ORIGINAL RESEARCH ORİJİNAL ARAŞTIRMA

DOI: 10.5336/ophthal.2024-103456

The Effects of Type 2 Diabetes Mellitus on Meibomian Gland Morphology and Tear Film Parameters: Cross-Sectional Study

Tip 2 Diabetes Mellitusun Meibomian Bez Morfolojisi ve Gözyaşı Filmi Parametreleri Üzerine Etkileri: Kesitsel Araştırma

Selma ÖZBEK UZMAN[a], Züleyha YALNIZ AKKAYA[a], Tülay OMMA[b], Alper ŞANLI[c], Ayşe TÜFEKÇİ BALIKÇI[a], Sevde Nur FIRAT[b], Ayşe BURCU[a]

[a]University of Health Sciences Ankara Training and Research Hospital, Department of Ophthalmology, Ankara, Türkiye
[b]University of Health Sciences Ankara Training and Research Hospital, Division of Endocrinology and Metabolism, Ankara, Türkiye
[c]Samsun Vezirköprü State Hospital, Clinic of Ophthalmology, Samsun, Türkiye

This study was presented as a poster at the Turkish Ophthalmological Association 2020, Virtual National Congress and Live Surgery Compound Meeting, December 9-13, 2020, Online, Türkiye.

ABSTRACT Objective: To evaluate the meibomian gland (MG) morphology and tear film parameters of patients with Type 2 diabetes mellitus (DM) and to compare them with healthy individuals. **Material and Methods:** Fifty-four eyes of 27 patients (DM group) with Type 2 DM and 50 eyes of 25 healthy individuals (control group) in terms of Ocular Surface Disease Index (OSDI) score, Schirmer's test, van Bijsterveld score (vBs), non-invasive break-up time (NiBUT) and MG morphologies (by non-contact, non-invasive infrared meibography) were evaluated and analyzed. **Results:** DM and control groups were similar in terms of mean age (p=0.51) and gender (p=0.78). In DM and control groups, respectively; OSDI; 15.3±3.7-11.9±2.7 (p=0.03), Schirmer; 10.3±3.4-12.5±3.2 mm (p<0.001), first NiBUT; 7.47±4.38-10.41±4.89 sec (p=0.002), mean NiBUT; 9.6±3.7 vs. 12.3±4.0 sec (p<0.001), meibo-degree; 1.59±1.20-0.82±1.04 units (p<0.001), meibo score 31.3±22.2%-18.5±16.9% (p<0.001) and vBs; were 3.8±2.4 and 2.2±1.7 (p<0.001). In the DM group, a significant relationship was found between the presence of retinopathy and Schirmer (p<0.001), first NiBUT (p<0.001), average NiBUT (p<0.001), meibo score (p<0.001) and vBs (p<0.001). **Conclusion:** Type 2 DM, negatively affects MG morphology and tear film layer. Evaluation of DM patients in terms of MG dysfunction and dry eye disease as well as retinopathy during routine examinations can ensure early diagnosis of MG dysfunction and dry eye disease, initiation of appropriate treatment and protection of the ocular surface.

Keywords: Meibomian gland dysfunction; meibography; meiboscore; Type 2 diabetes mellitus; dry eye disease

