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The Role of Inflammation in Meibomian Gland Loss and Tear Film Instability in Patients with Acne Vulgaris: A Correlation Study

Akne Vulgaris Hastalarında Meibomian Bez Kaybı ve Gözyaşı Film İnstabilitesinde İnflamasyonun Rolü: Bir Korelasyon Çalışması

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This study was presented as an oral presentation at 10th International Gevher Nesibe Medical Sciences Conference, February 3-5, 2023, Ankara, Türkiye.

ABSTRACT Objective: To examine the relationship of tear film instability and meibomian gland (MG) loss with inflammatory markers in female participants diagnosed with acne vulgaris (AV). **Material and Methods:** 75 eyes of 75 female participants diagnosed with AV were included in the study. All participants consist of patients who applied to the dermatology outpatient clinic and will be treated with isotretinoin. MG losses in meibography were examined. The correlation between the participants' NI-BUT parameters and the amount of MG loss with the Systemic Immune-Inflammation Index (SII), which is the value obtained from the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and platelet count×(NLR) was examined. **Results:** The mean age of the participants was 24.7±5 year. Mean NI_{first}-BUT value was found to be 4.8±3.4 sec. Mean $NI_{average}$-BUT value was found to be 7.4±3.1 sec. MG loss in the upper lid was found to be 37.4%±14.6%. The rate of MG loss in the lower lid was found to be 48.0 %±15.9%. There was no significant correlation between NI_{first}-BUT and $NI_{average}$-BUT value and NLR, PLR and SII (p>0.05). There was no significant correlation between upper& lower lid MG loss rate and NLR, PLR and SII (p>0.05). **Conclusion:** We observed that non-invasive tear break-up time parameters and MG loss were not correlated with inflammatory markers in patients with AV. We think that factors other than inflammatory parameters should be investigated as the etiological factor of MG loss and tear film instability in patients with AV.

Keywords: Meibomian glands; acne vulgaris; dry eye syndrome; tears; inflammation

ÖZET Amaç: Akne vulgaris (AV) tanılı kadın katılımcılarda, gözyaşı filmi instabilitesinin ve meibomian bez (MB) kaybının inflamatuar belirteçler ile olan ilişkisini incelemek. **Gereç ve Yöntemler:** AV tanılı 75 kadın katılımcının 75 gözü çalışmaya alındı. Bütün katılımcılar, dermatoloji polikliniğine başvuran ve isotretinoin tedavisi başlanacak hastalardan oluşmaktadır. Katılımcıların invaziv olmayan ilk gözyaşı kırılma zamanı ($İO_{ilk}$-GKZ) ve her katılımcı için ölçüm süresince, invaziv olmayan tüm gözyaşı kırılma zamanlarının ortalama ($İO_{ort}$-GKZ) değerlerine bakıldı. Meibografideki MB kayıp miktarları incelendi Katılımcıların İO-GKZ parametrelerinin ve MB kayıp miktarının nötrofil/lenfosit oranı (NLO), platelet/lenfosit oranını (PLO) ve platelet sayısı×(NLO)'dan elde edilen değer olan Sistemik İmmün-İnflamasyon İndeksi (Sİİ) arasındaki korelasyon incelendi. **Bulgular:** Katılımcıların ortama yaşı 24,7±5 idi. Ortama $İO_{ilk}$-GKZ değeri 4,8±3,4 sn olarak saptandı. Ortama $İO_{ort}$-GKZ değeri 7,4±3,1 sn olarak saptandı. Üst kapaktaki MB kayıp oranı %37,4±%14,6 olarak saptandı. Alt kapaktaki MB kayıp oranı %48±15,9 olarak saptandı. $İO_{ilk}$-GKZ değeri ile NLO, PLO ve Sİİ arasında korelasyon saptanmadı (p>0,05). Aynı şekilde $İO_{ort}$-GKZ değeri ile NLO, PLO ve Sİİ arasında korelasyon saptanmadı (p>0,05). Alt kapaktaki MB kayıp oranı ile NLO, PLO ve Sİİ arasında korelasyon saptanmadı (p>0,05). Üst kapaktaki MB kayıp oranı ile NLO, PLO ve Sİİ arasında da korelasyon saptanmadı (p>0,05). **Sonuç:** AV hastalarında invaziv olmayan gözyaşı kırılma zamanı parametreleri ile MB kaybının inflamatuar belirteçlerle bir korelasyon göstermediğini gözlemledik. AV hastalarındaki MB kaybı ve gözyaşı film düzensizliğinin etiyolojik faktörü olarak inflamatuar parametrelerin dışında başka etmenlerin araştırması gerektiğini düşünmekteyiz.

