RESEARCH ARTICLE / *Araştırma Makalesi*

Comparison of Dry Eye Findings in Diabetes Mellitus Patients with and without Diabetic Foot

Diyabetik Ayak Olan ve Olmayan Diabetes Mellitus Hastalarında Kuru Göz Bulgularının Karşılaştırılması

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Abstract

Introduction	To compare dry eye findings in diabetes mellitus patients with and without diabetic foot
Materials and Methods	Diabetes mellitus patients with and without diabetic foot were included in this controlled cross-sectional study. Tear break-up time (BUT) and Schirmer test results of each participant were noted. Ocular Surface Disease Index (OSDI) questionnaire was administered to each participant.
Results	There were 48 diabetic patients in the study; half of them had diabetic foot (n=24). The patients with and without diabetic foot were similar in age and sex distribution. The median levels of BUT (4.0 [3.0 – 6.0] seconds for the right eye, 4.5 [3.0 – 6.5] seconds for the left eye in patients with diabetic foot) (4.0 [3.8 – 6.2] seconds for the right eye, 5.0 [3.8 – 5.2] second for the left eye in patients without diabetic foot) and Schirmer's test (7.0 [5.0 – 17.0] mm for the right eye, 11.0 [6.8 – 17.0] mm for the left eye in patients with diabetic foot) (11.0 [7.0 – 15.8] mm for the right eye, 14.5 [6.5 – 18.5] mm for the left eye in patients without diabetic foot) were similar in both groups of patients. The scores of OSDI were similar in patients with diabetic foot (22.7 [13.5 – 36.2]) and without diabetic foot (28.4 [13.6 – 41.5]) (p=0.749).
Conclusion	The Schirmer test, BUT test, and OSDI score were lower in patients with diabetic foot, but they were not statistically significant. In future studies, peripheral neuropathy examination and corneal confocal microscopy may be beneficial when evaluating dry eye parameters in this group of patients.
Keywords	Diabetes mellitus, diabetic foot, dry eye, Schirmer test, tear break-up time test, OSDI

Öz

Amaç	*Diyabetik ayağı olan ve olmayan Diabetes Mellitus hastalarında kuru göz bulgularını karşılaştırmak.*
Yöntem ve Gereçler	*Bu kontrollü kesitsel çalışmaya diyabetik ayağı olan ve olmayan diabetes mellitus hastaları dahil edildi. Her katılımcının gözyaşı kırılma zamanı (BUT) ve Schirmer testi sonuçları not edildi. Her katılımcıya Oküler Yüzey Hastalık İndeksi (OSDI) anketi uygulandı.*
Bulgular	*Çalışmada 48 diyabet hastası vardı; yarısında diyabetik ayak vardı (n=24). Diyabetik ayağı olan ve olmayan hastaların yaş ve cinsiyet dağılımı benzerdi. Ortanca AMA seviyeleri (diyabetik ayaklı hastalarda sağ göz için 4,0 [3,0 – 6,0] saniye, sol göz için 4,5 [3,0 – 6,5] saniye) (sağ göz için 4,0 [3,8 – 6,2] saniye, 5,0 [3,8 – 5,2] saniye) ve Schirmer testi (diyabetik ayaklı hastalarda sağ göz için 7,0 [5,0 – 17,0] mm, sol göz için 11,0 [6,8 – 17,0] mm) (11,0) [7,0 – 15,8] mm, diyabetik ayak olmayan hastalarda sol göz için 14,5 [6,5 – 18,5] mm) her iki hasta grubunda benzerdi. OSDI skorları diyabetik ayaklı (22,7 [13,5 – 36,2]) ve diyabetik ayaksız (28,4 [13,6 – 41,5]) hastalarda benzerdi (p=0,749).*
Sonuç	*Schirmer testi, BUT testi ve OSDI skoru diyabetik ayaklı hastalarda daha düşüktü ancak istatistiksel olarak anlamlı değildi. Gelecekteki çalışmalarda bu hasta grubunda kuru göz parametrelerinin değerlendirilmesinde periferik nöropati incelemesi ve korneal konfokal mikroskopi yararlı olabilir*
Anahtar Kelimeler	*Diabetes mellitus, diyabetik ayak, kuru göz, Schirmer testi, gözyaşı kırılma zamanı testi, OSDI*