ÖZET Amaç: Tip 2 diabetes mellitus (DM) hastalarının meibomian bez (MG) morfolojisi ve gözyaşı filmi parametrelerinin değerlendirilmesi ve sağlıklı bireylerle karşılaştırılması amaçlandı. **Gereç ve Yöntemler:** Tip 2 DM'li 27 hastanın 54 gözü (DM grubu) ve 25 sağlıklı bireyin 50 gözü (kontrol grubu) çalışmaya alındı. Tüm olguların, Oküler Yüzey Hastalık İndeksi [Ocular Surface Disease Index (OSDI)] skoru, Schirmer testi, van Bijsterveld skoru (vBs), non-invaziv gözyaşı kırılma zamanı [non-invasive break-up time (NiBUT)] ve MG morfolojileri (temassız, non-invaziv kızılötesi meibografi cihazı ile) değerlendirildi ve analiz edildi. **Bulgular:** DM ve kontrol grubu, yaş ortalaması (p=0,51) ve cinsiyet (p=0,78) açısından benzerdi. DM ve kontrol gruplarında sırasıyla; OSDI; 15,3±3,7-11,9±2,7 (p=0,03), Schirmer; 10,3±3,4-12,5±3,2 mm (p<0,001), ilk NiBUT; 7,47±4,38-10,41±4,89 sn (p=0,002), ortalama NiBUT; 9,6±3,7-12,3±4,0 sn (p<0,001), meibo-derece; 1,59±1,20-0,82±1,04 birim (p<0,001), meibo skoru %31,3±22,2-%18,5±16,9 (p<0,001) ve vBs; 3,8±2,4 ve 2,2±1,7 (p<0,001) idi. DM grubunda retinopati varlığı ile Schirmer (p<0,001), ilk NiBUT (p<0,001), ortalama NiBUT (p<0,001), meibo skoru (p<0,001) ve vBs (p<0,001) arasında anlamlı ilişki saptandı. **Sonuç:** Tip 2 DM, MG morfolojisini ve gözyaşı filmi tabakasını olumsuz etkiler. DM hastalarının rutin muayenelerinde retinopati yanı sıra MG disfonksiyonu ve kuru göz hastalığı yönünden de değerlendirmelerinin yapılması, MG disfonksiyonu ve kuru göz hastalığının erken tanısı ile uygun tedavinin başlanmasını ve oküler yüzeyin korunmasını sağlayabilir.

Anahtar Kelimeler: Meibomian bez disfonksiyonu; meibografi; meiboskor; Tip 2 diabetes mellitus; kuru göz hastalığı

TO CITE THIS ARTICLE:
Özbek Uzman S, Yalnız Akkaya Z, Omma T, Şanlı A, Tüfekçi Balıkçı A, Fırat SN, et al. The effects of Type 2 diabetes mellitus on meibomian gland morphology and tear film parameters: Cross-sectional study. Turkiye Klinikleri J Ophthalmol. 2024;33(3):177-83.

Correspondence: Selma ÖZBEK UZMAN
University of Health Sciences Ankara Training and Research Hospital, Department of Ophthalmology, Ankara, Türkiye
E-mail: ozbekkselma@yahoo.com

Peer review under responsibility of Turkiye Klinikleri Journal of Ophthalmology.

Received: 16 Apr 2024 ***Received in revised form:*** 21 Jun 2024 ***Accepted:*** 22 Jun 2024 ***Available online:*** 09 Jul 2024

Diabetes mellitus (DM) is a chronic metabolic disorder caused by a disturbance in insulin secretion and/or its effects and is characterized by hyperglycemia. It can cause various ocular complications such as retinopathy, cataract, keratopathy and dry eye disease (DED).[1,2]

It has been reported that Type 2 DM may be a risk factor for DED and that the symptoms are worse than in non-diabetics.[3,4] The DED prevalence was documented as 54.3% in Type 2 DM, 7.7% in Type 1 diabetic children, and 0.96% in healthy children.[5]

There is no standard clinical evaluation method for meibomian gland dysfunction (MGD) and the epidemiological data are therefore limited with significant variance in the reported prevalence in the literature. The prevalence has been reported as 3.5-9.9% in Caucasians and 46.2-61.7% in Asians.[6-9]

The diagnosis of MGD and DED is made by querying the symptoms, evaluating the lid morphology, slit lamp examination of the ocular surface, determining the tear film stability that reflects lipid layer functions, measuring the tear amount that reflects aqueous layer functions, and staining the ocular surface that reflects the mucin layer functions.[10-12] The introduction of imaging methods and devices such as infrared meibography, the Keratograph 5M (Oculus, Wetzlar, Germany), and anterior segment optic coherence tomography in recent years has enabled an increase in the accuracy of DED and MGD diagnoses and their standardization.[13-17]

The aim of this study was to evaluate the effect of Type 2 DM on the meibomian gland (MG) morphology and dry eye parameters, and to compare these parameters with those of age- and gender-matched healthy subjects.

