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Evaluation of Dry Eye and Meibomian Gland Dysfunction with Meibography in Pseudoexfoliation Syndrome

Psödoeksfoliasyon Sendromunda Kuru Göz ve Meibomian Bez Disfonksiyonunun Meibografi ile Değerlendirilmesi

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ABSTRACT Objectives: To evaluate morphological changes caused by pseudoexfoliation (PEX) syndrome in meibomian glands with meibography. **Material and Methods:** 39 individuals with PEX syndrome and 42 individuals without PEX syndrome were included in the study. Meibomian glands, tear-film break-up time, tear volume and subjective symptoms of the study and control groups were evaluated with followings, respectively: meibography, non-invasive keratographic tear film break-up time (NIKBUT), Schirmer 1 test with anesthesia, ocular surface disease index (OSDI) questionnaire. **Results:** Schirmer 1 and NIKBUT values were found to be significantly lower in the participants with PEX syndrome compared to the control group ($p<0.001$, $p=0.012$; respectively). But the OSDI index and total meibograde values were found to be significantly higher in the PEX syndrome group compared to the control group ($p=0.002$, $p<0.001$; respectively). Additionally, in the PEX syndrome group, a negative correlation was determined between total meibograde value and NIKBUT value (r:-0.673; $p=0.001$) and a positive correlation was determined between total meibograde value and OSDI index score value (r: 0.515; $p<0.001$). No statistically significant correlation was determined between total meibograde value and Schirmer 1 value ($p=0.847$). **Conclusion:** PEX syndrome affects the ocular surface adversely. Causing the meibomian gland dropout by this syndrome is also among the mechanisms of this adverse effect. This condition should be considered for the diagnosis and treatment approach of dry eye disease in patients with PEX syndrome.

Keywords: Exfoliation syndrome; dry eye syndromes; meibomian glands

ÖZET Amaç: Psödoeksfoliasyon sendromunun (PES) meibomian bezlerinde yaptığı morfolojik değişiklikleri meibografi ile değerlendirmek. **Gereç ve Yöntemler:** PES'li 39 ve PES'i olmayan 42 kontrol grubu katılımcı çalışmaya alındı. Çalışma ve kontrol grubunun meibomian bezleri (MB), gözyaşı kırılma zamanı, gözyaşı miktarı ve subjektif semptomları, meibografi, noninvaziv keratografik gözyaşı kırılma zamanı (NİKGKZ), anestezili Schirmer 1 test ve oküler yüzey hastalık indeksi (OYHİ) ile değerlendirildi. **Bulgular:** Schirmer 1 ve NİKGKZ düşüklüğü PES grubunda kontrol grubuna göre istatistiksel olarak anlamlı idi (sırasıyla; $p<0.001$; $p=0.012$). OYHİ ve toplam meibograde değerleri yüksekliği ise PES grubunda kontrol grubuna göre istatistiksel olarak anlamlı idi (sırasıyla $p=0.002$; $p<0.001$). Ayrıca PES grubunda toplam meibograde değeri ile NİKGKZ değeri arasında negatif (r:-0.673; $p=0.001$), OYHİ değeri arasında ise pozitif (r: 0.515; $p=0.001$) korelasyon saptandı. Yine bu grupta toplam meibograde değeri ile Schirmer 1 testi değeri arasında anlamlı bir korelasyon saptanmadı ($p=0.847$). **Sonuç:** PES oküler yüzeyi olumsuz olarak etkilemektedir. Bu olumsuz etkilerin nedenleri arasında meibomian bez kaybı da vardır. Klinisyenler PES'lu hastalarda kuru göz teşhis ve tedavisine yaklaşımda bu durumu dikkate almalıdır.