INTRODUCTION

Diabetic foot ulcers are a common complication of diabetes. This complication negatively affects patients' quality of life and relationships. The cost of treatment of diabetic foot ulcers is high. Peripheral neuropathy, a chronic complication of diabetes, is one of the most crucial factors causing diabetic foot ulcers.[1,2] Although both vascular and metabolic factors are involved in the pathogenesis of the etiology of peripheral neuropathy, the exact mechanism is still not known.[2]

The cornea is one of the most sensitive tissues in the body. In diabetic patients, corneal sensitivity decreases together with the loss of corneal nerve fiber.[3] Corneal nerve fiber abnormalities are associated with the severity of neuropathy.[4,5] The decrease in corneal sensitivity in diabetic patients increases with the severity of neuropathy.[3]

Dry eye is a multifactorial disease of the ocular surface characterized by disruption of tear homeostasis. Symptoms of dry eye disease are eye discomfort and visual disturbances. In the last published consensus, neurosensorial abnormalities were included in the etiology of dry eye. It has been demonstrated that dry eye and diabetes mellitus have frequent associations.[6] The prevalence of dry eye in diabetic patients was 54.3% in the hospital-based study and 27.7% in the community-based study.[7,8] Corneal scarrings, ulceration, and secondary bacterial infection may develop in severely diabetic dry eyes. These complications are irreversible and reduce vision.[9]

Due to this informations, it is valuable to examine the dry eye parameters in patients with diabetic foot. To our knowledge, dry eye parameters have not been investigated before in patients with diabetic foot. We aimed to compare dry eye findings in diabetes mellitus patients with and without diabetic foot.

MATERIAL and METHODS

This study is a controlled cross-sectional study. A total of 48 patients, including 24 diabetes mellitus patients with diabetic foot and 24 diabetes mellitus patients without diabetic foot, who applied to Hitit University Faculty of Medicine, Department of Ophthalmology, were included in the study. The patients in the study were selected among the patients referred to our clinic for diabetic retinopathy screening from our hospital's diabetic foot service and outpatient clinic. Patients in the control group were determined voluntarily by age and gender matching among the patients who came to our clinic for routine examination.

Patients with glaucoma and receiving glaucoma treatment, patients using contact lenses, patients with a cerebrovascular accident, patients with eye trauma, patients with corneal disease and/or conjunctival disease, blepharitis, cancer patients, and patients with neuropathy due to another disease were not included in this study. Patients who had undergone eye surgery in the last six months had undergone intraocular injection or laser photocoagulation, received dry eye treatment, and are still receiving this treatment were excluded from the study.

The individuals included in the study are between the ages of 45-and 80. The types and duration of diabetes and the final HbA1c level of each patient were recorded. The visual acuity of all individuals was determined. The intraocular pressures of the individuals included in the study were measured with the Canon full autotonometer TX-F. We performed anterior segment and dilated fundus examinations of all individuals.

The tear break-up time (BUT) and Schirmer test results of each participant were noted. An Ocular Surface Disease Index (OSDI; Allergan, Inc, Irvine, CA, USA) questionnaire was administered to each participant.

A paper fluorescein strip moistened with saline was applied to the lower lid fornix without topical anesthetic. Patients were asked to blink several times to distribute the fluorescein on the corneal surface to determine the fluo-

rescein the BUT of the patients. Afterward, the patient was asked to wait without clipping, and the corneal surface was observed in the blue cobalt filter of the slit lamp. The time from the last blink of the eyelid to the appearance of the first dry black spot on the corneal surface was counted in seconds. This process was repeated for each eye.

For the Schirmer test of the patients, without using topical anesthesia, a standard Schirmer paper strip was placed on the 1/3 lateral edge of the lower eyelid, and the wetting level was read in millimeters after 5 minutes. This process was repeated for each eye.

The OSDI questionnaire is a 12-item subjective questionnaire to score patients' dry eye symptoms. This questionnaire was administered to each patient.