MATERIAL AND METHODS

Approval was obtained from the Ethics Committee of Ankara Training and Research Hospital for the study (date: July 10, 2020; no: E-20, 287), and the study was conducted in accordance with the principles of the 2013 Helsinki Declaration. Informed consent forms were obtained from all patients before the examinations. The 54 eyes of 27 patients who had presented to the eye outpatient department and received a diagnosis of Type 2 DM at least 5 years ago (the DM group) and the 50 eyes of 25 age- and gender-matched healthy subjects (the control group) were retrospectively evaluated. Exclusion criteria were being under 50 years old, the presence of an active ocular infection or inflammation, a history of ocular surgery, the use of eye drops containing preservatives or contact lenses, a history of rheumatoid disease, the use of medication that would affect tear production (antihistamines, tricyclic antidepressants etc.), the presence of additional pathologies that could cause ocular surface irregularity (pterygium, symblepharon, entropium, lagophthalmos, corneal dystrophies, previous keratitis, corneal scars, corneal ectasias etc.), and nasolacrimal duct obstruction.

All the participants were evaluated by the same investigator (SOU). An anterior and posterior segment examination with the slit lamp was performed first, followed by the administration of the Ocular Surface Disorders Index (OSDI) score. Then, the meiboscore (%) and meibograde (units), the non-invasive tear film first break-up time (NiBUT-first) (seconds) and the non-invasive tear film mean break-up time (NiBUT-mean) (seconds) were measured with a non-contact, non-invasive infrared meibography device [the Phoenix-meibography imaging module combined with the Sirius corneal topography device (CSO, Florence, Italy)]. Finally, Schirmer's test and conjunctival staining with the van Bijsterveld score (vBs) were evaluated.[18]

The OSDI was used to score the subject's symptoms in the last 2 weeks as related to eye dryness, the duration of such symptoms, their severity, and the effect on daily activities. The score was between 0 and 100 and a score above 13 was accepted to indicate dry eye.

The meiboscore value was determined as a percentage (%) of loss by determining the ratio between the MG areas of the upper eyelid and the total area as obtained by a non-contact, non-invasive infrared meibography device. A high meiboscore indicates more significant loss of the MGs. The meibograde was determined by using the previously determined meiboscore value and distributing it into various percentage slices with the automatic grading system

as specified in the Phoenix software (Grade 0: 0-10%, Grade 1: 10-25%, Grade 2: 25-50%, Grade 3: 50-75% Grade 4: ≥75%).

The conjunctival staining score was evaluated with the van Bijsterveld method.[18] The ocular surface was stained with fluorescein and then divided into three fields as the nasal conjunctiva, the cornea and the temporal conjunctiva, and each field was graded between 0 and 3 (0: no staining; 1: poor staining; 2: moderate staining; 3: diffuse staining).

The subject waited 20 minutes and a Schirmer test was performed without topical anesthesia to measure basal and reflex tear secretion. Wetting length was measured and recorded.

The fasting blood sugar (FBG, mg/dL) and hemoglobin A1c (HbA1c) (%) values in the last month were recorded from the charts of the diabetic patients. Patients without any diabetic retinopathy changes on posterior segment examination were placed into the "retinopathy absent" group. According to the Early Treatment Diabetic Retinopathy Study classification, those with findings of non-proliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR) were included in the "retinopathy present" group. Patients with glycemic control with diet were placed in the "diet-regulated" group and those regulated on oral anti-diabetics (OADs) and/or insulin in the "drug-regulated" group.

STATISTICAL ANALYSIS

The statistical analyses were performed with the SPSS for Windows 21.0 software (SPSS Inc. Chicago, USA). Normal distribution of the numerical data was checked with the Kolmogorov-Smirnov test. Descriptive statistics were expressed as mean±standard deviation when the numerical data showed a normal distribution and as median (minimum-maximum) when they did not. Student's t-test was used to determine the significance of the difference between two means or medians. Correlation between the subgroups was checked with Pearson's correlation analysis and the difference between the subgroups with one-way analysis of variance and Bonferroni correction. A p value lower than 0.05 was considered to indicate statistical significance.

RESULTS

We included the 54 eyes of 27 Type 2 DM patients (the DM group) and the 50 eyes of 25 healthy subjects (the control group) in this study. The mean age was 63.5±9.0 (50-86) years in the DM group with a female percentage of 51.9% while these values were 61.9±8.1 (50-78) years and 48% in the control group (p=0.51 and p=0.78).