Anahtar Kelimeler: Eksfoliasyon sendromu; kuru göz sendromları; meibomian bezler

Pseudoexfoliation syndrome (PEX) is a disorder in which unnatural fibrillar extracellular material accumulation is seen in ocular and systemic tissues.[1-3] This material shows an abnormal accumulation in ocular and many extra-ocular tissues.[1-3] In the eye, this material shows an abnormal accumulation in the anterior lens capsule, zonule of Zinn, pupillary edge, iridocorneal angle, and anterior part of the vitreous.[1-3] In PEX syndrome, this material also accumulates in the goblet cells, accessory lacrimal glands, and conjunctiva. Decreased tear-film break-up time (TBUT) and Schirmer 1 test re-

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sults in PEX syndrome were attributed to conjunctival involvement.[4]

Meibomian glands (MGs) are oil glands located in the upper and lower eyelids. These glands are in charge of the production of the lipid layer of tear film necessary for the lubrication of ocular surface and stable tear film.[5] Meibomian gland dysfunction (MGD) is a chronic disease causing irritative symptoms resulting in evaporative dry eye syndrome.[6] Clinically, MGD is diagnosed with slit-lamp examination and it is characterized by occlusion of the orifices, reduction in expressibility, telangiectasia in the orifices, and hyperemia, irregular eyelid margin, and trichiasis.[6] These findings result in MGs dropout which is the unique criteria in the grading of the disease.[6] MGD may cause an increase in tear film osmolarity, in ocular surface disease index (OSDI) questionnaire results and, a decrease in TBUT, and a change in meibum volume and characteristics.[6]

It is known that ocular surface diseases are seen more commonly in individuals with PEX syndrome.[7] Although studies investigating the association between PEX syndrome and tear film stability and tear secretion, and conjunctival goblet cell morphology and tear osmolarity were performed until today, there is no study performed in regards to assessment of MGD with meibography.[8-10] Our study aims to investigate ocular surface diseases in individuals with PEX syndrome by using meibography.

MATERIAL AND METHODS

This prospective study was performed in 81 patients over 50 years of age presenting to our department between September 9th, 2019 and December 20th, 2019. The study protocol was approved by the Recep Tayyip Erdogan University Ethics Committee of Non-invasive Clinical Research (Date: 17.07.2019, No: 2019/115). Throughout the study, the tenets of the Declaration of Helsinki were followed. Written informed consent was obtained from all patients before participation. The participants were divided into two groups as individuals with and without PEX syndrome. The participants with PEX syndrome who had PEX material in both eyes were included in the study. Individuals undergoing ocular surgery previously, using contact lens; individuals with eyelid closure problem, entropion, ectropion, nasolacrimal canal obstruction, punctum plug, ocular allergy; individuals using topical eye drops (such as steroids, topical cyclosporine-A, artificial tears, antiglaucoma and nonsteroidal anti-inflammatory drugs) which can affect lacrimal and MGs, individuals using antidepressant, corticosteroid, diuretic, and individuals with systemic disease such as diabetes mellitus, thyroid gland dysfunction, Behçet disease and additionally individuals smoking were not included in the study.

Detailed eye examination including Schirmer 1 test with anesthesia, NIKBUT and meibography were performed in all participants. Since topical anesthesia would cause false measurement of NIKBUT and tropicamide 0.5% would cause false measurement of Schirmer 1 and NIKBUT; order of examination was determined as first NIKBUT and meibography, Schirmer 1 test and then other detailed ophthalmological examinations. Slit-lamp examination of the anterior lens capsule and fundus examination were performed after pupillary dilation. The existence of accumulation of a distinctive fibrillar (pseudoexfoliative) material at the pupillary edge and in a target-like pattern on the anterior lens capsule is referred to as clinically significant PEX syndrome. Subjective symptoms of the participants of ocular irritation consistent with dry eye disease were evaluated using the OSDI questionnaire. Meibography and NIKBUT were performed by the Sirius (CSO, Florence, Italy) tomograph and corneal topographer. This device is equipped with the Phoenix-Meibography Imaging Module.

Three images were obtained from both eyes for meibography. First, the lower lid and then the upper lid was everted and then the image was obtained. High-quality images were obtained by a single author with a good focus and good eyelid eversion. These images were then chosen and given an identification number. The images were evaluated by two masked examiners (F.U. and F. S.) who were already trained on the evaluation of meibography photographs. Examiners evaluated the MGs of the participants using the meibograde procedure developed by Call, et al.[11] Meibograde procedure involves the shortening, distortion, and dropout of MGs. Each category was graded between 0 and 3 according to the extent of the

affected area of the eyelid: grade 0, no eyelid involvement; grade 1, affected area less than 33%; grade 2, affected area between 33% to 66%; and grade 3, affected area more than 66%. We used the mean value of the results of the two examiners in our study. Meibography images showing the morphological changes in the MGs of the upper and lower eyelids of patients with PEX syndrome are seen in Figure 1 and Figure 2.