Clinical Research Ethics Committee of Hitit University Faculty of Medicine approval was obtained. This study was carried out in accordance with the principles of the Declaration of Helsinki. Informed written consent was obtained from the participants prior to their admission into the study.

Statistical Analysis

For descriptive statistics, mean ± standard deviation was used to present continuous data with normal distribution. Median with minimum-maximum values was applied for continuous variables without normal distribution. Numbers and percentages were used for categorical variables. The Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests analyzed the normal distribution of the numerical variables.

The Independent Samples t-test compared two independent groups where numerical variables had a normal distribution. For the variables without normal distribution, the Mann-Whitney U test was applied in comparing two independent groups. The Pearson Chi-Square and Fisher's Exact tests were used to compare the differences between categorical variables in 2x2 tables. The Fisher Freeman Halton test was used in RxC tables.

In comparing more than two independent groups, the Kruskal Wallis test was used where numerical variables had no normal distribution.

For statistical analysis, "Jamovi project (2022), Jamovi (Version 2.2.5.0) [Computer Software] (Retrieved from https://www.jamovi.org) and JASP (Version 0.16) (Retrieved from https://jasp-stats.org) were used. In all statistical analyses, the significance level (p-value) was determined at 0.05.

RESULTS

There were 48 diabetic patients in the study; half of them had diabetic foot (n=24). The patients with and without diabetic foot were similar in age and sex distribution (Table 1). The patients with diabetic foot had a significantly longer duration of the disease and higher HbA1c levels than those without diabetic foot (p=0.006 and p=0.041).

Table 1. Demographic and clinical characteristics of the patients.

	Patients		p
	With diabetic foot (n=24)	**Without diabetic foot (n=24)**	
Age (year) †	60.8 ± 8.2	60.8 ± 8.1	0.986*
Sex ‡			
Male	15 (62.5)	15 (62.5)	0.999***
Female	9 (37.5)	9 (37.5)	
Duration of diabetes (year) †	16.0 ± 6.3	10.0 ± 7.8	**0.006***
HbA1c (%) §	8.6 [7.6 – 10.5]	7.3 [6.2 – 9.0]	**0.041****

†: Mean ± Standard deviation, ‡: n (%), §: median [min-max]
*. Independent Samples T-Test
**. Mann-Whitney U test
***. Pearson Chi-Square test

Ophthalmic assessments of the patients with and without diabetic foot are summarized in Table 2. The visual acuity of the right eye was significantly lower in diabetic foot patients (p=0.009). The visual acuity of the left eye, the levels of intraocular pressure, and the distribution of the ophthalmoscopic findings of the anterior chamber were similar in patients with and without diabetic foot (p>0.05). The proportion of proliferative retinopathy in patients with diabetic foot was higher than those without diabetic foot. The difference was insignificant. But we found a higher incidence of non-proliferative/simple retinopathy in diabetic foot patients (p<0.001). The median levels of the tear break-up time and Schirmer's test were similar in both groups of patients. The subgroupings based on the cut-off values of the tear break-up time and Schirmer's test revealed no significant differences for both eyes. The scores of OSDI were similar in patients with and without diabetic foot (p=0.749).

The comparison of the patients with normal ophthalmoscopic findings in the anterior chamber and the corneal punctate epitheliopathy revealed no significant differences in tear break-up time, Schirmer's test, the scores of OSDI (Table 3).

Table 2. Ophthalmic assessment of the patients with and without diabetic foot.