In the DM group, the mean duration of DM was 13.7±7.2 (5-26) years, the mean FBG 167±58.1 (95-319) mg/dL, and the mean HbA1c value 8.3±1.7 (5.7-11.5) %. The treatment was diet only in 6 patients (11.1%), oral antidiabetics in 28 patients (51.9%), and insulin in 20 patients (37%). Posterior segment examination showed absence of retinopathy in 24 eyes (44.4%), NPDR in 20 eyes (37%), and PDR in 10 eyes (18.5%).

The OSDI scores, conjunctival staining scores, meibograde (units) and meiboscore (%) values were statistically significantly higher in the DM group while the mean NiBUT-first (sec), NiBUT-mean (sec) and Schirmer values were statistically significantly lower (Table 1).

Table 2 presents the OSDI, Schirmer, NiBUT, meiboscore and vBs values of the DM group according to the HbA1c levels, presence of retinopathy, medication use, and duration of DM. A statistically significant association was found between retinopathy development and the OSDI, Schirmer, NiBUT,

TABLE 1: OSDI, Schirmer, NiBUT-first, NiBUT-mean, meibograde, meiboscore and vBs levels of the DM and control groups.

	DM group (n=54)	Control group (n=50)	p value
OSDI	15.3±3.7	11.9±2.7	<0.001*
Schirmer (mm)	10.3±3.4	12.5±3.2	<0.001*
NiBUT-first (sec)	7.4±4.3	10.4±4.8	0.002*
NiBUT-mean (sec)	9.6±3.7	12.3±4.0	<0.001*
Meibograde	1.5±1.2	0.8±1.0	<0.001*
Meiboscore (%)	31.3±22.2	18.5±16.9	<0.001*
vBs	3.8±2.4	2.2±1.7	<0.001*

Student's t-test, *p<0.05; OSDI: Ocular Surface Disease Index; NiBUT-first: Non-invasive tear film first break up time; NiBUT-mean: Non-invasive tear film mean break up time; vBs: van Bijsterveld score; DM: Diabetes mellitus.

TABLE 2: OSDI, Schirmer, NiBUT-first, NiBUT-mean, meiboscore and vBs levels of the DM group according to the HbA1c level, presence of retinopathy, drug use, and diabetes duration.

	Subgroup (n)	OSDI (score)	Schirmer (mm)	NiBUT-first (sec)	NiBUT-mean (sec)	Meiboscore (%)	vBs
HbA1c (%)	<6.5 (10)	15.6±4.1	9.9±3.6	8.6±4.9	10.7±3.9	20.4±14.0	3.9±2.6
	≥6.5 (44)	15.2±3.6	10.4±3.4	7.2±4.2	9.4±3.7	33.8±23.1	3.8±2.4
	p value	0.805	0.639	0.371	0.297	0.085	0.987
Retinopathy	absent (24)	14.2±3.3	13.0±1.8	10.5±4.4	12.1±3.8	19.9±17.6	2.3±1.6
	present (30)	16.2±3.8	8.2±2.9	5.0±2.3	7.6±2.2	40.5±21.5	5.1±2.3
	p value	0.055	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
Treatment	diet (6)	14.0±3.7	12.0±2.5	7.0±2.5	9.3±1.8	24.8±14.8	4.1±1.4
	drugs (48)	15.5±3.7	10.1±3.5	7.5±4.5	9.7±3.9	32.2±23.0	3.8±2.5
	p value	0.358	0.225	0.806	0.817	0.451	0.770
Duration of DM	≤10 year (26)	15.3±4.0	11.5±3.4	8.9±4.3	10.9±3.7	32.2±24.4	3.3±2.5
	>10 year (28)	15.2±3.5	9.2±3.1	6.1±4.0	8.4±3.4	30.6±20.5	4.3±2.2
	p value	0.923	0.012*	0.016*	0.016*	0.115	0.145

One way analysis of variance, *p<0.05; OSDI: Ocular Surface Disease Index; NiBUT-first: Non-invasive tear film first break up time (second); NiBUT-mean: Non-invasive tear film mean break up time; vBs: van Bijsterveld score; DM: Diabetes mellitus; HbA1c: Hemoglobin A1c.

meiboscore and vBs levels, and also between the DM duration and the Schirmer and NiBUT levels in the DM group (Table 2).