NIKBUT measurements were performed in the same room, under fixed humidity and temperature conditions. Three measurements were performed in the right and left eyes of each participant and an average of these 3 measurements were considered as the mean value. The tear map representing the regularity of the corneal surface of the participant was focused clearly on this procedure. The participant asked to blink twice fully. Immediately after opening the eye, an automatic stopwatch began to measure. The patient was asked to keep his/her eye open for the longest time possible. If the participant blinked his/her eye before distortion or diffused representing a break-up of tear film seen on the tear map, the test was repeated by asking the patient to blink his/her eye several times more for a few seconds. The automatic stopwatch was closed after the patient blinked his/her eye and it gave the average time between last blink and the first TBUT and all TBUTs between two blinks on tear map as value. In our study, we used the meantime.

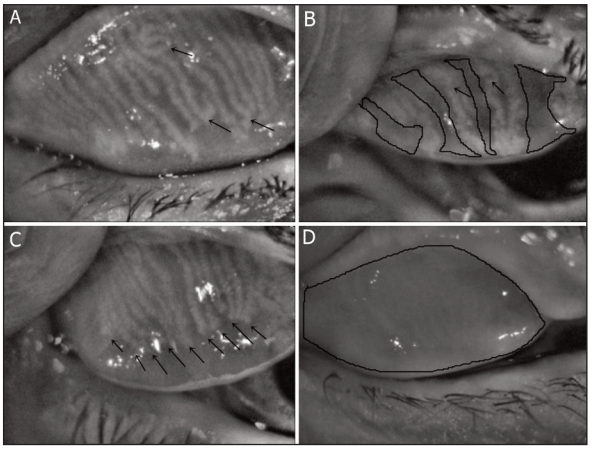

FIGURE 1: On the photographs of the upper eyelids of 4 different patients with pseudoexfoliation syndrome; (A) distortion in the meibomian glands (black arrow), (B) total dropout (outlined black) and distortion (black arrow), (C) shortening and correspondingly partial dropout (black arrow), (D) total dropout in all meibomian glands (outlined black) are seen.

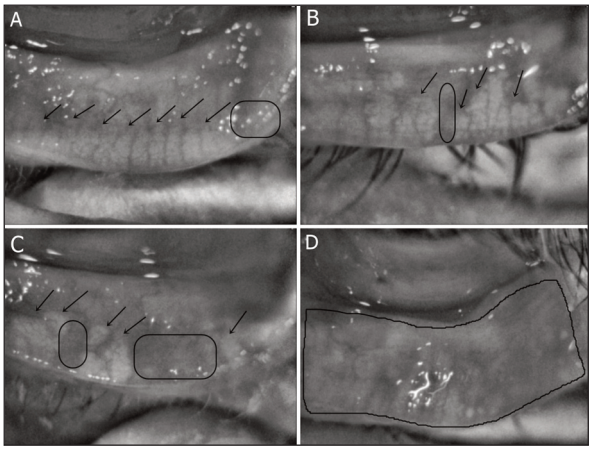

FIGURE 2: On the photographs of the lower eyelids of 4 different patients with pseudoexfoliation syndrome; (A) shortening in the meibomian glands and correspondingly partial dropout (black arrow), total dropout (outlined black), (B, C) shortening and correspondingly partial dropout (black arrow), total dropout (outlined black), (D) total dropout in all meibomian glands (outlined black) are seen.