Anahtar Kelimeler: Meibomian bezler; akne vulgaris; kuru göz sendromları; gözyaşları; inflamasyon

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Acne vulgaris (AV) constitutes a significant portion of the patients who apply to the dermatology outpatient clinic during adolescence.[1,2] Although its frequency among dermatological diseases changes with age, it is thought to be between 20 and 80% in adolescence.[1] The increased androgenic effect during adolescence triggers the pathological cascade in the pilosebaceous glands. Acne is caused by the triggering effect of increased androgenic effect in genetically suitable individuals and due to the abnormal functioning of pilosebaceous glands caused by bacterial and inflammatory processes.[3,4]

Meibomian glands (MG) are modified specific sebaceous glands located on the lids. They are arranged vertically on the lower and upper eyelids and cover the entire eyelid. Although their sizes and numbers vary between lower and upper eyelids, they serve the same purpose.[4] The lipid secretion produced by MG in the tars prevents rapid evaporation of tears.[5,6] The lipid portion of the tear film has a central role in tear film stability.[5,6]

As is the case with other sebaceous glands, MGs, as a modified sebaceous gland, is affected by hormonal and/or inflammatory changes.[7-11] In our previous study, we found decreased tear film stability and accompanying increased MG loss in patients with AV.[11] Muhafiz et al. found that the tear film pattern was more disturbed and MG losses was higher in patients with AV.[9] They attributed the MG loss in AV patients to the colonization of Propionibacterium acnes bacteria and the resulting inflammation.[9] In a study conducted with nodulocystic acne patients, Ozdemir et al. found that the tear film was more unstable in the patient group.[10] They did not perform meibography, and hence concluded that the changes in the ocular surface parameters were related to hormonal changes.[10]

The neutrophil, platelet and lymphocyte counts and the ratios of these counts to each other have been discussed in the literature. Neutrophils play a proinflammatory role. lymphocytes have an anti-inflammatory effect.[12] Systemic Immune-Inflammation Index (SII) is one of the new prognostic biomarkers.[13] High neutrophil and platelet counts and low lymphocyte counts indicate high SII values, affecting the inflammatory process.[13] SII, which is calculated by multiplying the platelet count with neutrophil/lymphocyte ratio (NLR) has been found to have predictive value for glaucoma, keratoconus, dry eye and retinal vascular occlusion.[14-17] Both SII and NLR rates were found higher in patients with uveitis and dry eye.[18] In the study conducted by Acet and Sarikaya it was found that MG loss rates was associated with inflammatory parameters in patients with polycystic ovary syndrome. They conclude that inflammation may be the etiological factor for MG loss in patients with polycystic ovary syndrome.[7]

In the present study, tear film stability and MG loss in patients with AV were analyzed and the extent of the effect of inflammatory processes on a possible MG and/or tear film disorder in AV patients was examined. Accordingly, the correlation between tear film parameters and MG loss rates with the rates of peripheral blood values were investigated in patients with AV.

MATERIAL AND METHODS

This study was designed as a prospective study. The study has Harran University Clinical Research Ethics Committee approval (date: August 16, 2021, no: HRU/21.14.31). Informed consent was obtained from all patients. The study was conducted in accordance with the principles set forth in the Declaration of Helsinki. The population of the study consisted of the patients who were diagnosed with AV by the dermatology clinic, planned to receive systemic isotretinoin treatment and referred to an ophthalmologist for routine eye examination. Given that the majority of potential volunteers with AV diagnosis were female patients, only female patients were included in order to avoid the possible confounding effects of gender on the peripheral blood values. Among the participants, those with dermatological diseases such as Sjögren's syndrome and contact dermatitis were excluded from the study. Individuals who were exempt from the exclusion criteria listed above were reviewed for their detailed ophthalmic history. Individuals with conditions causing ocular surface disease (surgery, contact lens wearer) were also excluded from the study.

Measurements and assessments were made in the following order;

1. Non-invasive tear break-up time (NI-BUT) evaluations were performed first. Before the measurement, the patients were asked to "blink twice with command during the procedure and then keep their eyes open for as long as possible". NI-BUT test was performed with the corneal topography device in only one eye (preferably right eye, left eye was also accepted if the right eye was not suitable) (Figure 1).