Evaluation according to the presence of retinopathy revealed a difference between the OSDI (p<0.001), Schirmer (p<0.001), NiBUT-first (p<0.001), NiBUT-mean (p<0.001), meiboscore (p<0.001) and vBs (p<0.001) levels between the control group and the patients with and without retinopathy. The reason for the difference between the three groups for OSD was the difference between the control group and the "retinopathy present" (p<0.001) and "retinopathy absent" (p=0.014) groups whereas the reason for the difference regarding the Schirmer, NiBUT-first, NiBUT-mean, meiboscore and vBs was the difference between the "retinopathy present" patients and the other groups [for the control group (p<0.001) and for the retinopathy absent patients (p<0.001)]. For all parameters, there was no difference between the control group and patients with no retinopathy, and also between patients with NPDR and patients with PDR.

When evaluated according to medication use, the OSDI (p<0.001), Schirmer (p=0.006), NiBUT-first (p=0.002), NiBUT-mean (p=0.002), meiboscore (p<0.001) and vBs levels (p<0.001) showed a statistically significant difference between the control group, diet-regulated Type 2 DM patients and medication-regulated Type 2 DM patients. The reason for this result was the difference found between the control group and the medication-regulated Type 2 DM patients (p<0.001 for OSDI, p=0.002 for the Schirmer value, p=0.009 for NiBUT-first, p=0.003 for NiBUT-mean, p=0.003 for meiboscore, and p<0.001 for the vBs). There was no significant difference between the control group and the diet-regulated Type 2 DM patients and also between the OAD-regulated and insulin-regulated Type 2 DM patients as concerns all the parameters.

DISCUSSION

We found significantly worse MG and tear film parameters in the DM group compared to the control group in addition to more severe MGD and DED in patients with retinopathy in this study.

"The International Meibomian Gland Dysfunction Workgroup Epidemiology and Risk Factor Determination Committee" report states that advanced age is one of the most important risk factors for MGD.[19] Advanced age results in an almost 50% decrease in the number of MGs due to atrophy.[11,19] The prevalence of MGD in subjects over 50 years of age has been reported to be more than 3 times that in younger subjects.[6-9,20] Den et al. have reported that

significant MG and lid margin anomalies rarely develop in patients aged 50 years or less while this incidence shows a significant increase in older subjects.[21] In addition to advanced age, female gender has also been shown to be an important risk factor for MGD development as androgens stimulate MG secretion and estrogens inhibit it.[22] We did not include patients aged 50 years or less in our study to eliminate such age- and gender-based changes mentioned in the literature, and our subjects in the DM and control groups had a similar mean age and gender distribution.

The 2017 DEWS report has indicated that diabetes could be a risk factor for dry eye.[3] Dogru et al. have found lower BUT and Schirmer scores in patients with poor blood sugar regulation, possibly due to the glycemic fluctuations and neuropathic damage affecting lacrimal gland innervation and secretory functions.[23] However, there are only a few studies on the MG changes and ocular surface problems of Type 2 DM patients. These studies have reported that MGD is more severe in Type 2 DM patients than normal subjects and that the diabetes duration is associated with the MG changes and dry eye symptoms.[15,16,23-25] Similar to the other reports, we found that the OSDI symptom score, conjunctival staining score, meiboscore, and meibograde values were statistically significantly higher in the Type 2 DM group than the control group while the Schirmer test, NiBUT-first, and NiBUT-mean levels were statistically significantly lower in the Type 2 DM group compared to the control group.