	Patients		p
	With diabetic foot (n=24)	Without diabetic foot (n=24)	
Visual acuity (logMAR)-right eye §	0.5 [0.4 – 0.7]	0.9 [0.5 – 1.0]	**0.009****
Visual acuity (logMAR)-left eye §	0.7 [0.2 – 0.8]	0.8 [0.5 – 0.9]	0.164**
Intraocular pressure-right eye (mmHg) †	16.6 ± 3.3	16.5 ± 3.6	0.934*
Intraocular pressure-left eye (mmHg) †	16.9 ± 3.6	17.4 ± 4.1	0.657*
Ophthalmoscopic findings of anterior chamber ‡			
Normal	21 (87.5)	19 (79.2)	0.701***
Corneal punctate epitheliopathy	3 (12.5)	5 (20.8)	
Ophthalmoscopic findings of posterior chamber/status of retinopathy ‡			
Normal	6 (25.0) a	20 (83.3) b	**<0.001*****
Proliferative	6 (25.0) a	2 (8.3) a	
Non-proliferative/simple	12 (50.0) a	2 (8.3) b	
Tear break-up time (sec)-right eye §	4.0 [3.0 – 6.0]	4.0 [3.8 – 6.2]	0.958**
<10 sec	21 (87.5)	23 (95.8)	0.609***
≥10 sec	3 (12.5)	1 (4.2)	
Tear break-up time (sec)-left eye §	4.5 [3.0 – 6.5]	5.0 [3.8 – 5.2]	0.908**
<10 sec	20 (83.3)	22 (91.7)	0.666***
≥10 sec	4 (16.7)	2 (8.3)	
Schirmer's test (mm)-right eye §	7.0 [5.0 – 17.0]	11.0 [7.0 – 15.8]	0.432**
<10 mm	14 (58.3)	11 (45.8)	0.563***
≥10 mm	10 (41.7)	13 (54.2)	
Schirmer's test (mm)-left eye §	11.0 [6.8 – 17.0]	14.5 [6.5 – 18.5]	0.627**
<10 mm	12 (50.0)	9 (37.5)	0.561***
≥10 mm	12 (50.0)	15 (62.5)	
OSDI §	22.7 [13.5 – 36.2]	28.4 [13.6 – 41.5]	0.749**

†: Mean ± Standard deviation, ‡: n (%), §: median [min-max]
OSDI: Ocular Surface Disease Index
*. Independent Samples T-Test
**. Mann-Whitney U test
***. Fisher's Exact or Fisher Freeman Halton test

The comparison of the patients according to retinopathy status revealed no significant differences in tear break-up time, Schirmer's test, the scores of OSDI (Table 4).

There was no significant correlation between the tear break-up time, Schirmer's test, OSDI and age, disease duration, and HbA1c levels in diabetic patients with and without diabetic foot.

Table 3. Association of tear break-up time, Schirmer's test, and OSDI scores with corneal punctate epitheliopathy. .

	Anterior chamber		p*
	Normal (n=40)	Corneal punctate epitheliopathy (n=8)	
Tear break-up time (sec)-right eye §	4.0 [3.0 – 7.0]	4.5 [4.0 – 5.2]	**0.966**
Tear break-up time (sec)-left eye §	4.5 [3.0 – 6.0]	5.0 [4.8 – 6.0]	0.474
Schirmer's test (mm)-right eye §	8.5 [5.0 – 15.5]	11.0 [5.8 – 17.2]	0.739
Schirmer's test (mm)-left eye §	14.5 [6.8 – 18.0]	9.0 [7.2 – 15.5]	0.551
OSDI §	22.7 [13.6 – 39.2]	38.5 [13.8 – 44.1]	0.399

§: median [min-max]
*. Mann-Whitney U test

Table 4. Association of tear break-up time, Schirmer's test, and OSDI scores with retinopathy status

	Retinopathy			p*
	Normal (n=26)	Proliferative (n=8)	Non-proliferative/ simple (n=14)	
Tear break-up time (sec)-right eye §	4.0 [3.0 – 5.8]	6.5 [5.2 – 7.2]	4.5 [4.0 – 5.8]	0.218
Tear break-up time (sec)-left eye §	4.5 [3.0 – 5.8]	4.5 [3.8 – 6.2]	5.0 [4.0 – 6.8]	0.693
Schirmer's test (mm)-right eye §	8.0 [5.2 – 17.2]	9.5 [4.8 – 12.8]	13.5 [6.2 – 17.0]	0.594
Schirmer's test (mm)-left eye §	10.0 [5.2 – 17.8]	17.0 [7.0 – 18.5]	15.0 [7.2 – 15.0]	0.752
OSDI §	21.2 [13.6 – 42.4]	22.4 [13.3 – 28.1]	25.8 [16.4 – 40.5]	0.759

§: median [min-max]
OSDI: Ocular Surface Disease Index
*. Kruskal Wallis H test

DISCUSSION

Our study compared dry eye parameters in Diabetes Mellitus patients with and without diabetic foot, whom we matched for age and sex. The Schirmer and BUT tests give us objective data; however, the OSDI questionnaire provides subjective and sensory data. Between these two groups, the Schirmer test, BUT test, and OSDI questionnaire were lower in patients with diabetic foot than in patients without diabetic foot, but they were not statistically significant.