2. Meibography of the upper and lower lids of each eye were taken: Analysis and markings were performed with the Sirius™ topography device and its specific software [Costruzione Strumenti Ophthalmici (CSO) S.r.l, Italy] by the same ophthalmologist (Y.A). The amounts of losses were calculated both in terms of percentage (%) of loss and as per the five-point grading system. In the five-point grading system, individuals with no loss, less than 25% loss, between 26% and 50% loss, between 51% and 75% loss, and over 75% loss were assessed as Grade 0, Grade 1, Grade 2, Grade 3, Grade 4, and Grade 5, respectively.[19] At least five separate meibography images were taken for each of the upper and lower eyelids. From among these five different meibography images, the three images with the best contrast and image quality were selected and the respective MG loss amounts were separately recorded. Subsequently, the MG loss amounts in the three meibography images created for each eyelid were summed and then divided by three. The result, which equaled to average loss amount of three different images, was used in the statistical analyses. Although the shots are taken by a meibography device, the amount of MG loss in meibography is calculated manually and may thus be subjective.[20] Choosing the three images with the best contrast and image quality from among five different images and getting the average loss amount of these three images minimizes the said subjectivity and misjudgment for MG loss rates in meibography (Figure 2).

3. Subjective ocular symptoms were assessed using the Ocular Surface Disease Index (OSDI): OSDI is a 12-item questionnaire that is designed to obtain a rapid evaluation of the symptoms of ocular discomfort that are compatible with dry-eye disease. The OSDI provides easier, quicker, and more reliable diagnosis of ocular surface disease and assesses the ocular findings related to dry-eye disease. The OSDI scores between 0 and 12 are considered normal, whereas the OSDI scores of 13 and above are considered abnormal.[21]

4. Peripheral whole blood count values, which were routinely requested from the patients who were

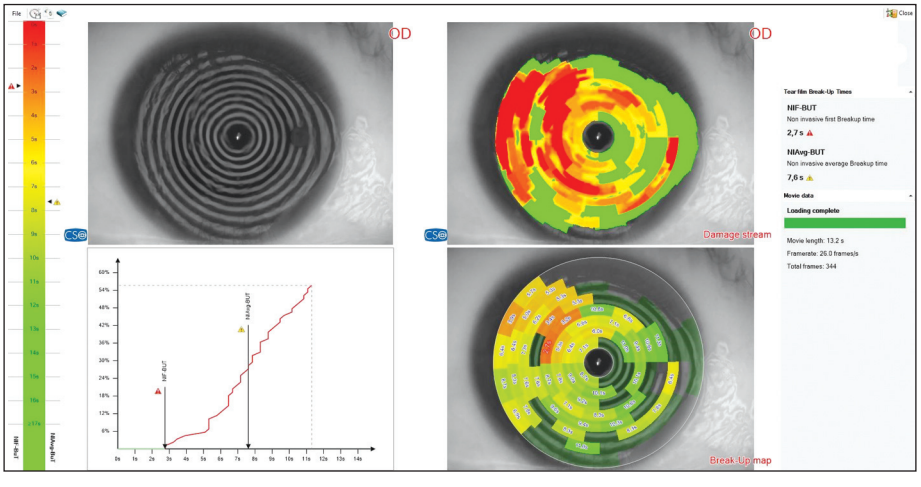

FIGURE 1: NI-BUT test results of one eye of a volunteer in the acne vulgaris group. Accordingly, the volunteer's NI_{first}-BUT and $NI_{average}$-BUT values were measured as 2.7 and 7.6 seconds, respectively. The first break-up appears to have occurred in the superotemporal area. In addition, it is seen that many break-up areas have occurred at different times on most of the corneal surface during the measurement.

NI_{first}-BUT: Non-invasive first tear break-up time; $NI_{average}$-BUT: Non-invasive tear break-up times.

FIGURE 2: Meibography analysis of a volunteer in the acne vulgaris group: Average meibomian gland loss rate was obtained from the 3 meibography images with the best image and contrast quality from both the upper and lower lids, and used in the statistical analyses. Accordingly, the volunteer's lower and upper lid loss rates were calculated as 37.86% and 55.23%, respectively.

planned to start on Isotretinoin treatment by the dermatology clinic, were obtained from the hospital database. Individuals whose blood samples had been taken before or after the day of ophthalmic examination were excluded from the study. Peripheral whole blood count values were reviewed using the neutrophil/lymphocyte ratio (N/L), platelet/lymphocyte ratio (P/L), and immune-inflammation index (SII) [platelet×(neutrophil/lymphocyte)] parameters.