Inflammation of the MG ducti with inflammatory cell infiltration and dilatation and atrophy of the acinar units has been shown in DM patients with the laser scanning confocal microscope.[11,26] Ductal obstruction results in decreased ocular surface lipid, collection of secretions within the gland, bacterial proliferation, increased lysosomal enzymes, and ocular surface inflammation.[11,27] The inflammatory response cause by DM can also induce MGD. The changes in the lipid content of the MGs can result in disturbed tear film stability.[24,25,27] The innervation abnormalities that develop in diabetic patients due to the common neuropathic damage can result in decreased tear production from the lacrimal gland and more severe evaporative dry eye symptoms.[15,16,23-25] The morphological and functional changes seen in the corneal nerves lead to decreased corneal sensitivity, decreasing the blinking frequency and disturbing the distribution of the tear fluid lipid layer.[11] The peripheral neuropathy that develops in diabetes also leads to weakened periorbital muscles and difficulty in secreting lipid from the MGs, resulting in MGD.[15,16,23] These changes reported in the literature could explain the underlying cause of the increased frequency of ocular discomfort symptoms and tear film abnormalities detected in the diabetic patient group in the current study.

The advances in imaging methods have enabled the use of non-invasive objective methods to detect MG changes and ensured a standard clinical evaluation.[11-17,26] Yu et al. have reported more severe dry eye symptoms and more prominent morphological, functional, and cytological changes in the MG in their study on Type-2 DM patients conducted with the Keratograph 5M system and laser scanning confocal microscopy.[15] The non-contact, non-invasive, infrared meibography device used in the current study together with the quantitatively determined meiboscore and NiBUT levels made it possible to objectively evaluate MGD.

The HbA1c level in DM has been reported to directly indicate the glycemic control within the last three months. It is not related to the diabetes duration while retinopathy is related to both the HbA1c level and the diabetes duration.[28] Seifart and Strempel have reported that the DED prevalence increased in Type 1 and Type 2 diabetics, and high Hb1Ac values and the presence of proliferative retinopathy were risk factors for increased DED severity.[29] Comparison of the DM group patients without retinopathy and those with non-proliferative or proliferative retinopathy in our study showed a significant difference regarding tear fluid and MG parameters depending on the presence of retinopathy. This difference could be due to the microangiopathic and neuropathic damage that also plays an important role in the pathogenesis of diabetic retinopathy. This finding indicates that evaluation of the ocular surface, MGs and tear film parameters in addition to the posterior segment is important during routine eye examination of DM pa-

tients. There was a statistically significant relationship between DM duration and the Schirmer test results and the NiBUT-first, NiBUT-mean and meiboscore values while the relationship with OSDI was not significant. The Schirmer test, NiBUT-first, NiBUT-mean and meiboscore values provide objective results but the OSDI results are subjective. The autonomic dysfunction and decreased corneal sensitivity developing in diabetic patients may result in an asymptomatic course of DED and MGD and therefore the inability to detect an increase in the OSDI score. A difference we found in this study between the control group and the diet-regulated Type-2 diabetics and the OAD- or insulin-regulated Type-2 diabetics could be due to the improved MGD parameters provided by the medication used. However, we did not find a significant correlation between the FBG and HbA1c levels and the DED and MGD parameters in the DM group. The reason could be the neutralization of the possible negative effects of the high FBG and HbA1c levels on the MG secretions by the OAD and insulin treatment used by 88.8% of the study group patients.

Our study has some limitations. First of all, our sample size was relatively small due to the rigid exclusion criteria. Secondly, variables such as glycemic control, the medication used, and the severity of diabetic retinopathy differed among the DM group subjects. Future studies could be planned with a larger number of diabetic patients grouped according to glycemic control, disease duration, drug use, and retinopathy severity.

The study has demonstrated that DED and MGD symptoms and findings increase in Type 2 DM patients compared to healthy subjects. The global diabetes prevalence is approximately 9.3% and is increasing.[30] This increases the possibility of a gradually larger number of patients also suffering diabetes-related eye problems such as DED and MGD and requiring treatment.

CONCLUSION

Type 2 DM results in a disturbed tear film layer and evaporative dry eye symptoms through its effect on the MG morphology function in correlation with disease duration and presence of retinopathy. The current advances in meibography technology have enabled detection of MG loss and tear film layer disturbances in a non-contact and objective manner.

