al., we also think that conjunctival involvement in BD, could develop independently from ocular involvement.[12] We believe that ocular tear film stability may be disturbed because of the changes in the conjunctival surface epithelium cells and reduction of goblet cells. However like other autoimmune diseases, genetic factors, endogenous stress, environmental factors such as infections and antigens may affect the ocular surface and lead to development of dry eye. So attention must be paid to tearfilm instability in inactive BD patients when surgical intervention such as photorefractive keratectomy and LASIK or LASEK surgery is planned.

Gunduz et al. also reported that test results of patients that receiving and not receiving immunosuppressive therapy were found to be statistically similar.[12] Consistently in our study, Schirmer test and BUT test results of BD patients subgroups that receiving and not receiving immunosuppressive therapy were found to be similar.

Among our patients, some of them had no history of ocular pathology and some of them were in remission for at least 1 year. We think that patients with history of ocular involvement and without eye involvement should be followed by specific time intervals and evaluated for changes of tear film functions. In our study we did not evaluate the degree of dry eye semptoms. We concluded that the degree of dry eye semptoms should also be evaluated with ocular surface diesease index.

Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

Idea/Concept: *Ayşe Aslıhan Karcı, Nurşad Çifci Aslan, Tuba Güler, Fulya Dörtbaş;* ***Design:*** *Ayşe Aslıhan Karcı, Nurşad Çifci Aslan;* ***Control/Supervision:*** *Ayşe Aslıhan Karcı, Nurşad Çifci Aslan, Tuba Güler, Fulya Dörtbaş;* ***Data collection and/or Processing:*** *Ayşe Aslıhan Karcı, Nurşad Çifci Aslan, Fulya Dörtbaş, Tuba Güler;* ***Analysis and/or Interpretation:*** *Ayşe Aslıhan Karcı, Nurşad Çifci Aslan;* ***Literature Review:*** *Ayşe Aslıhan Karcı, Nurşad Çifci Aslan;* ***Writing the Article:*** *Ayşe Aslıhan Karcı, Nurşad Çifci Aslan;* ***Critical Review:*** *Ayşe Aslıhan Karcı, Nurşad Çifci Aslan;* ***References and Fundings:*** *None;* ***Materials:*** *None;* ***Other:*** *Ayşe Aslıhan Karcı, Nurşad Çifci Aslan.*

REFERENCES

1. Yurdakul S, Yazici H. Behcet's syndrome. Best Pract Res Clin Rheumatol 2008;22(5):793-809.
2. Kitaichi N, Miyazaki A, Iwata D, Ohno S, Stanford MR, Chams H. Ocular features of Behcet's disease: an international collaborative study. Br J Ophthalmol 2007;91(12):1579-82.
3. Rohatgi J, Singal A. Ocular manifestations of Behcet's disease in Indian patients. Indian J Ophthalmol 2003;51(4):309-13.
4. Wong RC, Ellis CN, Diaz LA. Behcet's disease. Int J Dermatol 1984;23(1):25-32.
5. George RK, Chan CC, Whitcup SM, Nussenblatt RB. Ocular immunopathology of Behçet's disease. Surv Ophthalmol 1997;42(2):157-62.
6. Zeng J, Chen B. Severe primary ocular surface involvement in Behcet disease. Optom Vis Sci 2014;91(12):e301-4.
7. Bonfioli AA, Orefice F. Behçet's disease. Semin Ophthalmol 2005;20(3):199-206.
8. Evereklioglu C. Current concepts in the etiology and treatment of Behçet disease. Surv Ophthalmol 2005;50(4):297-350.
9. Merle H, Donnio A, Richer R, Dubreuil F, Arfi S. Isolated conjunctival ulcerations as the first sign of Behcet's disease. Eur J Ophthalmol 2006;16(5):751-2.
10. Cankaya C, Kalayci BN. Corneal Biomechanical Characteristics in Patıents with Behçet Disease. Semin Ophthalmol 2016;31(5):439-45.
11. Ozdamar Y, Berker N, Ertugrul G, Gurlevik U, Karakaya J, Ozkan SS. Is there a change of corneal thickness in uveitis with Behçet disease? Cornea 2010;29(11):1265-7.
12. Gunduz A, Cumurcu T, Demirel EE, Akpolat N, Karıncaoglu Y. The ocular surface in the Behçet's disease patient. Can J Ophthalmol 2012;47(5):429-34.
13. The International Study Group for Behçet's Disesae. Evaluation of diagnostic ('classification') criteria in Behçet's disease--towards internationally agreed criteria. Br J Rheumatol 1992;31(5):299-308.
14. Kanski JJ. Dry eye disorders. Kanski Clinical Ophthalmology. Chapter 7. 6thed. Philadelphia: Elsevier Health; 2007. p.209-11.
15. Doughty MJ, Zaman ML. Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. Surv Ophthalmol 2000;44(5):367-408.

16. Evereklioglu C, Er H, Türköz Y, Cekmen M. Serum levels of TNF-alpha, sIL-2R, IL-6 and IL-8 are increased and associated with elevated lipid peroxidation in patients with Behçet's disease. Mediators Inflamm 2002; 11(2):87-93.
17. Onder M, Gürer MA. The multiple faces of Behçet's disease and its aetiological factors. J Eur Acad Dermatol Venereol 2000;15(2):126-36.
18. Ahn JK, Yu HG, Chung H, Park YG. Intraocular cytokine environment in active Behçet uveitis. Am J Ohpthalmol 2006;142(3):429-34.
19. Tugal-Tutkun I, Cingü K, Kir N, Yeniad B, Urgancioglu M, Gül A. Use of laser flare-cell photometry to quantify intraocular inflammation in patients with Behçet's uveitis. Graefes Arch Clin Exp Ophthalmol 2008;246(8):1169-77.
20. Macdonald JM, Geroski DH, Edelhauser HF. Effect of inflammation on the corneal endothelial pump and barier. Curr Eye Res 1987;6(9):1125-32.
21. Evereklioglu C, Er H. Increased corneal thickness in active Behçet's disease. Eur J Ophthalmol 2002;12(1):24-9.
22. Matsuo T, Itami M, Nakagawa H, Nagayama M. The incidence and pathology of conjunctival ulceration in Behçet's disease. Br J Ophthalmol 2002;86(2):140-3.
23. Flammer J, Pache M, Resink T. Vasospasm, its role in the pathogenesis of diseases with particular reference to eye. Prog Retin Eye Res 2001;20(3):319-49.
24. Sari RA, Kiziltunç A, Taysi S, Akdemir S, Gündoğdu M. Levels of soluble E-selectin in patients with active Behcet's disease. Clin Rheumatol 2005;24(1):55-9.
25. Uchio E, Matsumoto T, Tanaka SI, Ohno S. Soluble intercellular adhesion molecule-1 (ICAM-1), CD4, CD8 and interleukin-2 receptor in patients with Behçet's disease and Vogt-Koyanagi-Harada's disease. Clin Exp Rheumatol 1999;17(2):179-84.
26. Stern ME, Schaumburg CS, Pflugfelder SC. Dry eye as a mucosal autoimmune disease. Int Rev Immunol 2013;32(1):19-41.
27. Tseng SC, Hirst LW, Maumenee AE, Kenyon KR, Sun TT, Green WR. Possible mechanisms for the loss of goblet cells in mucin-deficient disorders. Ophthalmology 1984;91(6): 545-52.
28. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop. Ocul Surf 2007;5(2):75-92.