Meibography and NI-BUT testing were performed with the Sirius™ [Costruzione Strumenti Ophthalmici (CSO) S.r.l, Italy] topography device. The videokeratoscopy in the topography device analyzes the information obtained from over 400 film frames at up to 25 frames per second that were created using the images reflected from the corneal surface, and produces quantitative results such as first tear break-up time (NI_{first}-BUT) and average of all tear break-up times ($NI_{average}$-BUT) for each participant (Figure 1).[20]

The device makes MGs visible by using its infrared light source. The loss of MG is determined both as a percentage (%) and according to the five-point grading system (Figure 2).[20]

STATİSTİCAL ANALYSİS

The descriptive statistics were expressed as mean with standard deviation values, median with minimum and maximum values, and frequency and ratio values. Kolmogorov-Smirnov test was used to determine whether the variables conform to the normal distribution. Spearman's correlation analysis was used for the correlation analyses. P value of less than 0.05 was considered statistically significant. SPSS 28.0 (Statistical Package for Social Sciences for Windows, version 28.0. IBM Corp. Armonk, NY, U.S., 2021) software package was used for statistical analyses.

RESULTS

This prospective study was conducted with 75 female AV patients. The mean age was 24.7±5 years (Table 1).

TABLE 1: Age characteristics, NI-BUT values and OSDI scores in participants.

		X̄±SD/n-%	Median
Age (years)		24.7±5.0	23.0
NI_{first}-BUT (sec)		4.8±3.4	4.0
$NI_{average}$-BUT (sec)		7.4±3.1	6.9
DMGD	(-)	17±22.7	
	(+)	58±77.3	
HMFLD	S.HMFLD	13±22.4	
	I.HMFLD	45±77.6	
OSDI	Normal	39±52.0	
	Abnormal	36±48.0	

NI_{first}-BUT: Non-invasive first break-up time test; $NI_{average}$-BUT: Average of non-invasive all break-up for each participants; DMGD: Indicates whether break-up occurred during the measurement; HMFLD: Refers to the superior and inferior half-area of the corneal surface; S. HMFLD: Superior hemifield; I. HMFLD: Inferior hemifield; OSDI: Ocular Surface Disease Index; "Normal" OSDI refers to scores between 0 to 12 points; "Abnormal" OSDI refers to scores equal to or higher than 13 points; SD: Standard deviation.

TABLE 2: The amount of MG loss in participants.

		X̄±SD/n-%	Median
SM Grade*	I	16±21.3	
	II	42±56.0	
	III	17±22.7	
SM-SCL (%)		37.4±14.6	38.3
IM Grade*	I	5±6.7	
	II	37±49.3	
	III	29±38.7	
	IV	4±5.3	
IM-SCL (%)		48.0±15.9	46.3
SM≥25	(-)	13±17.3	
	(+)	62±82.7	
		0	
IM≥25	(-)	5±6.7	
	(+)	70±93.3	

*These were evaluated according to the five-point grade system as: Grade 0: No loss; Grade 1: If there is less than 25% loss; Grade 2: If the loss rate is between 26% and 50%; Grade 3: If the loss rate is between 51-75%; and Grade 4: If the loss rate is above 75%.19; SM-Grade: Stands for grade-based meibography (MG) loss revealed by upper lid meibography; IM-Grade: Stands for grade-based meibography (MG) loss revealed by lower lid meibography; SM-SCL: Stands for percentage-based meibography (MG) loss revealed by upper lid meibography; IM-SCL: Stands for percentage-based meibography (MG) loss revealed by Lower lid meibography; SM≥25: Number of participants whose upper lid MG loss amount is more than 25%; IM≥25: Number of participants whose lower lid MG loss amount is more than 25%; MG: Meibomian gland; SD: Standard deviation.

The mean NI_{first}-BUT value in the participants was 4.8±3.4 seconds. At least one break-up was detected in 58 of 75 (77.3%) participants during the measurement. In 45 participants, the first break-up occurred in the inferior hemifield. Normal and abnormal OSDI was detected in a close ratio between participants (Table 1).

The mean amount of MG loss in the upper lid was 37.4%±14.6%. The mean amount of MG loss in the lower lid was 48.0±15.9%. Lower lid MG loss rate was above 25% in 70 of the participants (Table 2).

No correlation was detected between neither NI_{first}-BUT value nor $NI_{average}$-BUT value and inflammatory markers. Likewise, no correlation was found between MG loss parameters and inflammatory markers (Table 3).

TABLE 3: Analysis of the correlations, between NI-BUT parameters, lower and upper eyelid MG losses and inflammatory markers.