Many studies have studied the relationship between diabetes mellitus and dry eye.[10,11] In a study, it was found that dry eye was more common in diabetic patients with neuropathy than in diabetic patients without neuropathy, and they argued that this was due to decreased corneal sensitivity. Again, in this study, it was emphasized that corneal hyposensitivity might reduce symptoms.[12] The inverse relationship between corneal innervation and peripheral neuropathy has been shown previously.[13] Ocular surface abnormalities are parallel to diabetic peripheral neuropathy.[14] Neurosensory anomalies have taken place in the final consensus on the etiology of dry eye.[6]

In the study of Doğru et al., it was shown that corneal sensitivity decreased in diabetic patients. However, they argued that this decrease was not associated with the duration of diabetes and retinopathy.[15] We also did not find any relationship between dry eye parameters and retinopathy level, duration of diabetes, and HbA1c level in our study. Nitoda et al. found a correlation between corneal subbasal nerve plexus changes and the stage of diabetic retinopathy.[16] In a study that found a correlation between non-invasive BUT and OSDI and HbA1c, it did not specify the presence of diabetic foot, and the mean BUT of the patients was higher than the mean value of the two groups in our study.[17]

Corneal confocal microscopy studies suggest that it can detect early neuropathy by demonstrating corneal nerve fiber loss and changes.[18,19] Corneal nerve fiber loss was correlated with peripheral neuropathy.[16] As neuropathy becomes more severe, corneal sensitivity decreases more.[20] We did not evaluate the presence and level of neuropathy in our study, but peripheral neuropathy is involved in the etiology of diabetic foot ulcers.[21] The dry eye parameters in our study were not significantly different in these two groups because the neuropathy of our control group patients might be similar to our patient group with diabetic foot. This supports the reduction of corneal nerve cells before the development of diabetic foot as emphasized by Dehghani et al..[22] In this case, corneal confocal microscopy may be valuable.

Decreased corneal sensitivity may cause evaporation on the ocular surface with a decrease in blink rate in patients. This situation has been demonstrated in diabetic patients.[23] It is known that reflex tear secretion decreases as corneal sensitivity decreases.[24] BUT results in our study support the evaporation mechanism in dry eye cases based on neuropathy.

Herlyn et al. found significant corneal subbasal nerve changes between diabetic patients with and without a diabetic foot in their study with corneal confocal microscopy.[21] According to the results of our study, the reflection of this situation on dry eye symptoms may occur late. In the study of Zhivov et al. in diabetic foot patients, corneal confocal microscopy parameters decrease as the Wagner score increases. In this study, peripheral neuropathy and corneal neuropathy were also correlated, and corneal tenderness was inversely correlated with the Wagner score.[25] In other words, the more severe the diabetic foot, the more corneal nerve damage increases, and corneal sensitivity decreases. We did not classify our diabetic foot patients in stages. Although there was no statistical difference between the two groups in our study, the lower OSDI score in patients with diabetic foot may be attributed to loss of corneal sensitivity and neuropathy.

Limitations of our study are the absence of peripheral or corneal neuropathy and corneal sensitization data. These parameters can be evaluated together with dry eye findings in diabetic foot patients in the future. The strengths of our study are age and gender matching between groups. This is the first study to evaluate dry eye parameters in diabetic patients with and without diabetic foot.

CONCLUSIONS

We did not find any statistical difference in dry eye parameters in the patient group with and without diabetic foot. In future studies, peripheral neuropathy examination and corneal confocal microscopy may be beneficial when evaluating dry eye parameters in this group of patients.

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Disclosure of interest

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Authorship Contributions

Concept: HBÇ. Design: GGÖ, HBÇ. Data Collection or Processing: GGÖ, MK. Analysis or Interpretation: GGÖ, OD. Literature Search: GGÖ. Writing: GGÖ.

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