For Schirmer 1 test with anesthesia, topical anesthetic eye drop (proparacaine hydrochloride 0.5%) was administered into the conjunctival sac of both eyes of the patient and waited for 10 minutes. Excess tears in the conjunctival cul-de-sacs were cleaned using a cotton-tipped applicator. A strip of filter paper (no. 41 Whatman) was folded as its tip to be 5 mm in length and then placed at the middle-lateral one-third junction point of the lower eyelid with the eyelash without touching the eyelashes and cornea. The participants were asked to close their eyes gently. After 5 minutes, the filter paper strip was taken and the wetting part of it starting from the folding angle was measured.

The OSDI is a questionnaire consist of 12 questions and these are partitioned into three groups. The first group of them includes questions about the ocular symptoms of dry eye syndrome. The second group of them are about vision-related function. And the third group of them includes questions regarding environmental triggers. The OSDI questionnaire is graded on a scale ranging from 0 to 4 according to frequency of symptoms over time.

STATISTICAL ANALYSIS

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for the

statistical analysis. During the evaluation of the study data, descriptive statistical methods (mean, standard deviation, median, and frequency, percentage, minimum and maximum) were used. The conformity of the quantitative data to a normal distribution was tested by using the Kolmogorov-Smirnov test and the graphical assessments. Student t-test was used for the intergroup comparisons of quantitative variables with normal distribution and Mann Whitney U test was used for the intergroup comparisons of quantitative variables without normal distribution. Pearson's Chi-square test was used for the comparison of qualitative data. Spearman's and Pearson correlation analysis were used for evaluation of the correlations between the variables. A p-value of <0.05 was accepted as statistical significance.

RESULTS

There were 39 participants (20 males, 19 females) in the PEX group and 42 participants (20 males, 22 females) in the control group. The median age of the PEX group was 70 (60-88) years and the median age of the control group was 73(55-89) years. No statistically significant difference was determined between groups according to the gender (p=0.457, p=0.457) (Table 1).

Measurements of Schirmer 1 tests of the PEX and the control groups were 7 (4-20), 12.50 (3.50-20.50); respectively. The lower values of measurements of the Schirmer I test of the PEX group compared to the control group were statistically significant (p<0.001) (Table 1).

Measurements of NIKBUT of the PEX and the control groups were 7.45 (2.75-15.55), 9.95 (1.95-16.50); respectively. The lower values of measurements of NIKBUT of the PEX group compared to the control group were statistically significant (p=0.012) (Table 1).

OSDI scores of the PEX and the control groups were 31.30 (6.80-62.50), 17.35 (3.10-50.00); respectively. The higher values of OSDI scores of the PEX group compared to the control group was statistically significant (p=0.002) (Table 1).

The mean and median values of the upper eyelid, lower eyelid and total eyelid (the upper eyelid + lower eyelid) meibogrades of the PEX group were 5.96±1.70, 5 (2.50-6.00), 5.44±1.21; respectively. The mean and median values of the upper eyelid, lower eyelid and total eyelid (the upper eyelid + lower eyelid) meibogrades of the control group were 4.43±1.28, 4 (1-6), 4.12±1.08; respectively. The mean higher values of the upper eyelid, lower eyelid and total eyelid (the upper eyelid + lower eyelid) meibogrades of the PEX group compared to the control group were statistically significant (all p<0.001) (Table 1).

Additionally, a correlation analysis performed between total meibograde values and mean Schirmer

TABLE 1: The demographics, dry eye tests, and meibogrades of the groups.

	Control Group (Mean, SD, Median, Minimum, Maximum)					PEX Group (Mean, SD, Median, Minimum, Maximum)					p-value
Sex N (K/E)	22/20					19/20					0.457[d]
Age (years)	70.48	6.51	70.00	60.00	88.00	72.72	7.58	73.00	55.00	89.00	0.077[b]
Schirmer 1 (mm)	12.10	4.67	12.50	3.50	20.50	8.18	3.91	7.00	4.00	20.00	**<0.001[b]
NIKBUT (s)	10.18	4.35	9.95	1.95	16.60	7.69	3.12	7.45	2.75	15.55	*0.012[b]
OSDI score	18.60	13.19	17.35	3.10	50.00	28.64	14.20	31.30	6.80	62.50	**0.002[b]
Upper meibograde	4.43	1.28	4.25	1.50	6.50	5.96	1.70	6.00	2.50	9.00	**<0.001[a]
Lower meibograde	3.81	1.30	4.00	1.00	6.00	4.92	1.07	5.00	2.50	6.00	**<0.001[b]
Total meibograde	4.12	1.08	4.25	1.75	6.25	5.44	1.21	5.50	2.75	7.50	**<0.001[a]

a= Student t Test b= Mann Whitney U Test d: Pearson's Chi-square test

*p<0.05, **p<0.01

NIKBUT: Non-invasive keratographic break-up time; OSDI: Ocular surface disease index; N: Count; SD; Standard deviation.