Routine evaluation of the tear film layer and MGs, especially in patients with long DM duration and retinopathy, could be useful for early detection of DED and MGD, initiation of treatment, and ocular surface protection.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Selma Özbek Uzman;* ***Design:*** *Selma Özbek Uzman;* ***Control/Supervision:*** *Ayşe Burcu;* ***Data Collection and/or Processing:*** *Selma Özbek Uzman, Alper Şanlı, Tülay Omma, Sevde Nur Fırat;* ***Analysis and/or Interpretation:*** *Selma Özbek Uzman, Tülay Omma, Züleyha Yalnız Akkaya;* ***Literature Review:*** *Selma Özbek Uzman, Ayşe Tüfekçi Balıkçı;* ***Writing the Article:*** *Selma Özbek Uzman;* ***Critical Review:*** *Selma Özbek Uzman, Züleyha Yalnız Akkaya, Ayşe Burcu;* ***References and Fundings:*** *Selma Özbek Uzman;* ***Materials:*** *Selma Özbek Uzman, Alper Şanlı, Sevde Nur Fırat, Ayşe Tüfekçi Balıkçı.*

REFERENCES

1. Shih KC, Lam KS, Tong L. A systematic review on the impact of diabetes mellitus on the ocular surface. Nutr Diabetes. 2017;7(3):e251. [Crossref] [PubMed] [PMC]
2. Vieira-Potter VJ, Karamichos D, Lee DJ. Ocular Complications of Diabetes and Therapeutic Approaches. Biomed Res Int. 2016;2016:3801570. [Crossref] [PubMed] [PMC]
3. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, et al. TFOS DEWS II Definition and Classification Report. Ocul Surf. 2017;15(3):276-83. [Crossref] [PubMed]
4. Yoo TK, Oh E. Diabetes mellitus is associated with dry eye syndrome: a meta-analysis. Int Ophthalmol. 2019;39(11):2611-20. [Crossref] [PubMed]
5. Wang S, Jia Y, Li T, Wang A, Gao L, Yang C, et al. Dry eye disease is more prevalent in children with diabetes than in those without diabetes. Curr Eye Res. 2019;44(12):1299-305. [Crossref] [PubMed]
6. Schein OD, Muñoz B, Tielsch JM, Bandeen-Roche K, West S. Prevalence of dry eye among the elderly. Am J Ophthalmol. 1997;124(6):723-8. [Crossref] [PubMed]
7. McCarty CA, Bansal AK, Livingston PM, Stanislavsky YL, Taylor HR. The epidemiology of dry eye in Melbourne, Australia. Ophthalmology. 1998;105(6):1114-9. [Crossref] [PubMed]
8. Lekhanont K, Rojanaporn D, Chuck RS, Vongthongsri A. Prevalence of dry eye in Bangkok, Thailand. Cornea. 2006;25(10):1162-7. [Crossref] [PubMed]
9. Lin PY, Tsai SY, Cheng CY, Liu JH, Chou P, Hsu WM. Prevalence of dry eye among an elderly Chinese population in Taiwan: the Shihpai Eye Study. Ophthalmology. 2003;110(6):1096-101. [Crossref] [PubMed]
10. Wise RJ, Sobel RK, Allen RC. Meibography: A review of techniques and technologies. Saudi J Ophthalmol. 2012;26(4):349-56. [Crossref] [PubMed] [PMC]
11. Bolaç Unculu R, Yıldız HE, Serin D, Turan Vural E, Buttanrı İB. Cilt Yoluyla Levator Rezeksiyonu Yapılan Hastalarda Kuru Göz Parametrelerinin ve Meibomian Bez Morfolojisinin Değerlendirilmesi [Evaluation of Dry Eye Parameters and Meibomian Gland Morphology in Patients Who Underwent Transcutaneous Levator Resection]. Turkiye Klinikleri J Ophthalmol. 2018;27(4):255-9. [Crossref]
12. Akova YA, Asena L, Yonca A. Meibomian bez disfonksiyonu [Meibomian gland dysfunction: review]. Turkiye Klinikleri J Ophthalmol. 2014;23(3):172-83. [Link]
13. Abdelfattah NS, Dastiridou A, Sadda SR, Lee OL. Noninvasive Imaging of Tear Film Dynamics in Eyes With Ocular Surface Disease. Cornea. 2015;34 Suppl 10:S48-52. [Crossref] [PubMed]