		NLR	PLR	SII
NI_{first}-BUT	r value	0.120	0.097	0.075
	p value	0.364	0.464	0.571
$NI_{average}$-BUT	r value	-0.019	0.130	-0.040
	p value	0.886	0.325	0.762
SM-SCL	r value	0.037	0.116	0.107
	p value	0.750	0.321	0.361
IM-SCL	r value	0.087	0.091	0.094
	p value	0.459	0.439	0.425

Spearman's correlation analysis.
NI_{first}-BUT: Non-invasive first break-up time test; $NI_{average}$-BUT: Average of non-invasive all break-up for each participants; SM-SCL: Stands for percentage-based meibography (MG) loss revealed by upper lid meibography; IM-SCL: Stands for percentage-based meibography (MG) loss revealed by Lower lid meibography; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; SII: Systemic Immune-Inflammation Index [platelet count×(neutrophil/lymphocyte)]; MG: Meibomian gland.

DISCUSSION

In our previous study, it was observed that the $NI_{average}$-BUT and NI_{first}-BUT values of AV patients were significantly shorter than those of control subjects, indicated that the tear film was more unstable in AV patients than in control subjects.[11] AV is a hormonal and inflammatory disease affecting the pilosebaceous glands.[8-10] The symptom that prompts AV patients to apply to the dermatology clinics is generally facial rash.[22,23] The literature on the relationship between eye and AV focuses on the ocular surface effect of Isotretinoin, which is mostly used in the treatment of AV disease.[24,25] The possibility that the tear film may

be affected by hormonal and inflammatory pathologies in AV has not been adequately addressed in the literature. In this context, the sample of present study consisted of volunteers between the ages of 18-39 who were diagnosed with AV but did not receive any treatment.[24-26] In addition, only female patients were included in the study in order to rule out any hormonal effect caused by gender, thus providing an opportunity to better observe the net effects of AV on the tear film. As mentioned above, the ocular surface effects of Isotretinoin used in the treatment of AV are well established in the literature.[9,24,25] Ozdemir et al. reported that the tear film was more unstable in patients diagnosed with nodulo cystic acne, and Muhafiz et al. reported that the tear film was more unstable in patients with AV.[9,10] However, in both studies, tear film stability was measured with the fluorescein break-up time test. On the other hand, Acet and Bilik in their study in which they compared the tear film noninvasively, found a more impaired tear film stability compared to the control group in patients with AV.[11] In 3 studies that mentioned above, the one of causes of tear film impairment in AV patients had been suspected as inflammation, but since inflammatory markers were not studied, a conclusion was reached at the level of inferences.[9-11] Could inflammation be an effective etiological factor? In present study, we found that $NI_{average}$-BUT and NI_{first}-BUT parameters, which are two indicators of tear film stability, did not show a correlation with inflammatory markers. According to these results, we can say that at least systemic inflammatory factors do not play an active role in tear film instability in patients with AV. We think that local microbial or inflammatory factors may play a more prominent role. In order to support this inference, is need for further studies that local inflammatory factors are also examined.

In present study, we found the mean MG loss in the upper eyelid to be 37.4% it found the mean MG loss rate of the lower lids to be 48%. In our previous case-control study, we found that MG loss was significantly higher in AV patients.[11] Similar results were also found in the study of Muhafiz et al.[9] In the correlation analysis we conducted in this study, we did not find any correlation between MG loss and inflammatory markers. Propionibacterium acnes colonised in the MGs causing obstruction of the orifices. Toxins or other enzymes released from bacteria disrupt the epithelial cells of the MG and finally leading to MG atrophy. In addition, it was found that patient with MG dysfunction had higher rate of anaerobic microorganisms (about 3/4 of these microorganisms consist of Propionibacterium acnes) compared to healthy participants.[27,28] The fact that both NI-BUT parameters and MG loss rates were not found to have a statistically significant relationship with inflammatory markers in correlation analyses. It Suggests that the tear film instability and MG loss in patients with AV may occurred as a result of hormonal or local factor rather than inflammatory factors.

The limitation of this study was that the effect of hormonal and/or other factors on the extent of the tear film instability and/or MG loss in AV was not investigated.

CONCLUSION

Systemic inflammatory markers do not play an active role in MG loss and tear film instability in AV patients. In addition to local factors, other etiological factors should be investigated in MG loss and tear film instability of patients with AV.

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: *Yakup Acet;* ***Design:*** *Yakup Acet;* ***Control/Supervision:*** *Yakup Acet;* ***Data Collection and/or Processing:*** *Yakup Acet;* ***Analysis and/or Interpretation:*** *Yakup Acet;* ***Literature Review:*** *Yakup Acet;* ***Writing the Article:*** *Yakup Acet, Yaşar Dağ;* ***Critical Review:*** *Yakup Acet, Yaşar Dağ;* ***References and Fundings:*** *Yakup Acet;* ***Materials:*** *Yakup Acet.*

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