1, NIKBUT and OSDI score values of the PEX group was performed. A negative and statistically significant correlation was determined between total meibograde value and NIKBUT value (as total meibograde value increased NIKBUT value decreased) (r:-0,673; p=0.001) (Table 2, Figure 3). A positive and statistically significant correlation was determined between total meibograde measurement and OSDI score value (as total meibograde value increased OSDI score value increased) (r: 0.515; p=0.001) (Table 2, Figure 4). No statistically significant correlation was determined between total meibograde value and Schirmer 1 value (p=0.847).

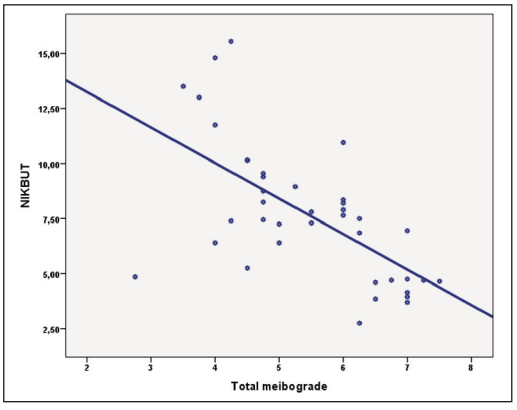

FIGURE 3: Correlation between total meibograde and non-invasive keratographic break-up time measurements.

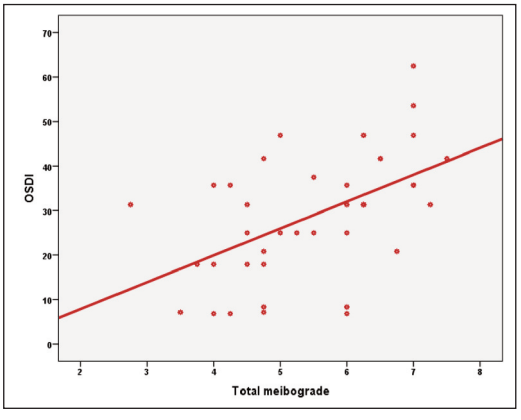

FIGURE 4: Correlation between total meibograde and ocular surface disease index measurements.

DISCUSSION

PEX syndrome is a condition with a course of low-grade inflammation. In the studies performed, many authors found that the rate of inflammatory cytokine in plasma and aqueous humor of patients with PEX syndrome to be higher compared to the control group. Puustjärvi et al. reported that the level of homocysteine in plasma and aqueous humor of individuals with PEX syndrome to be higher compared to the control group.[12] Higher levels of homocysteine are associated with elevated circulating levels of many inflammatory mediators including interleukin-6 and C-reactive protein.[13] Sorkhabi et al. reported that the plasma levels of tumor necrosis factor-alpha and high-sensitivity C-reactive protein of individuals with PEX syndrome to be higher compared to the control group.[14] Proinflammatory cytokines have an important role in the physiology and pathophysiology of the eye. These cytokines participate in many physiological activities such as extracellular matrix, vascular permeability, and intraocular pressure regulation.

PEX syndrome is also a condition with a clinical course of ischemia in the ocular tissues. Visontai et al. reported that PEX syndrome caused an increase in carotid artery stiffness.[15] Onaizah et al. reported that an increase in carotid artery stiffness caused a decrease in blood flow in the carotid artery.[16] The upper and lower eyelids consisting of MGs are fed by the ophthalmic artery and the lacrimal artery which are branches of the internal carotid artery. In the studies performed on rats by Hausman et al., the authors reported that the presence of both energy and perfect blood flow was necessary for lipid synthesis.[17] Nichols et al. reported that a decrease in the meibomian lipid synthesis caused excessive keratinization

TABLE 2: Correlations between total meibograde and ocular surface parameters according to PEX group.