14. Arita R, Itoh K, Inoue K, Amano S. Noncontact infrared meibography to document age-related changes of the meibomian glands in a normal population. Ophthalmology. 2008;115(5):911-5. [Crossref] [PubMed]
15. Yu T, Shi WY, Song AP, Gao Y, Dang GF, Ding G. Changes of meibomian glands in patients with type 2 diabetes mellitus. Int J Ophthalmol. 2016;9(12):1740-4. [PubMed] [PMC]
16. Sandra Johanna GP, Antonio LA, Andrés GS. Correlation between type 2 diabetes, dry eye and Meibomian glands dysfunction. J Optom. 2019;12(4):256-62. [Crossref] [PubMed] [PMC]
17. Klamann MK, Maier AK, Gonnermann J, Klein JP, Pleyer U. Measurement of dynamic ocular surface temperature in healthy subjects using a new thermography device. Curr Eye Res. 2012;37(8):678-83. Retraction in: Curr Eye Res. 2015;40(12):1296. [Crossref] [PubMed]
18. Lemp MA. Report of the National Eye Institute/Industry workshop on Clinical Trials in Dry Eyes. CLAO J. 1995;21(4):221-32. [PubMed]
19. Schaumberg DA, Nichols JJ, Papas EB, Tong L, Uchino M, Nichols KK. The international workshop on meibomian gland dysfunction: report of the subcommittee on the epidemiology of, and associated risk factors for, MGD. Invest Ophthalmol Vis Sci. 2011;52(4):1994-2005. [Crossref] [PubMed] [PMC]
20. Mathers WD, Lane JA. Meibomian gland lipids, evaporation, and tear film stability. Adv Exp Med Biol. 1998;438:349-60. [Crossref] [PubMed]
21. Den S, Shimizu K, Ikeda T, Tsubota K, Shimmura S, Shimazaki J. Association between meibomian gland changes and aging, sex, or tear function. Cornea. 2006;25(6):651-5. [Crossref] [PubMed]
22. Sullivan DA, Sullivan BD, Ullman MD, Rocha EM, Krenzer KL, Cermak JM, et al. Androgen influence on the meibomian gland. Invest Ophthalmol Vis Sci. 2000;41(12):3732-42. [PubMed]
23. Dogru M, Katakami C, Inoue M. Tear function and ocular surface changes in noninsulin-dependent diabetes mellitus. Ophthalmology. 2001;108(3):586-92. [Crossref] [PubMed]
24. Lin X, Xu B, Zheng Y, Coursey TG, Zhao Y, Li J, et al. Meibomian Gland Dysfunction in Type 2 Diabetic Patients. J Ophthalmol. 2017;2017:3047867. [Crossref] [PubMed] [PMC]
25. Ekın MA, Ugurlu SK, Imre SS, Kahraman HG. The role of meibomian gland dysfunction on the development of dry eye disease in patients with facial nerve palsy. Arq Bras Oftalmol. 2021;85(2):128-35. [Crossref] [PubMed]
26. Eom Y, Lee JS, Kang SY, Kim HM, Song JS. Correlation between quantitative measurements of tear film lipid layer thickness and meibomian gland loss in patients with obstructive meibomian gland dysfunction and normal controls. Am J Ophthalmol. 2013;155(6):1104-10.e2. [Crossref] [PubMed]
27. Ibrahim OM, Matsumoto Y, Dogru M, Adan ES, Wakamatsu TH, Goto T, et al. The efficacy, sensitivity, and specificity of in vivo laser confocal microscopy in the diagnosis of meibomian gland dysfunction. Ophthalmology. 2010;117(4):665-72. [Crossref] [PubMed]
28. Lind M, Pivodic A, Svensson AM, Ólafsdóttir AF, Wedel H, Ludvigsson J. HbA1c level as a risk factor for retinopathy and nephropathy in children and adults with type 1 diabetes: Swedish population based cohort study. BMJ. 2019;366:l4894. [Crossref] [PubMed] [PMC]
29. Seifart U, Strempel I. Trockenes Auge und Diabetes mellitus [The dry eye and diabetes mellitus]. Ophthalmologe. 1994;91(2):235-9. German. [PubMed]
30. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al; IDF Diabetes Atlas Committee. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019;157:107843. [Crossref] [PubMed]