		Total meibograde
NIKBUT	r	-0.673‡
	p	0.001**
OSDI score	r	0.515
	p	0.001**
Schirmer 1	r	-0.032
	p	0.847

‡r:Spearman's correlation analysis, r:Pearson correlation analysis
**p<0.01

of the MGs ductal epithelium and MGs obstruction.[18] Jester et al. reported that excessive keratinization of the MGs ductal epithelium caused ductal occlusion and plugging and this lead to meibomian gland dropout.[19]

MGs are important for ocular surface health.[20] In the investigation performed using meibography in patients with many inflammatory diseases of the conjunctiva and the eyelid like contact lens wear, topical glaucoma medications, systemic diseases such as vitiligo, rosacea and lamellar ichthyosis, significantly higher dropout was observed in MGs compared to the healthy control group.[21-25]

We also speculated that PEX syndrome caused MGs dropout due to its both inflammatory and ischemic characteristics. Due to ischemia caused by PEX syndrome, blood flow reaching to MGs would decrease, expressed meibum grade would decrease and this would lead to epithelial hyperkeratinization, obstruction and plugging and then meibomian gland dropout. Besides, inflammation caused by PEX syndrome would support this condition. Our study result occurred as we predicted. We found the rate of meibomian gland dropout to be higher in the participants with PEX syndrome compared to the healthy control group.

Kozobolis et al. reported that Schirmer 1 and TBUT test results to be lower in the individuals with PEX syndrome compared to the healthy control group.[8] They attributed lower TBUT time test results in this study to basic feature alteration in conjunctival goblet cell morphology. However, the authors stated that further studies were required to understand the exact mechanism. In our study, we also found Schirmer 1 and TBUT test results to be lower in the individuals with PEX syndrome compared to the healthy control group. But we think that the deficiency of the lipid layer of the tear film caused by the meibomian gland dropout provided more contribution to low TBUT test results. Our study provides an important contribution to delineate the etiology of lower TBUT test results in individuals with PEX syndrome.

As it was in our study, lower Schirmer 1 and TBUT test results in the individuals with PEX syndrome compared to the healthy control group were shown in many studies.[7-9,26-28] Kocabeyoglu et al. reported that OSDI score to be higher in the individuals with PEX syndrome compared to the healthy control group.[27] In our study, we also found the OSDI score to be significantly higher in individuals with PEX syndrome. Potemkin, et al. reported that the rates of MGD and meibomian ductus obstruction to be significantly higher in individuals with PEX syndrome compared to the healthy control group.[29] We mentioned the study showing the relationship between the meibomian ductus obstruction and the meibomian gland dropout earlier. This study of Potemkin et al. supports our study indirectly.

CONCLUSION

Meibography is a valuable non-invasive method which can be used to assess dry eye seen in the patients with PEX syndrome. Meibomian gland dropout can lead to evaporative-type dry eye disease by causing a deficiency in the lipid layer of the tear film. Our study result shows that the meibomian gland dropout is statistically higher in individuals with PEX syndrome compared to the healthy control group. While the clinicians are evaluating the dry eye disease in individuals with PEX syndrome, they should also perform meibography and administer efficient treatment for etiology in addition to tests such as Schirmer 1, TBUT and OSDI questionnaire.

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: *Murat Okutucu;* ***Design: Control/Supervision:*** *Murat Okutucu;* ***Data Collection and/or Processing:*** *Murat Oku-*

tucu; ***Analysis and/or Interpretation:*** *Murat Okutucu;* ***Literature Review:*** *Murat Okutucu, Hüseyin Fındık, Mehmet Gökhan Aslan;* ***Writing the Article:*** *Murat Okutucu, Hüseyin Fındık, Mehmet Gökhan Aslan;* ***Critical Review:*** *Murat Okutucu, Hüseyin Fındık, Mehmet Gökhan Aslan;* ***References and Fundings: Materials:*** *Murat Okutucu.*

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